

**Food and Drug Administration
Center for Drug Evaluation and Research**

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting

September 9, 2024

Location: The FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993-0002. The public will also have the option to participate, and the advisory committee meeting will be heard, viewed, captioned, and recorded through an online teleconferencing and/or video conferencing platform.

Topic: The Committee discussed new drug application 213972, for oral sulopenem etzadroxil/probenecid tablets consisting of 500 milligrams (mg) sulopenem etzadroxil and 500 mg probenecid, submitted by Iterum Therapeutics US Ltd., for the proposed indication of treatment of uncomplicated urinary tract infections (uUTI) caused by designated susceptible bacteria in adult women 18 years of age and older.

These summary minutes for the September 9, 2024 meeting of the Antimicrobial Drugs Advisory Committee Meeting of the Food and Drug Administration were approved on

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I certify that I attended the September 9, 2024 meeting of the Antimicrobial Drugs Advisory Committee Meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

LaToya Bonner, PharmD
Acting Designated Federal Officer
AMDAC

Lindsey Baden, MD
Acting Chairperson, AMDAC

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting September 9, 2024

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 9, 2024, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Iterum Therapeutics US Ltd. The meeting was called to order by Lindsey R. Baden, MD (Acting Chairperson). The conflict-of-interest statement was read into the record by LaToya Bonner, PharmD (Acting Designated Federal Officer). There were approximately 70 people in attendance in person and approximately 310 people online. There were two Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The Committee discussed new drug application 213972, for oral sulopenem etzadroxil/probenecid tablets consisting of 500 milligrams (mg) sulopenem etzadroxil and 500 mg probenecid, submitted by Iterum Therapeutics US Ltd., for the proposed indication of treatment of uncomplicated urinary tract infections (uUTI) caused by designated susceptible bacteria in adult women 18 years of age and older.

Attendance:

Antimicrobial Drugs Advisory Committee Members Present (Voting): Michael Green, MD, MPH; Sally A. Hunsberger, PhD; Nimish Patel, PharmD, PhD; Federico Perez, MD, MS

Antimicrobial Drugs Advisory Committee Members Not Present (Voting): Nina M. Clark, MD; W. David Hardy, MD; Stacey R. Rose, MD; George K. Siberry, MD, MPH; Sankar Swaminathan, MD

Antimicrobial Drugs Advisory Committee Member Present (Non-Voting): Richa S. Chandra, MD, MBA (*Industry Representative*)

Temporary Members (Voting): Lindsey R. Baden, MD (*Acting Chairperson*); Barbara M. Gripshover, MD, FIDSA; Elizabeth Joniak-Grant, PhD (*Patient Representative*); Roger Lewis, MD, PhD; Arjun Srinivasan, MD; Roblena Walker, PhD (*Acting Consumer Representative*)

FDA Participants (Non-Voting): John Farley, MD, MPH; Peter Kim, MD, MS; Ramya Gopinath, MBBS; Angela Kopack, MD; Xianbin Li, PhD; Jalal Sheikh, PhD; Henrietta Abodakpi, PharmD, PhD; Daniel Rubin, PhD; Dakshina Chilukuri, PhD; Avery Goodwin, PhD
Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD, MBA

Open Public Hearing Speakers Present: Neha J. Ahmad, MD, MPH (Public Citizen’s Health Research Group); Diana Zuckerman, PhD (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee

Lindsey R. Baden, MD
Acting Chairperson, AMDAC

Conflict of Interest Statement

LaToya Bonner, PharmD
Acting Designated Federal Officer, AMDAC

FDA Opening Remarks

Peter Kim, MD, MS
Director
Division of Anti-Infectives (DAI)
Office of Infectious Diseases (OID)
Office of New Drugs (OND)
CDER, FDA

APPLICANT PRESENTATIONS

Iterum Therapeutics

Introduction

Michael Dunne, MD, FIDSA
Board Member, Consultant
Iterum Therapeutics

Unmet Need

Marjorie Golden, MD, FIDSA
Site Chief, Infectious Disease
St. Raphael Campus
Yale New Haven Hospital

Efficacy, Microbiology and Pharmacology

Michael Dunne, MD, FIDSA

Safety

Steven Aronin, MD, FIDSA
Senior VP and Head of Clinical Development
Iterum Therapeutics

Benefit-Risk

Michael Dunne, MD, FIDSA

Clarifying Questions

FDA PRESENTATIONS

Efficacy and Safety Assessments

Angela Kopack, MD
Clinical Reviewer
DAI, OID, OND, CDER, FDA

Xianbin Li, PhD
Statistical Reviewer
Division of Biometrics IV
Office of Biostatistics
Office of Translational Sciences (OTS)
CDER, FDA

Microbiology Assessment

Jalal Sheikh, PhD
Clinical Microbiology Reviewer
DAI, OID, OND, CDER, FDA

Clinical Pharmacology Assessment

Henrietta Abodakpi, PharmD, PhD
Clinical Pharmacology Reviewer
Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology
OTS, CDER, FDA

Clarifying Questions

LUNCH

Clarifying Questions

OPEN PUBLIC HEARING

Charge to the Committee

Peter Kim, MD, MS

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** The Applicant is seeking an indication for sulopenem etzadroxil/probenecid in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infection (uUTI) caused by designated susceptible microorganisms. Discuss the overall benefits and risks for the use of sulopenem etzadroxil/probenecid for this indication.

Committee Discussion: *The Committee acknowledged that the efficacy of sulopenem for treatment of uUTI in adult women was demonstrated in the two phase 3 trials conducted by the Applicant, albeit in discordant populations, but expressed concern about the possibility of increased antimicrobial resistance to carbapenems related to the use of this drug for empiric treatment of uUTI in an ambulatory setting. Additionally, while the Committee members also acknowledged the potential utility of an oral penem drug for treatment of uUTI due to resistant organisms such as extended-spectrum β -lactamase (ESBL)-producers, uUTI that failed treatment with first-line drugs, or uUTI in women intolerant of first-line drugs, they noted that FDA-approved carbapenems are generally the “last resort” option in the*

antimicrobial armamentarium for resistant gram-negative infections and are usually reserved for the treatment of culture-proven infections. A rise of resistance to carbapenems could therefore represent a significant risk both to individual patients and to society as a whole. The Committee noted multiple issues with the unrestricted use of sulopenem etzadroxil/probenecid as a first-line drug for treatment of uUTI, including possible off-label use, especially given the current general lack of effective antimicrobial stewardship in ambulatory settings. The Committee discussed the feasibility of requiring culture and susceptibility confirmation prior to prescribing sulopenem but ultimately suggested a restriction of use in labeling to indicate sulopenem etzadroxil/probenecid for treatment of uUTI in adult women at higher risk of, or with proven treatment failure with first line agents, or who have limited or no alternative oral antibacterial treatment options. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Considering the totality of the evidence in this application, discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem etzadroxil/probenecid.

***Committee Discussion:** The Committee felt that sulopenem etzadroxil/probenecid should not be used empirically and in an unrestricted fashion for treatment of uUTI in adult women, primarily due to the possibility of increased cross-resistance to carbapenem drugs. In light of the concerns expressed during the discussion of Question #1, the Committee members felt that the indication proposed by the Applicant was too broad and requested information on the mechanisms available to FDA to restrict the use of sulopenem etzadroxil/probenecid. Collectively, the Committee recommended a restricted indication for sulopenem etzadroxil/probenecid and limitations of use to ensure that the drug was not used as step-down treatment following initial intravenous treatment of either cUTI or cIAI given sulopenem's failure to demonstrate benefit in the phase 3 clinical trials for these indications. There was discussion on stricter labeling options, such as a boxed warning or inclusion of a requirement for culture and susceptibility testing prior to prescribing sulopenem and all Committee members were agreed on the urgent need for rapid development of diagnostic testing. The Committee also discussed modalities to track antimicrobial resistance development following potential introduction of sulopenem etzadroxil/probenecid to the U.S. market and all members agreed that post-marketing surveillance would be essential. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:08 p.m. ET.