

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

**Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting  
October 16, 2019**

Location: The FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The committee discussed new drug application (NDA) 209445, cefiderocol lyophilized powder for intravenous administration, submitted by Shionogi Inc., for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis due to gram-negative bacteria in patients with limited or no alternative treatment options.

These summary minutes for the October 16, 2019 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on December 9, 2019.

I certify that I attended the October 16, 2019 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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/s/

Lauren Tesh Hotaki, PharmD, BCPS, BCIDP  
*Designated Federal Officer, AMDAC*

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/s/

Lindsey R. Baden, MD  
*Chairperson, AMDAC*

**Summary Minutes of the Antimicrobial Drug Advisory Committee (AMDAC)  
Meeting  
October 16, 2019**

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 16, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Shionogi Inc. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict of interest statement was read into the record by Lauren Tesh Hotaki, PharmD, BCPS, BCIDP (Designated Federal Officer). There were approximately 150 people in attendance. There were five Open Public Hearing (OPH) 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 (NDA) 209445, cefiderocol lyophilized powder for intravenous administration, submitted by Shionogi Inc., for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis due to gram-negative bacteria in patients with limited or no alternative treatment options.

**Attendance:**

**Antimicrobial Drugs Advisory Committee Members Present (Voting):** Lindsey R. Baden, MD (Chairperson); Nina M. Clark, MD; Dean A. Follmann, PhD; Michael Green, MD, MPH; Barbara M. Gripshover, MD; Jennifer Le, PharmD, MAS; Ighovwerha Ofotokun, MD, MSc; George K. Siberry, MD, MPH; Roblena E. Walker, PhD (Consumer Representative); Peter J. Weina, PhD, MD

**Antimicrobial Drugs Advisory Committee Member Present (Non-voting):** Nicholas A. Kartsonis, MD (Industry Representative)

**Antimicrobial Drugs Advisory Committee Members Not Present (Voting):** CAPT Timothy H. Burgess, MD, MPH, FACP; Joanna M. Schaeffer, MD, PhD; Sankar Swaminathan, MD

**Temporary Members (Voting):** Frank R. DeLeo, PhD; Arthur G. Lyons, PhD, MD, COL; Susanne May, PhD; Thomas A. Moore, MD; David “Davey” Smith, MD, MAS (via phone); Jill M. Thomas (Patient Representative)

**FDA Participants (Non-voting):** John Farley, MD, MPH; Sumathi Nambiar, MD, MPH; Edward Weinstein, MD, PhD; Shabnam Naseer, DO, MS; Daniel Rubin, PhD; Kalavati Suvarna, PhD

**Designated Federal Officer (Non-voting):** Lauren Tesh Hotaki, PharmD, BCPS, BCIDP

**Open Public Hearing Speakers:** Stephanie Fox-Rawlings, PhD (National Center for Health Research); Dana Byrne, MD, MSCE; Marcus Zervos, MD; Jose Alexander, MD, D(ABMM), SM, MB(ASCP) (AdventHealth Orlando); Kate Dzintars, PharmD, BCPS-AQID

*The agenda was as follows:*

Call to Order and Introduction of Committee	<b>Lindsey R. Baden, MD</b> Chairperson, AMDAC
Conflict of Interest Statement	<b>Lauren Tesh Hotaki, PharmD, BCPS, BCIDP</b> Designated Federal Officer, AMDAC
FDA Introductory Comments	<b>Edward Weinstein, MD, PhD</b> Clinical Team Leader Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
<b>APPLICANT PRESENTATIONS</b>	<b>Shionogi Inc.</b>
Introduction to the Cefiderocol Program	<b>Tsutaе “Den” Nagata, MD, PhD, FFPM</b> Chief Medical Officer Shionogi & Co., Ltd.
Medical Need	<b>George H. Karam, MD, MACP</b> Paula Garvey Manship Chair of Medicine Louisiana State University School of Medicine
Microbiology and Clinical Pharmacology of Cefiderocol	<b>Roger Echols, MD, FIDSA</b> Principal Member Infectious Disease Drug Development Consulting, LLC Medical Consultant to Shionogi & Co., Ltd.
cUTI Efficacy and Safety, Other Cefiderocol Studies	<b>Simon Portsmouth, MD, FRCP</b> Executive Medical Director Clinical Development Shionogi Inc.

**APPLICANT PRESENTATIONS (CONT.)**

Benefit/Risk of Cefiderocol for cUTI

**David Paterson, MBBS, PhD, FRACP, FRCPA**

Infectious Disease Physician  
Royal Brisbane and Women's Hospital  
Professor of Medicine  
University of Queensland, Australia

Clarifying Questions

**BREAK**

**FDA PRESENTATIONS**

Clinical Microbiology Considerations

**Kalavati Suvarna, PhD**

Clinical Microbiology Reviewer  
DAIP, OAP, OND, CDER, FDA

Efficacy Assessment of Cefiderocol for  
the Treatment of cUTI

**Daniel Rubin, PhD**

Biometrics Reviewer  
Division of Biometrics IV, Office of  
Biostatistics  
Office of Translational Sciences, CDER, FDA

Clinical Assessment and Safety of  
Cefiderocol for the Treatment of cUTI

**Shabnam Naseer, DO, MS**

Clinical Reviewer  
DAIP, OAP, OND, CDER, FDA

Statistical Assessment of the Study in  
Carbapenem-Resistant Organisms  
(CREDIBLE-CR)

**Daniel Rubin, PhD**

Clinical Assessment of the CREDIBLE-  
CR Study

**Shabnam Naseer, DO, MS**

Summary Comments

**Edward Weinstein, MD, PhD**

Clarifying Questions

**LUNCH**

**OPEN PUBLIC HEARING**

Questions to the Committee/Committee  
Discussion

**BREAK**

Questions to the Committee/Committee  
Discussion (cont.)

**ADJOURNMENT**

*Questions to the Committee:*

1. **DISCUSSION:** Please discuss your evaluation of the mortality imbalance observed in the CREDIBLE-CR study with respect to the overall risk benefit assessment for cefiderocol and provide recommendations for labeling and/or the need for additional studies.

**Committee Discussion:** *The committee voiced concern regarding the increased mortality in the cefiderocol treatment group of the CREDIBLE-CR study and was unsure whether the mortality results represented a genuine safety signal or noise, due to the descriptive, post-hoc, interpretation of the study results in a small sample of patients with severe infections. Some committee members stated that new study(ies) need to be conducted with a randomized, double-blind design that is powered for assessing mortality, specifically looking at more severe infections like bloodstream infections and pneumonia, including those due to multi-drug resistant organisms such as Acinetobacter baumannii. It was recommended that the mechanisms associated with the increase in cefiderocol minimum inhibitory concentrations be identified. One committee member also noted that studies should include combination therapy in the cefiderocol group to mirror clinical practice in patients with limited or no treatment options in severe infections. Another member noted that studies should focus on the presence of infection with endpoints of clinical cure or microbiologic eradication instead of clinical improvement. The committee noted that, if approved for complicated urinary tract infections (cUTI), cefiderocol labeling should explicitly state the safety concerns for cefiderocol if used off-label for the treatment of other infections. In addition, it was recommended that the labeling should also include the risk of acquired resistance while on cefiderocol. A few panel members recommended including a boxed warning for indications other than cUTI and referring providers to the CREDIBLE-CR study results for further information. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Has the Applicant provided substantial evidence of the efficacy and sufficient evidence of the safety of cefiderocol for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis in patients with limited or no alternative treatment options?
  - a. If yes, please provide any recommendations concerning labeling.
  - b. If no, what additional studies/analyses are needed?

**Vote Result:**                      Yes: 14                      No: 2                      Abstain: 0

**Committee Discussion:** *The majority of the committee voted “Yes”, that the Applicant provided substantial evidence for the treatment of cUTI including pyelonephritis in patients with limited or no alternative treatment options. The committee noted the label should indicate warnings for mortality, with some members recommending a boxed warning to communicate the safety concern for off-label use of cefiderocol for treatment of infections other than cUTI. Additional comments advised monitoring of hematologic and liver laboratory values, as well as assessing the risk of arrhythmia and seizure potential with therapy. It was noted that the label should include details on the recommended infusion rate for the indication. The committee members who voted “No” explained that the Applicant had not provided sufficient evidence for the proposed indication. These members had concern for the mortality difference in the CREDIBLE-CR study. There was also concern for how cefiderocol could be used off-label once approved. In addition, there was concern that since the cUTI study was a single noninferiority trial, substantial evidence of efficacy was not provided. Therefore, they recommended that another study be conducted, possibly with a superiority design. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:02 p.m.