Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

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

Topic: The committee discussed new drug applications 209006 and 209007, solithromycin capsules and solithromycin for injection, sponsored by Cempra Pharmaceuticals, Inc., respectively for the proposed indication of treatment of community-acquired bacterial pneumonia (CABP). These summary minutes for the November 4, 2016 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on February 14, 2017.

I certify that I attended the November 4, 2016 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/

Lauren D. Tesh, PharmD, BCPS
Designated Federal Officer, AMDAC

/S/

Lindsey R. Baden, MD
Chairperson, AMDAC

Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

The following is final report of the Antimicrobial Drugs Advisory held on November 4, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anti-Infective Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm496389.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Antimicrobial Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 4, 2016, at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Cempra Pharmaceuticals, 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 D. Tesh, PharmD, BCPS (Designated Federal Officer). There were approximately 200 people in attendance for the meeting. There were six (6) Open Public Hearing speakers.

Issue: The committee discussed new drug applications 209006 and 209007, solithromycin capsules and solithromycin for injection, sponsored by Cempra Pharmaceuticals, Inc., respectively for the proposed indication of treatment of community-acquired bacterial pneumonia (CABP).

Attendance:

Antimicrobial Drugs Advisory Committee Members Present (Voting): Ellen M. Andrews, PhD (Consumer Representative); Lindsey R. Baden, MD (Chairperson); Demetre C. Daskalakis, MD, MPH; Michael D. Green, MD, MPH; Barbara M. Gripshover, MD; Jonathan, Honegger, MD; Vincent Lo Re, MD, MSCE; Marc H. Scheetz, PharmD, MSc; Peter Weina, MD, PhD, FACP, FIDSA

Antimicrobial Drugs Advisory Committee Members Not Present (Voting): Amanda H. Corbett, PharmD, BCPS, FCCP; Dean A. Follmann, PhD; Luis Z. Ostrosky, MD; Joanna M. Schaenman, MD, PhD

Antimicrobial Drugs Advisory Committee Members Not Present (Non-Voting): Nicholas A. Kartsonis, MD (Industry Representative)

Temporary Members (Voting): Thomas D. Boyer, MD; William M. Lee, MD, FACP, FAASLD; J. Stephen Mikita, JD (Patient Representative); Michael Proschan, PhD

Acting Industry Representative to the Committee (Non- Voting): Douglas S. Levine, MD

FDA Participants (Non-Voting): Edward M. Cox, MD, MPH; Sumathi Nambiar, MD, MPH; Yuliya I. Yasinskaya, MD; Ramya Gopinath, MD; Mark I. Avigan, MD, CM; Daniel B. Rubin, PhD

Open Public Hearing Speakers: Lance B. Price, PhD (Antibiotic Resistance Action Center); Paul M. Tulkens, MD, PhD (Louvain Drug Research Institute); Emily Heil, PharmD, BCPS-AQ ID, AAHIVP (Society of Infectious Diseases Pharmacists); Brain W. Carlin, MD, FCCP, FAARC, MAACVPR; Aymarah M. Robles, MD; Celeste Reese, MD

The agenda was as follows:

Call to Order and Introduction of Committee	**Lindsey R. Baden, MD** Chairperson, AMDAC
Conflict of Interest Statement	**Lauren D. Tesh, PharmD, BCPS** Designated Federal Officer, AMDAC
FDA Introductory Remarks	**Sumathi Nambiar, MD, MPH** Division Director Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Cempra Pharmaceuticals, Inc.**
Introduction	**Prabhavanthi Fernandes, PhD** President and CEO Cempra, Inc.
Unmet Need in CABP	**Julio Ramirez, MD** Professor of Medicine Chief, Division of Infectious Diseases University of Louisville
Microbiology and PK/PD	**Prabhavathi Fernandes, PhD**
Solithromycin Phase 3 Study Design	**David Oldach, MD** Chief Medical Officer Cempra, Inc.
Efficacy	**Anita Das, PhD** Biostatistics Cempra Consultant
Safety	**David Oldach, MD** **Paul Watkins, MD**

	Director, University of North Carolina School of Pharmacy Institute for Drug Safety Sciences

APPLICANT PRESENTATIONS (CONT.)

Primary Care Perspective	**Steve Vacalis, DO** Family Medicine Physician CaroMont Family Medicine

Clarifying Questions to the Presenters

BREAK

FDA PRESENTATIONS

Presentation of Clinical Efficacy	**Daniel B. Rubin, PhD** Statistical Reviewer Division of Biometrics IV Office of Biostatistics Office of Translational Sciences (OTS), CDER, FDA
Presentation of Clinical Safety	**Ramya Gopinath, MD** Medical Officer DAIP, OAP, OND, CDER, FDA
Presentation of Clinical Pharmacology	**Yongheng Zhang, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology IV Office of Clinical Pharmacology, OTS, CDER, FDA

Clarifying Questions to the Presenters

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE**: Has the Applicant provided substantial evidence of the efficacy of solithromycin for the treatment of community acquired bacterial pneumonia (CABP)?

   a. If yes, please provide recommendations for labeling.

   b. If no, please discuss additional studies/analyses that are needed.

Vote Result: **Yes: 13** **No: 0** **Abstain: 0**

Committee Discussion: *The committee voted unanimously that there was substantial evidence provided for the efficacy of solithromycin for the treatment of community acquired bacterial pneumonia (CABP). Committee members agreed that in both Phase 3 trials noninferiority of solithromycin to moxifloxacin was demonstrated. While the committee noted that a loading dose was appropriate for the oral therapy only regimen, a loading dose was not felt to be appropriate or necessary when changing from IV to oral therapy.*

Concerns regarding adequate controls to ensure the appropriate use of solithromycin were discussed. It was recommended that future studies should include: patient reported outcomes along with investigator-reported outcomes, more frequent monitoring of liver function tests, evaluation of specific interactions of solithromycin with other drugs metabolized by CYP 3A4, and patients with multi-drug resistant pathogens, renal impairment, and significant pre-existing liver dysfunction. In order to prevent inappropriate use of solithromycin, the committee recommended that product labeling should warn providers not to exceed the duration of therapy intended for CABP. Please see the transcript for details of the committee discussion.

2. **VOTE**: Has the risk of hepatotoxicity with solithromycin been adequately characterized?

   a. If yes, please provide any recommendations for labeling.

   b. If no, please discuss additional studies that are needed to further characterize the risk.

Vote Result: **Yes: 1** **No: 12** **Abstain: 0**

Committee Discussion: *The majority of the committee voted "No," indicating that the risk of hepatotoxicity has not been adequately characterized with solithromycin, primarily due to the small size of the safety database. The committee noted that the significant incidence of hepatic enzyme elevations in the Phase 3 trials, the range of hepatotoxicity patterns, and the structural similarity of solithromycin to another FDA-approved ketolide, telithromycin, suggested the potential for similar postmarketing safety concerns. They also noted that the timing of hepatic enzyme elevation and the safety in various demographic subgroups and specific populations at*

risk (e.g. patients with renal failure) have not been adequately characterized. Members recommended that in future studies, the Sponsor should evaluate a greater number and demographically diverse patients (including minorities) to appropriately characterize the risk. The committee recommended that the FDA carefully consider the type of clinical studies required for approval or being condition(s) for approval. Some committee members suggested either conducting a Phase 3 study pre-approval with increased sample size, or a Phase 4 study with more frequent measurement of hepatic parameters, especially in patients re-exposed to solithromycin. There was some discussion among the committee members as to whether the observed hepatotoxicity was idiosyncratic or exposure-related. The one member who voted "Yes" believed that solithromycin would improve CABP survival rates, and that the risk of hepatotoxicity could be addressed with proper labeling, antimicrobial stewardship and surveillance. Please see the transcript for details of the committee discussion.

3. **VOTE**: Do the efficacy results of solithromycin for the treatment of CABP, outweigh the risks including hepatotoxicity?

    a. If yes, please provide any recommendations for labeling.

    b. If no, please discuss additional studies/analyses that are needed.

    Vote Result: Yes: 7 No: 6 Abstain: 0

Committee Discussion: *A slight majority of the committee voted "Yes," indicating that the efficacy of solithromycin for the treatment of CABP outweighs the risks, including hepatotoxicity. Some committee members expressed some ambivalence regarding their decision, but noted that with adequate labeling and education of patients and providers, safety concerns could potentially be addressed. A few committee members noted that solithromycin should not be used as first-line therapy for CABP, but only when other treatment alternatives were not appropriate. Some members who voted "Yes" stated that current oral antibacterial therapy options are limited and solithromycin may fulfil an unmet need for the treatment of patients with CABP due to macrolide-resistant organisms.*

Committee members who voted "No," suggested that a strong drug-induced liver injury (DILI) signal was evident in the current solithromycin trials. Some members recommended the development of a risk evaluation and mitigation strategy (REMS), safety monitoring tools, or post-marketing surveillance contingencies. They also felt that additional larger studies were needed to properly evaluate the risk for DILI. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:26 pm.