Location: The Marriott Inn and Conference Center, University of Maryland University College,
The Ballroom, 3501 University Blvd. East, Hyattsville, Maryland 20783.

Topic: The committee discussed new drug application (NDA) 206494 for ceftazidime-
avibactam for injection, submitted by Cerexa Inc., for the proposed indications of:
Complicated Intra-abdominal Infections, Complicated Urinary Tract Infections,
including Acute Pyelonephritis and Limited Use Indication: Aerobic Gram-negative
Infections with Limited Treatment Options.

These summary minutes for the December 5, 2014 meeting of the Anti-Infective Drugs Advisory
Committee of the Food and Drug Administration were approved on January 27, 2015.

I certify that I attended the December 5, 2014 meeting of the Anti-Infective Drugs Advisory
Committee of the Food and Drug Administration and that these minutes accurately reflect what
transpired.

/s/ Moon Hee V. Choi, PharmD
Acting Designated Federal Officer, AIDAC

/s/ CAPT Monica E. Parise, MD
Chairperson, AIDAC
Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting
December 5, 2014

The following is the final report of the Anti-Infective Drugs Advisory Committee meeting held on December 5, 2014. 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/ucm385739.htm

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

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on December 5, 2014, at the College Park Marriott Hotel and Conference Center, University of Maryland University College (UMUC), 3501 University Blvd, East, Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by CAPT. Monica Parise, MD (Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Acting Designated Federal Officer). There were approximately 150 people in attendance. There were six (6) Open Public Hearing speakers.


Attendance:
Anti-Infective Drugs Advisory Committee Member Present (Voting): Ellen M. Andrews, PhD (Consumer Representative); Lindsey R. Baden, MD; Alan J. Magill, MD; Luis Z. Ostrosky, MD; CAPT Monica E. Parise, MD (Chairperson)

Anti-Infective Drugs Advisory Committee Members Not Present (Voting): Antonio Carlos Arrieta, MD; Marc H. Scheetz, PharmD, MSc; Yu Shyr, PhD

Anti-Infective Drugs Advisory Committee Member Present (Non-Voting): Patrick Robinson, MD (Industry Representative)

Temporary Members (Voting): Diane M. Cappelletty, PharmD; John P. Dekker, MD, PhD; Dean Follmann, PhD; Debra McCall, BS, MBA (Patient Representative); Thomas A. Moore, MD, FACP, FIDSA; L. Barth Reller, MD; Paige E. Waterman, MD
FDA Participants (Non-Voting): Edward Cox, MD, MPH; Sumati Nambiar, MD, MPH; Benjamin Lorenz, MD; Seong Jang, PhD; Margaret Gamalo-Siebers, PhD

Open Public Hearing Speakers: Anna Mazzucco, PhD (National Center for Health Research); Amanda Jezek (Infectious Diseases Society of America); Margaret Swetz; Jason Gallagher, PharmD, PCCP, BCPS; Jerome J. Schentag, PharmD; Richard Bruno, MD (National Physicians Alliance)

The meeting agenda proceeded as follows:

| Call to Order and Introduction of Committee | CAPT Monica Parise, MD  
|                                           | Chairperson, AIDAC |
| Conflict of Interest Statement            | Moon Hee V. Choi, PharmD  
|                                           | Acting Designated Federal Officer, AIDAC |
| FDA Introductory Remarks                  | Edward Cox, MD, MPH  
|                                           | Director  
|                                           | Office of Antimicrobial Products (OAP)  
|                                           | Office of New Drugs (OND), CDER, FDA |
|                                           | Sumati Nambiar, MD, MPH  
|                                           | Director  
|                                           | Division of Anti-Infective Products (DAIP)  
|                                           | OAP, OND, CDER, FDA |

**APPLICANT PRESENTATIONS**  
Cerexa, Inc.

**Introduction**  
Kristina Haeckl, RAC  
Executive Director, Regulatory Affairs  
Cerexa, Inc.

**Unmet Need**  
Keith Kaye, MD, MPH  
Corporate Medical Director, Infection Prevention, Epidemiology, and Antimicrobial Stewardship  
Detroit Medical Center & Wayne State University

**Microbiology, Clinical Pharmacology & PK/PD**  
Ian A. Critchley, PhD  
Vice President, Microbiology  
Cerexa, Inc.

**Clinical Efficacy**  
David Friedland, MD  
Vice President, Clinical Development  
Cerexa, Inc.
APPLICANT PRESENTATIONS (cont.)

Safety

Angela Talley, MD
Associate Director, Clinical Development
Cerexa, Inc.

Conclusions

David Friedland, MD

Clarifying Questions

BREAK

FDA PRESENTATIONS

The Microbiology of Ceftazidime-Avibactam (CAZ-AVI)

Avery Goodwin, MS, PhD
Microbiology Reviewer
DAIP, OAP, OND, CDER, FDA

NDA 206494: Ceftazidime-Avibactam (CAZ-AVI) Clinical Pharmacology

Seong H. Jang, PhD
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology IV
Office of Clinical Pharmacology
Office of Translational Sciences (OTS)
CDER, FDA

Clinical Efficacy of Ceftazidime-Avibactam for the Treatment of cUTI and cIAI

Margaret Gamalo-Siebers, PhD
Mathematical Statistician
Division of Biometrics IV
Office of Biostatistics (OB), OTS, CDER, FDA

Ceftazidime-Avibactam: Overview of Safety

Benjamin Lorenz, MD
Medical Officer
DAIP, OAP, OND, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT
Question to the Committee:

1. VOTE: Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated intra-abdominal infections, when limited or no alternative treatments are available?

   Vote: Yes: 11  No: 1  Abstain: 0

   a. If yes, please provide any recommendations concerning labeling.
   b. If no, what additional studies/analyses are needed?

Committee Discussion: The majority of the committee agreed that the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated intra-abdominal infections, when limited or no alternative treatments are available with the data presented. Some committee members noted that ceftazidime-avibactam would serve as a treatment option when limited or no alternate options are available, but would like to see the final vetting of Phase 3 results and continued long-term assessment, such as an additional mandatory Phase 4 study in patients with resistant pathogens, to fully determine the safety and efficacy of ceftazidime-avibactam. Most committee members were concerned about the imbalance in mortality and clinical response in subjects with baseline moderate renal impairment. One member stated that this was an important “red flag” and patients requiring dosing adjustments due to renal impairment should be excluded from receiving CAZ-AVI until more data are available for appropriate dosing recommendations. One committee member recommended therapeutic dose monitoring to help determine the correct dose. Another committee member recommended that the Agency should reconsider the indication and label as Phase 3 data emerge. One committee member suggested a Risk Evaluation and Mitigation Strategy to avoid wide use, and restrict the use of ceftazidime-avibactam in those patients with resistant pathogens who would most benefit from the treatment. One committee member who voted “No” and did not agree that the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated intra-abdominal infections when limited or no alternative treatments are available, noted that there is no regulatory mechanism to enforce the limited use labeling and concern regarding safety and lack of efficacy in patients with baseline renal impairment from the Phase 3 complicated intra-abdominal trial. Please see the transcript for details of the committee discussion.
2. **VOTE:** Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated urinary tract infections, including pyelonephritis, when limited or no alternative treatments are available?

**Vote:**  
Yes: 9  
No: 3  
Abstain: 0

a. If yes, please provide any recommendations concerning labeling.  
b. If no, what additional studies/analyses are needed?

**Committee Discussion:** The majority of the committee agreed that the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated urinary tract infections, including pyelonephritis, when limited or no alternative treatments are available. One committee member who voted “No” noted that the available Phase 2 safety and efficacy data for the proposed indication of complicated urinary tract infections, including pyelonephritis, is not sufficient and that Phase 3 data would be necessary to determine the safety and efficacy of ceftazidime-avibactam. Two committee members, who also voted “No”, noted that they were concerned about the high (40%) failure rate, for which it was unclear how much could be attributed to pharmacokinetic/pharmacodynamic considerations. Please see the transcript for details of the committee discussion.

3. **VOTE:** Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) when limited or no alternative treatments are available?

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

a. If yes, please provide any recommendations concerning labeling.  
b. If no, what additional studies/analyses are needed?

**Committee Discussion:** The committee unanimously voted “No” and agreed that the applicant did not demonstrate substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) when limited or no alternative treatments are available. The majority of committee members noted that Phase 3 efficacy data would be necessary to determine the safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) when limited or no alternative treatments are available. One committee member noted that the proposed indication is the most difficult to diagnose and treat and human clinical data are needed. Another member was concerned
that prematurely approving for this indication could limit the collection of additional crucial data. Please see the transcript for details of the committee discussion.

4. **VOTE:** Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (hospital-acquired bacterial pneumonia/ventilator-associated pneumonia and bacteremia) when no adequate treatment options are available?

**Vote:** Yes: 1  No: 11  Abstain: 0

   a. If yes, please provide any recommendations concerning labeling.
   b. If no, what additional studies/analyses are needed?

**Committee Discussion:** The majority of the committee voted “No” and agreed that the applicant did not demonstrate substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (hospital-acquired bacterial pneumonia/ventilator-associated pneumonia and bacteremia) when no adequate treatment options are available. One member noted that, unlike urinary tract or intra-abdominal infections, infections of the lung are different and not generally amenable to surgical procedures. The majority of the committee members agreed that Phase 3 clinical data in humans would therefore be needed to determine the safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (hospital-acquired bacterial pneumonia/ventilator-associated pneumonia and bacteremia). One committee member noted that even without supportive human data, however, an option with limited data is better than no option at all. For one committee member, the “Yes” vote was motivated by the need to send a message of flexibility to pharmaceutical companies. Most of the committee members noted that absence of this indication in the label would not preclude “off-label” use. Some members noted that it would be helpful for prescribers to have non-clinical data (whether in the label or in published data), particularly for lung penetration. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 2:55 p.m.