

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

**Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting
November 29, 2012**

Location: DoubleTree by Hilton Hotel Washington, DC-Silver Spring,
8727 Colesville Road, Silver Spring, Maryland 20910

Issue: The committee discussed new drug application (NDA) 22407, VIBATIV (telavancin hydrochloride) sterile powder for injection, submitted by Theravance, Inc., for the requested indication of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-susceptible and –resistant isolates) or *Streptococcus pneumoniae* (penicillin susceptible isolates).

These summary minutes for the November 29, 2012 Anti-Infective Drugs Advisory Committee Meeting were approved on January 2, 2013.

I certify that I attended the November 29, 2012 Anti-Infective Drugs Advisory Committee Meeting and that these minutes accurately reflect what transpired.

/signed/

Diane P. Goyette, RPh, JD
Designated Federal Officer, AIDAC

/signed/

Thomas Moore, MD, FACP, FIDSA
Chair, AIDAC

Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting November 29, 2012

The following is the final report of the Anti-Infective Drugs Advisory Committee (AIDAC) meeting held on November 29, 2012. 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/ucm293600.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 November 29, 2012 at the DoubleTree by Hilton Hotel Washington DC-Silver Spring, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Theravance, Inc. The meeting was called to order by Thomas A. Moore, MD, FACP, FIDSA (Chairperson); the conflict of interest statement was read into the record by Diane Goyette, RPh, JD (Designated Federal Officer). There were approximately 160 people in attendance. There was one Open Public Hearing speaker.

Issue: The committee discussed new drug application (NDA) 22407, VIBATV (telavancin hydrochloride) sterile powder for injection, and the requested indication of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-susceptible and –resistant isolates) or *Streptococcus pneumoniae* (penicillin susceptible isolates).

Attendance:

AIDAC Members Present (Voting):

Diane Cappelletty, PharmD; Archana Chatterjee, MD, PhD; Sheldon Kaplan, MD; Thomas Moore, MD, FACP, FIDSA (*Chairperson*); CAPT Monica Parise, MD; Yu Shyr, PhD; Kurt Stevenson, MD, MPH

AIDAC Members Not Present (Voting):

Paul Auwaerter, MD; Christopher Carpenter, MD; Michael Neely, MD; Melvin Weinstein, MD; Kathleen Young (*Consumer Representative*)

AIDAC Member Present (Non-Voting):

Patrick A. Robinson, MD (*Industry Representative*)

Temporary Members (Voting):

Wallace Kemper Alston, MD, MPH; William Calhoun, MD; Dean Follman, PhD; Matthew Goetz, MD; Peter Katona, MD, FACP, FIDSA; J. Stephen Mikita, JD (*Patient Representative*); Rodney Mullins (*Acting Consumer Representative*); Judith Voynow, MD

FDA Participants (Non-Voting):

John Jenkins, MD; Edward Cox, MD, MPH; Lisa LaVange, PhD; Katherine Laessig, MD; Benjamin Lorenz, MD; Scott Komo, Dr. PH

Designated Federal Officer (Non-Voting): Diane Goyette, RPh, JD

Open Public Hearing Speaker: Jennifer N. Yttri, PhD (National Research Center for Women and Families)

The agenda proceeded as follows:

Call to Order and Introduction of Committee

Thomas A. Moore, MD, FACP, FIDSA
Chairperson, AIDAC

Conflict of Interest Statement

Diane Goyette, RPh, JD
Designated Federal Officer, AIDAC

Welcome and Introductory Remarks

Katherine Laessig, MD
Deputy Director
Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND), CDER, FDA

SPONSOR PRESENTATIONS

Theravance, Incorporated

Introduction

Rebecca Coleman, PharmD
VP, Regulatory Affairs & Quality
Theravance, Inc.

Medical Need

Marin Kollef, MD
Professor of Medicine, Pulmonary and
Critical Care
Washington University
St. Louis, MO

Efficacy

Steven Barriere, PharmD
VP, Clinical & Medical Affairs
Theravance, Inc.

Safety

Mathai Mammen, MD, PhD
SVP, Research and Early Clinical Development
Theravance, Inc.

SPONSOR PRESENTATIONS (CONT.)

Benefit Risk

Louis Saravolatz, MD
Professor of Medicine, Infectious Diseases
St. John Hospital
Detroit, MI

Conclusion

Steve Barriere, PharmD

Clarifying Questions from the
Committee

BREAK

FDA PRESENTATIONS

Presentation of Regulatory History and
Safety: Telavancin for Nosocomial
Pneumonia

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

Presentation of Efficacy: Telavancin for
Nosocomial Pneumonia

Scott Komo, DrPH
Statistical Reviewer
Division of Biometrics IV
Office of Biostatistics
Office of Translational Sciences, CDER, FDA

Clarifying Questions from the
Committee

LUNCH

Open Public Hearing Session

Charge to the Committee

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

Considering the totality of data presented, including the analyses of clinical cure and 28-day all-cause mortality:

1. *Due to the discussions that transpired at the meeting, the wording of question #1 was modified to the following:*

Do the results provide substantial evidence of the safety and effectiveness of telavancin for the requested indication of treatment of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible isolates of the following microorganisms: *Staphylococcus aureus* (both MSSA and MRSA) and *Streptococcus pneumoniae*? **(Vote)**

YES: 6 NO: 9 ABSTAIN: 0

Committee Discussion: *Considering the totality of data presented, including the analyses of clinical cure and 28-day all-cause mortality, the majority of the committee voted “No” on whether the results provide substantial evidence of the safety and effectiveness of telavancin for the requested indication of treatment of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible isolates of the following microorganisms: *Staphylococcus aureus* (both MSSA and MRSA) and *Streptococcus pneumoniae*. The committee members who voted “Yes” noted that the data showed the drug to be as good as vancomycin for the requested indication and approval would provide patients and clinicians with an additional treatment option. One member noted increased evidence of renal injury related to the use of vancomycin in these patients, as dosage levels increased with decreasing effectiveness of the drug. However, a majority of committee members were concerned that telavancin had shown non-inferiority to vancomycin in only one of two studies and that the drug seemed to pose mortality risks in renally impaired patients. Several committee members noted that approval was not warranted for a *Streptococcus pneumoniae* indication, where effective treatments already exist. Please see the transcript for details of the committee discussion.*

- a. If yes, please provide any recommendations concerning labeling.

Committee Discussion: *The committee suggested that information related to safe use in patients with renal impairment be included in the product labeling. One member noted that labeling should reflect the mortality data according to baseline renal function and creatinine clearance levels found in the sponsor’s data. The committee also noted the disagreement between FDA and the sponsor regarding the degree of renal impairment where adverse effects of the drug became a risk and advised additional discussion between FDA and the sponsor on this matter. Please see the transcript for details of the committee discussion.*

- b. If no, what additional studies/analyses are needed?

Committee Discussion: *Some of the committee members who voted “No” stated that additional data showing non-inferiority to vancomycin are needed, and more evidence to establish threshold creatinine clearance levels to guide the use of telavancin in patients with renal impairment needs to be development. Please see the transcript for details of the committee discussion.*

2. Do the results provide substantial evidence of the safety and effectiveness of telavancin for the treatment of nosocomial pneumonia when other alternatives are not suitable? **(Vote)**

YES: 13 NO: 2 ABSTAIN: 0

Committee Discussion: *The majority of the committee agreed that the results provide substantial evidence of the safety and effectiveness of telavancin for the treatment of nosocomial pneumonia when other alternatives are not suitable. In particular, most of the committee noted that approval would be important for the treatment of nosocomial pneumonia due to MRSA and certain cases of MSSA (eg., in the case of a beta lactam allergy). A few committee members did not agree that there is substantial evidence of the safety and effectiveness of telavancin (even when other alternatives are not suitable) due to remaining concerns about mortality risks in patients with renal impairment. Please see the transcript for details of the committee discussion.*

- a. If yes, please provide recommendations concerning labeling, particularly labeling concerning the use in patients with renal dysfunction.

Committee Discussion: *The majority of committee members who voted “Yes” said use of the drug should be limited to situations where alternative treatments are not available, and these limitations should be included in the labeling. Most committee members stated that telavancin should be reserved for use in nosocomial pneumonia caused by MRSA. A few committee members noted that use of the drug product could be appropriate in some other circumstances where alternative therapies are not well tolerated. The committee strongly advised there be cautionary labeling related to use of telavancin in renal dysfunction and suggested further consideration of appropriate renal function threshold levels to be included in the labeling. Please see the transcript for details of the committee discussion.*

- b. If no, what additional studies/analyses are needed?

Committee Discussion: *The committee agreed that additional analyses and discussions related to the appropriate renal function thresholds need to be conducted to properly label telavancin for use in renal impairment. Committee members were divided about whether a creatinine clearance below 30 mL/min, as favored by the sponsor’s analysis or a creatinine clearance at or below 50 mL/min, as used in FDA analyses was most appropriate or predictive of drug treatment risk. Please see the transcript for details of the committee discussion.*

3. The nephrotoxicity of telavancin has been established based on experience with treatment of complicated skin and skin structure infections. For the treatment of nosocomial pneumonia, are there any additional comments or further recommendations, particularly concerning the use in patients with baseline renal dysfunction? If so, what are these recommendations?

(Discussion)

***Committee Discussion:** The committee recommended that warnings regarding telavancin for nosocomial pneumonia should be at least comparable to warnings included in the labeling of the drug for complicated skin and skin structure infections. They noted that the patients receiving telavancin for a nosocomial pneumonia indication would generally be sicker and more medically vulnerable, thus labeling should advise extreme caution when using the drug in patients with creatinine clearance levels between 30 mL/min to 50 mL/min. Several committee members noted that the renal effects would likely be a manageable toxicity, and all committee members advised more analysis regarding nephrotoxicity and particular warnings related to the degree of renal impairment. One member expressed concern with the sponsor's data showing congestive heart failure and multiple organ failure that was not discussed at the meeting, and noted that these should be looked at more closely to see if there is a safety issue. Another committee member pointed out the need for pediatric studies of agents for this indication. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:00 p.m.