CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 25, 2009
To:	Wiley Chambers, M.D., Director (Acting) Division of Anti-Infective and Ophthalmology Products (DAIOP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	Kate Heinrich., MA, Health Education Reviewer, Division of Risk Management (DRISK) Brian Gordon, MA, Social Science Reviewer, (DRISK)
Subject:	Addendum to Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Vibativ (telavancin hydrochloride)
Application Type/Number:	NDA 22-110
Applicant/sponsor:	Theravance Inc.
OSE RCM #:	2009-542

1 INTRODUCTION

This memo is in response to the recent submission of the revised Risk Evaluation and Mitigation Strategy (REMS) for Vibativ (telavancin) as well as the Sponsor's responses to the Agency's comments sent to the company on August 13, 2009.

The proposed REMS for telavancin includes a Medication Guide, a communication plan, and a timetable for submission of assessments. The Division of Risk Management completed a review of the proposed REMS for telavancin on July 14, 2009. The review included a number of comments regarding the proposed REMS and REMS-related materials.

2 MATERIAL REVIEWED

- Response to Comments on REMS Received 13 August 2009, submitted to NDA 22-110 by Theravance on August 18, 2009. This submission includes the response to those comments and the following revised REMS documents:
    - Vibativ Proposed REMS Document – redline
    - Vibativ Proposed REMS Document – clean
    - REMS Supporting Document – redline
    - REMS Supporting Document - clean
    - Vibativ Dear Healthcare Provider Letter – redline
    - Vibativ Dear Healthcare Provider Letter - clean
    - Vibativ Medication Guide – redline
    - Vibativ Medication Guide – clean

3 DISCUSSION/COMMENTS

The Sponsor provided responses to our comments. We accepted all of the sponsor's comments that they provided in a separate document. However we have incorporated some of the details provided by the sponsor to our comments into the REMS document for clarity.

Comments for the Sponsor:

1) A redlined REMS document is provided that incorporates a more detailed description of how you intend to distribute the DHCP letter through both electronic and hardcopy delivery to reach the target audience as well as clarifying language concerning the timetable for submission of assessments. The REMS sponsor has also been removed.
2) As the REMS document has not gone through final FDA clearance, it may be subject to further modifications.

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_____ § 552(b)(5) Deliberative Process

Risk I

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/s/

KATE A HEINRICH
08/25/2009

CLAUDIA B KARWOSKI
08/27/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 10, 2009
To:	Wiley Chambers, M.D., Director (Acting) Division of Anti-Infective and Ophthalmology Products (DAIOP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	Kate Heinrich., MA, Health Education Reviewer, Division of Risk Management (DRISK) Brian Gordon, MA, Social Science Reviewer, (DRISK)
Subject:	Addendum to Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
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1 INTRODUCTION

This memo is in response to the recent submission of the revised Risk Evaluation and Mitigation Strategy (REMS) for Vibativ (telavancin) as well as the Sponsor's responses to the Agency's comments sent to the company on July 16, 2009.

The proposed REMS for telavancin includes a Medication Guide, a communication plan, and a timetable for submission of assessments. The Division of Risk Management completed a review of the proposed REMS for telavancin on July 14, 2009. The review included a number of comments regarding the proposed REMS and REMS-related materials.

2 MATERIAL REVIEWED

- Response to Comments on REMS Received 16 July 2009, submitted to NDA 22-110 by Theravance on July 30, 2009. This submission includes the response to those comments and the following revised REMS documents:
    - Vibativ Proposed REMS Document – redline
    - Vibativ Proposed REMS Document – clean
    - REMS Supporting Document – redline
    - REMS Supporting Document - redline
    - Vibativ Dear Healthcare Provider Letter – redline
    - Vibativ Dear Healthcare Provider Letter - redline
    - Vibativ Medication Guide – redline
    - Vibativ Medication Guide – clean

3 DISCUSSION/COMMENTS

The Sponsor accepted most of the comments REMS document and other REMS materials sent to them on July 16, 2009 and or discussed with them at a teleconference on July 28, 2009. Below we summarize areas where agreement has not fully been reached:

- The Sponsor did not agree that the Dear Healthcare Professional (HCP) letter must be mailed to the complete target audience as specified in our July 16, 2009 comments (item 3, A. ii). They propose instead to distribute the letter either through hardcopy mailings by U.S. mail, email, or other technologies to reach the target audience. They believed that this method of distributing the Dear HCP letter consistent with the Guidance for Industry – Using Electronic Means to Distribute Certain Product Information.
- The Sponsor identified a number of challenges to our comment that their REMS Assessment Plan needs to include an assessment of patients' understanding of the safe use and serious risks associated with Vibativ. These challenges include:
    - Women of childbearing potential represent a subset of patients who will receive VIBATIV, and may result in a small sample

- VIBATIV treatment is of limited duration, which poses a finite opportunity to survey a patient with the expectation of reasonable ability or necessity for recall
- The patient's underlying medical condition may limit their ability to participate in the survey

These limitations will be reflected in the Sponsor's patient assessment proposal. They also state that they believe the emphasis of assessments should focus on the HCPs which will represent a more robust sample.

Comments for DAIOP:

1) The last REMS objective "To inform HCPs and patients about the Pregnancy Registry for patients exposed to VIBATIV during pregnancy" will not be modified. We have spoken with the Richardae Araojo from the MHT and they will recommend removing the language "[redacted] from the pregnancy registry to coincide with the labeling. b(4)

Comments/questions for the Sponsor regarding Item 3, A, ii:

1) We can appreciate your desire to pursue alternative forms of communication to distribute the DHCP letter. However, the reach of electronic distribution as compared to mailing a letter to the target audience is not known. We are concerned that there will be providers that are not reached through the use of electronic distribution, as this is a voluntary action on the part of each individual provider. Provide the distribution lists you will be using to identify and contact targeted providers. Provide an explanation of the following:
   a. how you plan to identify and reach which targeted providers are or are not on any electronic distribution list.
   b. describe what you mean by "other technologies"

2) As the regulations are stated in 21 CFR 200.5, mailing of important safety information about drugs should be distinctive in appearance so that it will be promptly recognized and read. The term 'Important Drug Warning' is in all caps, bold, in red, and enclosed in a red box. It is not clear how you will ensure that this important safety message is distinguished and recognized from other promotional or informational e-mails sent from the company. Describe how you will distinguish this e-mail communication from other promotional communication.

3) Explain how the proposed e-mail will not be rerouted by SPAM filters and therefore not reach the target population at all.

4) In the DHCP letter, include the actual toll free number when discussing how to request additional copies of the Medication Guide so that it reads: "Additional copies of the Medication Guide will also be available via sales and/or clinical

representatives, the product website and by request through Astellas at 1-800-727-7003."

Comments for the Sponsor regarding Item 4, A:

1. It is important to assess the patient's understanding of the potential risk of fetal development toxicity if women are exposed to VIBATIV while pregnant. While we acknowledge the challenges, we suggest you consider ways to increase participation of patients in the assessment.

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/s/

MARY J DEMPSEY
08/11/2009
checked/signed into DAARTS for Kate Heinrich

CLAUDIA B KARWOSKI
08/11/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

MEMORANDUM

Date:	July 14, 2009
To:	Wiley Chambers, M.D., Director (Acting) Division of Anti-Infective and Ophthalmology Products (DAIOP)
Thru	Claudia Karwoski, Pharm.D., Director (Acting) Division of Risk Management (DRISK)
From:	**OSE Vibativ Risk Management Team** **Scientific Lead**: Kate Heinrich., MA, Health Education Reviewer, Division of Risk Management (DRISK) **Team Members:** Suzanne Berkman Robottom, Pharm.D., Senior Drug Risk Management Analyst , Team Leader (DRISK) Mary Dempsey, Risk Management Program Coordinator (DRISK) Brian Gordon, MA, Social Scientist, (DRISK) Darrell Jenkins, MPH, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE), Jeffrey Trunzo, R.Ph., M.B.A., Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications (DDMAC)
Subject:	Review of Proposed Risk Evaluation and Mitigation Strategy (REMS), submitted March 13, 2009
Drug Name(s):	Vibativ (telavancin hydrochloride)
Application Type/Number:	NDA 22-110
Applicant/sponsor:	Theravance Inc.
OSE RCM #:	2009-542

INTRODUCTION

This review follows a request from the Anti-Infective and Ophthalmology Products (DAIOP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Vibativ (telavancin), submitted on March 13, 2009.

Vibativ (telavancin hydrochloride) is a once-daily intravenous antibiotic with a proposed indication for the treatment of patients completed skin and skin structure infections (cSSSI) by susceptible isolates of the following Gram-positive microorganisms:

- Staphylococcus aureus [including methicillin-susceptible and –resistant isolates]
- Streptococcus pyogenes, Streptococcus agalactiae Streptococcus anginosus group (includes S. anginosus, S. intermedius and S. constellatus)
- Enterococcus faecalis (vancomycin-susceptible isolates only)

1 BACKGROUND

On February 20, 2009, DAIOP issued a Complete Response letter to Theravance, Inc., that a REMS was necessary to address new safety information with Vibativ. In particular, the risk of teratogenicity was to be addressed. The letter specified that the REMS consist of a Medication Guide, a Communication Plan, and a timetable for the submission of assessments of the REMS.

Per the CR letter, the Communication Plan must include a DHCP letter that provides information on fetal effects of Vibativ seen in animal studies and appropriate pregnancy prevention measures, including a definition of women of child-bearing potential to help in determining the childbearing status of all women, appropriate pregnancy testing requirements, and detailed information about appropriate contraceptive methods to prevent pregnancy.

Theravance Inc. submitted their REMS for Vibativ (telavancin) on March 13, 2009. The REMS consists of a Communication Plan with a Dear Healthcare Provider Letter and the other elements specified in the CR letter.

DRISK provided interim comments on Theravance's March 13, 2009 submission to DAIOP on May 19, 2009. Theravance submitted a revised REMS, REMS Supporting Document, and DHCP letter in response to interim DRISK comments on June 12, 2009.

2 MATERIAL REVIEWED

- Complete Response letter, dated February 20, 2009 from FDA requiring submission of a REMS to address the risk of teratogenicity.
- Theravance's Proposed REMS and Proposed REMS amendment submitted March 13, 2009 and June 12, 2009, respectively; contents include:
    - Proposed REMS
    - Dear Healthcare Professional letter
    - REMS Supporting Document

3 SPONSOR'S PROPOSED REMS

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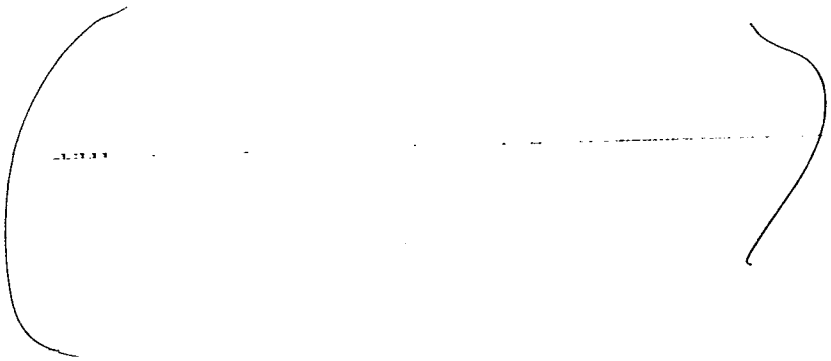
Rems 2



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4 CONCLUSIONS AND RECOMMENDATIONS

The Division of Risk Management in the Office of Surveillance and Epidemiology finds the elements and certain aspects of the proposed REMS for Vibativ generally acceptable. However, we have identified a number of issues that we believe need resolution before the REMS can be approved. Comments for the Sponsor:

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/s/

Mary Dempsey
7/14/2009 11:33:00 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
7/15/2009 08:04:02 AM
DRUG SAFETY OFFICE REVIEWER