

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022407Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTI-INFECTIVE PRODUCTS

NDA/BLA #s: 022407
Products: VIBATIV (telavancin) for injection, 250 mg and 750 mg.
APPLICANT: Theravance, Inc.
FROM: Sumathi Nambiar MD MPH, Deputy Director for Safety
DATE: June 12, 2013

The purpose of the memorandum is to document the rationale for modifying the REMS for VIBATIV (telavancin) for injection.

VIBATIV (telavancin) for injection, 250 mg and 750 mg was approved on September, 11, 2009, under NDA 22110 for the treatment of complicated skin and skin structure infections. The drug was approved with a REMS, and the most recent REMS modification was approved on July 27, 2011, to ensure the benefits of the drug outweighed the risk of fetal developmental toxicity. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

On July 12, 2012, Theravance, Inc. submitted NDA 22407 for a new indication, hospital-acquired bacterial pneumonia/ventilator associated bacterial pneumonia (HABP/VABP). A complete response letter was issued on February 22, 2013 as the sponsor did not have an acceptable manufacturing facility. On March 13, 2013, the sponsor submitted a response to the complete response letter. The complete response submission includes a proposed REMS for VIBATIV (telavancin) for injection that reflects the serious risks associated with the drug, including the HABP/VABP indication. On June 18, 2013, Theravance, Inc. submitted correspondence to NDAs 22110 and 22407, referencing the proposed REMS submission dated March 13, 2013 to NDA 22407, and stating that the proposed REMS also comprised a proposed modification to the approved REMS under NDA 22110.

On May 31, 2013, the Hospira manufacturing facility was found to be acceptable. At this time an approval action is planned for this NDA. As NDA 22407 is a type 9 NDA, once an approval action is taken, this NDA will be administratively closed and all further submissions will be made to NDA 22110.

Data included in NDA 22407 showed a serious risk of increased mortality in VIBATIV-treated patients with HABP/VABP with pre-existing creatinine clearance of ≤ 50 mL/min. This was noted in two Phase 3 trials in HABP/VABP comparing telavancin to vancomycin.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for VIBATIV (telavancin) for injection to ensure that the benefits of the drug outweigh the risks of:

1. Increased mortality seen in VIBATIV (telavancin) -treated patients with HABP/VABP with pre-existing creatinine clearance of ≤ 50 mL/min.
2. Risk of fetal developmental toxicity seen in three animal species at clinically relevant doses.

In reaching this determination, we considered the following:

- A. Hospital Acquired Pneumonia (HAP) is currently the second most common nosocomial infection in the United States, and is associated with high mortality and morbidity.^{1,2} The presence of HAP increases hospital stay by an average of 7 to 9 days per patient. Available data suggest that HAP occurs at a rate of between 5 and 10 cases per 1,000 hospital admissions. HAP accounts for up to 25% of all ICU infections and for more than 50% of the antibiotics prescribed.³ Ventilator-associated pneumonia (VAP) occurs in 9–27% of all intubated patients.^{4,5} The crude mortality rate for HAP may be as high as 30 to 70%.
- B. Hospital acquired bacterial pneumonia/ventilator-associated bacterial pneumonia is a serious and potentially fatal illness and is also associated with significant morbidity.
- C. VIBATIV (telavancin) is active against methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with HABP/VABP. Only a few therapeutic options are available for the treatment of HABP/VABP due to MRSA.
- D. Given the safety concerns with increased mortality in HABP/VABP patients with pre-existing creatinine clearance ≤ 50 ml/min and the risk of fetal developmental toxicity, the product will only be indicated for use in patients when other therapeutic options cannot be provided. E
- E. VIBATIV (telavancin) can cause adverse reactions including nephrotoxicity, taste disturbance, nausea, vomiting, and foamy urine. Decreased efficacy among patients treated for skin and skin structure infections with moderate/severe pre-existing renal impairment can also occur. VIBATIV (telavancin) can cause prolongation of the QT interval and should be

¹ Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med* Vol 171. 388–416, 2005

² Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R, Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and Prevention. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004;53(RR-3):1–36.

³ Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical ICUs in the United States: National Nosocomial Infections Surveillance System. *Crit Care Med* 1999;27:887–892.

⁴ Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867–903.

⁵ Rello J, Ollendorf DA, Oster G, Montserrat V, Bellm L, Redman R, Kollef MH. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002;122:2121.

used with caution in patients taking drugs known to prolong the QT interval. VIBATIV (telavancin) interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time.

F. VIBATIV (telavancin) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for VIBATIV (telavancin). FDA has determined that VIBATIV (telavancin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of VIBATIV (telavancin). FDA has determined that VIBATIV (telavancin) is a product for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use VIBATIV (telavancin).

When NDA 22407 is approved, the elements of the modified REMS will remain a Medication Guide, a communication plan and a timetable for submission of assessments of the REMS.

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/s/

SUSMITA SAMANTA
06/21/2013

SUMATHI NAMBIAR
06/21/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Addendum to the January 7, 2013
Final Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: June 20, 2013

Reviewer: Bob Pratt, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Through: Cynthia LaCivita, Pharm.D.
Risk Management Analyst Team Leader
DRISK

Division Director: Claudia Manzo, Pharm.D.
DRISK

Drug Name(s): Vibativ (telavancin)

Dosage and Route: 10 mg/kg intravenous infusion

Application Type/Number: NDA 22110
NDA 22407

TSI: 840, 841

Applicant/sponsor: Theravance

OSE RCM #: 2012-1966

1. INTRODUCTION

This review provides Division of Risk Management (DRISK) comments on the proposed REMS for Vibativ (telavancin) NDAs 22110 and 22407.

The REMS proposal includes a Medication Guide (MG), a communication plan (CP), and a timetable for submission of assessments.

The review of the MG was done under a separate cover by Shawna Hutchins, Division of Medical Policy Programs (DMPP) and recorded in DARRTS May 30, 2013.

2. MATERIAL REVIEWED

- January 7, 2013, DRISK REMS Review
- June 14, 2013, Applicant submission to NDA 22110 of REMS modification; REMS Interim Assessment (cross referenced to NDA 22407, June 17, 2013)
- June 18, 2013, Applicant submission to NDA 22110 of REMS modification; REMS, Dear Healthcare Provider Letter
- June 18, 2013 Applicant submission to NDA 22407 of REMS amendment; REMS, Dear Healthcare Provider Letter
- June 20, 2013, Applicant submission to NDA 22110 of REMS modification; REMS Supporting Document
- June 20, 2013 Applicant submission to NDA 22407 of REMS amendment; REMS Supporting Document

3. DISCUSSION AND RECOMMENDATIONS

The applicant's submission of the REMS, REMS Supporting Document, Dear Healthcare Provider Letter, and REMS Interim Assessment submitted to NDAs 22110 and 22407 are acceptable to DRISK.

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/s/

ROBERT G PRATT
06/20/2013

CLAUDIA B MANZO
06/20/2013
concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
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Final Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: June 7, 2013

Reviewer: Bob Pratt, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Through: Cynthia LaCivita, Pharm.D.
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Drug Name(s): Vibativ (telavancin)

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NDA 22407

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OSE RCM #: 2012-1966

1. INTRODUCTION

This review provides Division of Risk Management (DRISK) comments on the proposed REMS for Vibativ (telavancin) NDAs 22110 and 22407.

The REMS proposal includes a Medication Guide (MG), a communication plan (CP), and a timetable for submission of assessments.

The review of the MG was done under a separate cover by Shawna Hutchins, Division of Medical Policy Programs (DMPP) and recorded in DARRTS May 30, 2013.

2. MATERIAL REVIEWED

- January 7, 2013, DRISK REMS Review
- January 28, 2013, Applicant submission to NDA 22110 of REMS amendment, REMS Supporting Document, and Dear Healthcare Provider Letter
- February 11, 2013, Applicant submission to NDA 22407 of amendment of proposed REMS and REMS Supporting Document. (Dear Healthcare Provider Letter submitted to NDA 22407 on February 7, 2013)

-  (b) (4)

3. DISCUSSION AND RECOMMENDATIONS

The applicant has submitted an amendment to the proposed REMS modification for NDA 22110 and NDA 22407. The REMS, REMS Supporting Documents, and Dear Healthcare Provider Letters submitted to NDAs 22110 and 22407 contain the same content, and DRISK finds these materials to be acceptable. However, the applicant is seeking approval of a single REMS that would now be approved under two separate NDAs (the REMS would previously have been approved under NDA 22110 alone, but the applicant withdrew the pertinent efficacy supplement). Therefore, both NDA numbers need to be listed on the first page of the REMS and REMS Supporting Document; the date of the most recent REMS modification should also be noted on the first page of the REMS as well as in the timetable for submission of assessments section (see attached REMS). The applicant will need to resubmit the REMS and REMS Supporting Document to NDA 22110 and NDA 22407 with these administrative changes prior to approval.

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/s/

ROBERT G PRATT
06/07/2013

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06/07/2013
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Addendum to the January 7, 2013
Final Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: March 4, 2013

Reviewer: Bob Pratt, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Through: Cynthia LaCivita, Pharm.D.
Risk Management Analyst Team Leader
DRISK

Division Director: Claudia Manzo, Pharm.D.
DRISK

Drug Name(s): VIBATIV (telavancin)

Dosage and Route: 10 mg/kg intravenous infusion

Application Type/Number: NDA 022110 (b) (4)

TSI: 840, 841

Applicant/sponsor: Theravance

OSE RCM #: 2012-1966

1. INTRODUCTION

This review provides Division of Risk Management (DRISK) recommendations on the following:

- The revised, proposed Risk Evaluation and Mitigation Strategy (REMS) modification received [REDACTED] (b) (4) to NDA 022110 [REDACTED] (b) (4)

The revised REMS proposal includes a Medication Guide (MG), a communication plan (CP), and a timetable for submission of assessments. The subject of this review is the REMS. We note the MG is reviewed by the Division of Medical Policy Programs (DMPP) under separate cover.

2. MATERIAL REVIEWED

- [REDACTED] (b) (4) DRISK REMS Review
- [REDACTED] (b) (4), Applicant submission of revised REMS, REMS Supporting Document, and Dear Healthcare Provider Letter

3. DISCUSSION AND RECOMMENDATIONS

The applicant has submitted a REMS modification to NDA 022110. DRISK finds the revised REMS documents and Dear Healthcare Provider Letter to be acceptable (see attachment). [REDACTED] (b) (4) the date of the most recent REMS modification should be noted on the first page of the REMS as well as in the timetable for submission of assessments section. The applicant will need to resubmit the REMS with this information prior to approval.

The MG is reviewed by the Division of Medical Policy Programs (DMPP) under separate cover.

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ROBERT G PRATT
03/04/2013

CLAUDIA B MANZO
03/05/2013
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTI-INFECTIVE PRODUCTS

NDA/BLA #s: 022407
Products: VIBATIV (telavancin) for injection, 250 mg and 750 mg.
APPLICANT: Theravance, Inc.
FROM: Sumathi Nambiar MD MPH, Deputy Director for Safety
DATE: January 28, 2013

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

VIBATIV (telavancin) for injection, 250 mg and 750 mg was approved on 9/11/2009 under NDA 22110 for the treatment of complicated skin and skin structure infections. The drug was approved with a REMS, and the most recent REMS modification was approved on 7/27/11, to ensure the benefits of the drug outweighed the risk of fetal developmental toxicity. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

On 07/12/2012, Theravance, Inc. submitted NDA 22407 for a new indication, hospital-acquired bacterial pneumonia/ventilator associated bacterial pneumonia (HABP/VABP). Subsequently, Theravance, Inc. decided to pursue approval of the new indication through an efficacy supplement to NDA 22110; approval of this sNDA is pending, as of the date of this memo.

Data included in NDA 22407 showed a serious risk of increased mortality in VIBATIV-treated patients with HABP/VABP with pre-existing creatinine clearance of ≤ 50 mL/min. This was noted in two Phase 3 trials in HABP/VABP comparing telavancin to vancomycin.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for VIBATIV (telavancin) for

injection, 250 mg and 750 mg to ensure that the benefits of the drug outweigh the following risks:

1. Increased mortality seen in VIBATIV (telavancin) -treated patients with HABP/VABP with pre-existing creatinine clearance of ≤ 50 mL/min.
2. Risk of fetal developmental toxicity seen in three animal species at clinically relevant doses.

In reaching this determination, we considered the following:

- A. Hospital Acquired Pneumonia (HAP) is currently the second most common nosocomial infection in the United States, and is associated with high mortality and morbidity.^{1,2} The presence of HAP increases hospital stay by an average of 7 to 9 days per patient. Available data suggest that HAP occurs at a rate of between 5 and 10 cases per 1,000 hospital admissions. HAP accounts for up to 25% of all ICU infections and for more than 50% of the antibiotics prescribed.³ Ventilator-associated pneumonia (VAP) occurs in 9–27% of all intubated patients.^{4,5} The crude mortality rate for HAP may be as high as 30 to 70%.
- B. Hospital acquired bacterial pneumonia/ventilator-associated bacterial pneumonia is a serious and potentially fatal illness and is also associated with significant morbidity.
- C. VIBATIV (telavancin) is active against methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with HABP/VABP. Only a few therapeutic options are available for the treatment of HABP/VABP due to MRSA.
- D. Given the safety concerns with increased mortality in HABP/VABP patients with pre-existing creatinine clearance ≤ 50 ml/min and the risk of fetal developmental toxicity, the product will only be indicated for use in patients when other therapeutic options cannot be provided.
- E. VIBATIV (telavancin) can cause adverse reactions including nephrotoxicity, taste disturbance, nausea, vomiting, and foamy urine. In clinical trials, decreased efficacy has been seen among VIBATIV-treated patients with skin and skin structure infections with moderate/severe pre-existing renal impairment. VIBATIV (telavancin) can cause prolongation of the QT interval and should be used with caution in patients taking drugs

¹ Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med* Vol 171. 388–416, 2005

² Tablan OC, Anderson LJ, Besser R, et al. Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and Prevention. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004;53(RR-3):1–36.

³ Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical ICUs in the United States: National Nosocomial Infections Surveillance System. *Crit Care Med* 1999;27:887–892.

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known to prolong the QT interval. VIBATIV (telavancin) interferes with some laboratory coagulation tests, including prothrombin time, international normalized ratio, and activated partial thromboplastin time.

F. VIBATIV (telavancin) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for VIBATIV (telavancin). FDA has determined that VIBATIV (telavancin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of VIBATIV (telavancin). FDA has determined that VIBATIV (telavancin) is a product for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use VIBATIV (telavancin).

The elements of the REMS will be a Medication Guide, a communication plan and a timetable for submission of assessments of the REMS.

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/s/

JOSEPH C DAVI
02/12/2013

SUMATHI NAMBIAR
02/12/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 4, 2013

Reviewers: Robert Pratt, Pharm. D., Risk Management Analyst, Division of Risk Management (DRISK)
Kate Oswell, M.A., Health Communications Analyst, DRISK

Through: Cynthia LaCivita, Pharm.D., Risk Management Analyst Team Leader, DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name(s): VIBATIV (telavancin)

Dosage and Route: 10mg/kg intravenous infusion

Application Type/Number: NDA 022407

Applicant/sponsor: Theravance

OSE RCM #: 2012-1966

1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates the sponsor's proposed risk evaluation mitigation strategy (REMS) for VIBATIV (telavancin) submitted December 5, 2012 for NDA 022407. VIBATIV (NDA 022110) was approved on September 11, 2009 for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria. It was approved with a REMS that targeted the risk of teratogenicity. The REMS includes a Medication Guide (MG) and communication plan (CP).

2. BACKGROUND

Nosocomial pneumonia (NP) remains an important cause of morbidity in hospitalized patients and is the leading cause of death among hospital-acquired infections, with associated mortality estimates that range from 20 to 50 percent. NP is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. Etiologic pathogens include a variety of Gram positive and Gram-negative bacteria that are often resistant to multiple antibacterial drugs. Estimates of incidence range from four to seven episodes per 1,000 hospitalizations.¹

Telavancin is a semisynthetic lipoglycopeptide antibiotic approved for the treatment of cSSSI caused by susceptible isolates of various Gram-positive bacteria (NDA 022110). The recommended dosing is 10mg/kg by intravenous infusion once every 24 hours. Telavancin is primarily eliminated by the kidney, and patients with renal impairment require dosage adjustments. VIBATIV (NDA 022407) is currently under review for the proposed indication of treatment of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (which will be referred to as nosocomial pneumonia for the purpose of this review) caused by susceptible strains of the following Gram positive bacteria: *Staphylococcus aureus*, including methicillin-sensitive and methicillin-resistant isolates (MSSA and MRSA, respectively) and *Streptococcus pneumoniae*. The proposed dosing and dosage adjustments for use of telavancin in the treatment of NP are the same as for cSSSI.

Based on limb defects observed in reproductive toxicology studies and the potential for teratogenicity, a REMS was approved under NDA 022110. The elements of the REMS include a MG and a CP, with the goal to avoid unintended exposure of pregnant women to the product. A second significant risk was identified in the NP studies in support of NDA 022407, a risk of increased mortality among patients with pre-existing creatinine clearance <50 mL/min and who received telavancin, relative to those receiving the comparator, vancomycin. The sponsor proposes a second REMS program that would focus on communicating to clinicians this risk of increased mortality for patients with pre-existing severe renal dysfunction.

3. REGULATORY HISTORY

VIBATIV, NDA 022407, was initially submitted January 23, 2009 before the approval of VIBATIV, NDA 022110. Due to the FDA regulatory bundling procedures each indication

¹ File, TM. Epidemiology, pathogenesis, microbiology, and diagnosis of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults. In: UpToDate, Bartlett JG (Ed), UpToDate, Waltham, MA, 2012.

received separate NDA numbers. It is reasonable to expect that if NDA 022407 is approved, both indications will be tracked under one NDA number. Therefore, since the first VIBATIV approval has a REMS that includes a MG and a CP, the proposed indication will need to be approved with a REMS. NDA 022407 was issued Complete Responses in November 2009 and December 2010 for application deficiencies.

4. MATERIAL REVIEWED/REFERENCED

NDA 022407

- January 23, 2009 initial submission
- September 25, 2009 FDA Clinical Review
- November 23, 2009 FDA issued Complete Response (CR)
- December 22, 2009 applicant submitted CR
- January 26, 2010 FDA issued incomplete response letter
- June 30, 2010 applicant submitted CR
- December 21, 2010 FDA issued CR
- July 12, 2012 applicant submitted CR, class 2 resubmission
- November 29, 2012 Anti-Infective Drugs Advisory Committee Meeting: FDA Briefing Package and slide set
- December 5, 2012 applicant submitted proposed REMS
- December 21, 2012 sponsor information request e-mail, amended REMS document. (Sponsor instructed to submit a REMS modification to NDA 022110 and a modified REMS proposal to NDA 022407 for the purpose of merging the approved REMS and its Supporting Document, with the proposed REMS and its Supporting Document. The sponsor was also sent a redlined amended REMS for guidance.)

5. RESULTS OF REVIEW

5.1. OVERVIEW OF CLINICAL PROGRAM

Telavancin was studied in two randomized, double-blind Phase 3 clinical trials that enrolled 1,503 adult patients to receive either telavancin or vancomycin for the treatment of NP. The primary efficacy endpoint was specified as clinical response (determined by the investigator) in a test of non-inferiority. The studies were conducted from 2005-2007. After subsequent FDA Advisory Committee meetings and a separate FDA workshop, it was concluded that non-inferiority studies for nosocomial pneumonia must use all-cause mortality for the primary endpoint. Although the pre-specified endpoint of clinical response was met in both telavancin NP trials, the studies did not provide sufficient evidence of non-inferiority compared to vancomycin for the mortality endpoint; in what FDA considered to be the primary efficacy population, the non-inferiority margin of 10% was exceeded in one study and equal to the margin in the second study, and the application received a Complete Response. The sponsor

resubmitted the application for reanalysis and a discussion of the scientific issues before the Anti-Infective Drugs Advisory Committee.

5.2. SAFETY

The product labeling for NDA 022110, approved for the treatment of cSSSI contains a boxed warning for fetal risk of adverse developmental outcomes with use during pregnancy. Additional labeled warnings and precautions include new onset or worsening renal impairment, decreased efficacy with moderate/severe baseline renal impairment, infusion-related reactions, *Clostridium difficile*-associated disease, QTc prolongation, and coagulation test interference.

Nephrotoxicity

Telavancin exposure was associated with evidence of nephrotoxicity in the two Phase 3 clinical studies of NP. There was a consistent pattern of mean increases in serum creatinine and decreases in creatinine clearance in the telavancin groups compared with the vancomycin groups of both trials. Among patients with abnormal baseline creatinine (>1.2 mg/dL), more telavancin-treated patients experienced treatment-emergent renal adverse events compared with patients treated with vancomycin. Regarding the effect of baseline renal function on mortality, subgroup analyses identified a trend of increased mortality with telavancin relative to vancomycin as baseline renal impairment increased in the all-treated and primary efficacy populations. However, the relationship between the creatinine clearance strata and mortality trend differed somewhat between the two studies. Additional subgroup analyses identified congestive heart failure and the use of nephrotoxic medications at baseline as other risk factors for renal injury that may have influenced mortality.

QT Prolongation

As part of the NDA for cSSSI, the sponsor performed a QT study that demonstrated telavancin prolonged the QTc interval a mean change of about 4 msec from baseline. In the two NP clinical studies, 24 patients (12 telavancin- and 12 vancomycin-treated) exhibited maximum post-baseline QTcF values >500 msec during study participation. Of the 24 patients, 16 (eight patients in each treatment group) also exhibited a maximum increase from baseline in QTcF >60 msec. No patients treated with either study medication experienced torsades de pointes.

Pulmonary embolism

Eight patients experienced a pulmonary embolism (PE) that was assessed as a serious treatment-emergent adverse event by investigators; seven patients were telavancin-treated and one was vancomycin-treated. There was a temporal association of telavancin exposure with the development of PE, but some of the narratives provided by the sponsor were not of sufficient detail to assess causality. None of the events were assessed as treatment-related by the investigators.

5.3. ADVISORY COMMITTEE

Telavancin for the treatment of NP was presented at the November 29, 2012 Anti-Infective Drugs Advisory Committee Meeting. The Committee was asked two questions regarding the evidence of safety and effectiveness of telavancin in treating NP as well as to discuss the use of telavancin in patients with baseline renal dysfunction. When asked if the data supported safety and efficacy for the treatment of nosocomial pneumonia caused by MRSA, MSSA, and *Streptococcus pneumoniae*, the committee was divided with nine members voting no and six yes. However, if the indication were limited to the treatment of NP when other alternatives are not suitable, the committee voted 13-1 in favor of telavancin, though most members suggested its use should be limited to the treatment of MRSA. Several committee members also offered advice on limitations for use related to baseline renal impairment and creatinine clearance thresholds.

5.4. PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

Safety-related postmarketing requirements have not been determined at the time of this review.

5.5. REMS

5.5.1. SPONSOR'S PROPOSED REMS

On December 5, 2012, the sponsor proposed a second, unique REMS program to NDA 022407 that includes a CP and timetable for submission of assessments. The CP consists of a Dear Healthcare Provider (DHCP) Letter to be distributed to clinicians involved in the treatment of patients with NP that focuses on communicating to clinicians the risk of increased mortality with telavancin versus vancomycin in patients with pre-existing renal impairment being treated for NP. The stated goal of the sponsor's proposed REMS is to avoid unnecessary mortality. Assessments of the extent to which the elements are meeting the goal will be based on knowledge, attitude, and behavior surveys of HCPs that will be developed after product labeling and educational materials are finalized. The assessments will be submitted to FDA 18 months, 3 years, and 7 years from approval.

Reviewer's Comment: The sponsor's stated goal is to avoid unnecessary telavancin-associated mortality. This goal may be difficult to define and achieve and cannot be easily measured. As the communication plan serves to inform healthcare professionals (HCPs) likely to prescribe or dispense telavancin about the differential mortality risk, the informing of HCPs should be identified as the goal of the REMS. We communicated the change in REMS goal to the sponsor in the December 21, 2012, information request (referenced in Section 4 and Appendix 2).

6. DISCUSSION

The first telavancin approval, NDA 022110, required a REMS that includes a MG and a CP to address the potential risk for teratogenicity. If NDA 022407 is approved for NP, it must be approved with the same REMS requirement and any changes to the approved REMS (e.g., a new goal) to address the risk of increased mortality in patients with renal impairment. Theravance will need to submit a REMS modification to NDA 022110 with a separate but identical submission to NDA 022407.

For NDA 022407, the sponsor has proposed a REMS with a CP to address the risk of increased mortality relative to vancomycin in patients with baseline renal impairment being treated for NP. The CP activities are similar to what was included in the approved REMS, i.e., a Dear Healthcare Provider and Dear Professional Society letters that target the prescribing population with a product website that contains links to the DHCP letter and package insert. DRISK is recommending the approved REMS to include information about the increased risk of mortality (see Appendix 1 for the redlined REMS). DRISK's proposed goals of the VIBATIV REMS are:

- A. To inform healthcare professionals (HCP) about the increased risk of mortality associated with VIBATIV in patients with pre-existing creatinine clearance of ≤ 50 mL/min being treated for nosocomial pneumonia (NP), including ventilator-associated pneumonia.
- B. To avoid unintended exposure of pregnant women to VIBATIV through:
 - Educating healthcare professionals and patients on the potential risk of fetal developmental toxicity if women are exposed to VIBATIV while pregnant
 - Informing HCPs that a serum pregnancy test should be performed before initiating therapy with VIBATIV in Females of Reproductive Potential (FRP)
 - Informing HCPs that FRP, including those being treated in the outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during VIBATIV use.

The modified REMS would include the MG which would be distributed in accordance with 21 CFR 208.24, and is intended to follow the FDA Guidance on Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) 2011.

As previously described, subgroup analyses of the telavancin trials in the indicated population identified a trend of increased mortality relative to vancomycin as baseline renal impairment increased. Additional analyses identified other factors that may have impacted mortality (e.g., congestive heart failure; other nephrotoxins). The risk of differential mortality has been addressed in labeling for other antibiotics; however, the risk has mainly been associated with use outside of the indication. For example, tigecycline, a tetracycline-class antibiotic approved in 2005, added a bolded warning and precaution in 2010 for increased all-cause mortality across Phase 3 and 4 clinical trials for tigecycline-treated patients versus comparator-treated patients. The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia (VAP), and the labeling carries an additional warning for greater mortality in patients with VAP relative to comparator-treated patients. Tigecycline is not approved for the treatment of NP, including VAP. A second example is found with linezolid, an oxazolidinone antibiotic approved in 2000 for the treatment of NP and other Gram-positive infections. Linezolid added a warning in 2008 for a mortality imbalance observed in patients with intravascular catheter-related infections treated with linezolid relative to vancomycin/dicloxacillin/oxacillin. Linezolid is not approved for the treatment of catheter-related or catheter-site infections.

The increased risk of mortality associated with compromised renal function and telavancin is in the proposed indicated population: patients treated for nosocomial pneumonia (NP), including ventilator-associated pneumonia. In considering the regulatory actions taken for differential mortality risk in the examples of tigecycline and linezolid cited above, warnings with specific reference to unapproved indications were added to the product labeling. The increased mortality risk observed with telavancin treatment is higher than what was observed in the tigecycline and linezolid studies, and is with reference to an approved indication (in the event NDA 022407 receives approval). DRISK and DAIP are in agreement that risk mitigation measures in addition to labeling will be needed to address this risk of differential mortality for an approved indication.

7. CONCLUSION

Nosocomial pneumonia is a serious condition and the leading cause of death among hospital-acquired infections. In the pivotal clinical studies of telavancin for the treatment of NP, the evidence of benefit is complex to evaluate and a trend of increased mortality was identified for telavancin relative to vancomycin as baseline renal impairment increased. It seems reasonable to conclude that risk mitigation measures in addition to labeling are needed to address the risk of differential mortality should telavancin receive approval.

Because of the potential risk for teratogenicity and the risk of increased mortality relative to vancomycin in patients with baseline renal impairment being treated for nosocomial pneumonia, NDA 022407 cannot be approved without a REMS that addresses both risks. The elements of the REMS should include a Medication Guide and a communication plan to address the risks of teratogenicity and differential mortality.

8. RECOMMENDATIONS

The sponsor should be provided with the following comments regarding the proposed REMS:

1. Resubmit the following:

- a. The amended REMS document (see FDA revisions in track changes to the REMS document)
- b. REMS Supporting Document revised to align with changes in the REMS document.
- c. A revised Dear Healthcare Provider Letter addressing the risk of teratogenicity and increased mortality

2. Resubmission Instructions

- a. Submit an amendment to the proposed REMS for telavancin.
- b. Include all of your REMS materials in the submission. For example, your REMS document, all materials that are appended to your REMS document (including the newly requested materials), and your REMS Supporting Document.

- c. For any REMS materials that are being revised, provide both a clean and tracked changes version.

Submit all REMS materials in MS Word format. If certain documents, such as the REMS website are only in PDF format, they may be submitted as such. However, our preference is that as many materials as possible be provided in MS Word.

3. The REMS assessment plan should include but is not limited to the following:
 - a. The results of surveys assessing healthcare professionals' and patients' understanding of:
 - the potential risk of fetal developmental toxicity if women are exposed to VIBATIV while pregnant.
 - b. The results of surveys assessing healthcare professionals' understanding of:
 - the increased risk of mortality in VIBATIV-treated patients with creatinine clearance of <50ml/min being treated for hospital acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP).
 - the need to monitor renal function (serum creatinine and creatinine clearance) prior to initiating therapy with VIBATIV, during therapy (every 48 to 72 hours or more frequently if clinically indicated), and at the end of therapy
 - the need to perform a serum pregnancy test prior to initiating therapy with VIBATIV in Females of Reproductive Potential (FRP).
 - the need to counsel FRP, including those being treated in the outpatient setting, about pregnancy prevention and use of effective contraception during VIBATIV use.
 - c. A summary and analysis of maternal and fetal outcomes for all reported pregnancies (from any data source) including:
 - a cumulative number of all fetal exposures and outcomes reported
 - a root cause analysis to investigate the pregnancies reported with VIBATIV (telavancin) use in the U.S.
 - d. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with CFR 208.24. (This may be achieved through the patient survey.)
 - e. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
 - f. An assessment and conclusion of whether each goal of the REMS is being met, and whether any modifications to the REMS are needed.

APPENDICES

Appendix 1: Redlined revisions to telavancin REMS

Appendix 2: Information request to sponsor 12/21/2012

6 Page(s) of Draft Labeling have been
Withheld in Full as b4 (CCI/TS) immediately
following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT G PRATT
01/05/2013

CLAUDIA B MANZO
01/07/2013
concur