

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022407Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader / Medical Officer Review

Date	June 17, 2013
From	Benjamin Lorenz, MD
Subject	Cross-Discipline Team Leader Review Medical Officer Review
NDA/BLA # Supplement#	022-407, Class 2 Resubmission eCTD Seq #s: 128-133
Applicant	Theravance, Inc
Date of Submission	March 13, 2013
PDUFA Goal Date	September 13, 2013
Proprietary Name / Established (USAN) names	Vibativ (telavancin hydrochloride)
Dose forms / Strength	Sterile, lyophilized powder, 250 mg, 750 mg Recommended dose: 10 mg/kg IV every 24 hours
Proposed Indications(s)	Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia caused by susceptible isolates of <i>Staphylococcus aureus</i>
Recommended action	Approval

1. Introduction

This submission includes an update to the Vibativ® (telavancin for injection) NDA to address the deficiencies as described in the Complete Response letter dated February 22, 2013. Also included is the Applicant's proposed final labeling, which includes the additional treatment indication for hospital-associated and ventilator-acquired bacterial pneumonia (or HABP/VABP caused by susceptible isolates of *Staphylococcus aureus*). Although, upon final review of the July 12, 2012 Class 2 resubmission, the Division determined that the clinical and statistical issues with the two registrational HABP/VABP trials were substantially resolved, the NDA was not approvable due to CGMP deficiencies at (b) (4), the sole drug product manufacturing facility. The Applicant has now withdrawn the (b) (4) facility from the NDA and submitted updated proposals to meet the manufacturing requirements for a new facility with Hospira in McPherson, KS.

2. Background

Telavancin, a semisynthetic derivative of vancomycin and a first-in-class lipoglycopeptide antibacterial drug, was first approved on September 11, 2009 for use in the treatment of complicated skin and skin structure infections (cSSSI) (NDA 022-110). The Applicant, Theravance Inc., submitted a separate NDA (022-407) for the treatment of nosocomial pneumonia (NP). In June 2010, the Applicant resubmitted the application to include missing mortality data and additional post-hoc analyses of mortality, but the Division concluded that the application could not be approved because one of the two nosocomial pneumonia studies failed to demonstrate non-inferiority when assessing 28-day all-cause mortality. Following a Formal Dispute Resolution Request and an appeal for approval of the NDA on the basis of efficacy as assessed by clinical response, the Applicant agreed to resubmit the application for further discussion at a meeting of the Anti-Infective Drug Advisory Committee (held on November 29, 2012). The majority of the Committee voted to recommend a limited approval, whereby telavancin should only be used for the treatment of nosocomial pneumonia when alternative antibacterial agents are not suitable. Although the Division agreed that the application was approvable (as recommended by the AIDAC with accompanying labeling warning about nephrotoxicity and the risk of increased mortality associated with baseline renal dysfunction) the sole manufacturer of telavancin, (b) (4) had been placed on a manufacturing hold. With the majority of labeling concerns agreed upon, however, the Applicant had not yet completed requirements for readiness at the new manufacturing site, Hospira's McPherson facility in Kansas.

Before the sole manufacturing facility for the Vibativ drug product, (b) (4) issued a distribution hold in November 2011, batches from two of the last three lots had been released to their former distributor and marketing partner, Astellas. Those lots were held at (b) (4) and after purchase, Theravance had planned to release the remaining product under NDA 022-110, their previously approved cSSI indication. Certificates of analyses for release testing performed by (b) (4) on these two lots found that they met the release specifications when tested in November 2011; however, violations reported at (b) (4) included deficiencies in sterility assurance, and the third lot had been held for investigation due to increased (b) (4). According to evaluations of the Office of Compliance and ONDQA team, who cited problems such as (b) (4) and (b) (4), the facility in (b) (4) was not acceptable. As a result, since December 2011, Vibativ has been on the Drug Shortage list.

Due to the aforementioned manufacturing issues, the Division recommended that the Applicant seek approval of the new indication through NDA 022-110 instead, by submitting an additional supplement (b) (4)

(b) (4) These manufacturing issues, in context of the pending action for the NP indication, were discussed at a Center Director Briefing Meeting on January 23, 2013. Given the lack of readiness at the new manufacturing facility at Hospira McPherson, and the Establishment Evaluation System (EES) status for (b) (4) at “withhold” and subsequent consent decree with the FDA (applicable to the lots released prior to the hold), the Division deferred action on NDA 022-407 pending the Applicant’s demonstration of accordance with CGMP guidelines. The Agency was also unable to come to a regulatory resolution regarding the manufacturing issues pursuant to the formal approval of the new indication and labeling as submitted to NDA 022-110. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In the Complete Response letter, sent February 22, 2013, the Division outlined the requirements for resubmission, including any revisions to the revised labeling and medication guide, as well as acknowledgements of their pediatric requirements and updates to their safety evaluations and risk evaluation and mitigation strategy (REMS).

For further details regarding the clinical review of the application for nosocomial pneumonia, please also refer to the original NDA review by Dr. Alfred Sorbello, dated September 25, 2009,

and my previous reviews (for the second and third resubmissions, respectively) for NDA 022-407 dated December 21, 2010 and February 2, 2013.

3. CMC/Device

Due to the manufacturing issues as described above in the Background Section (Section 2), the Applicant withdrew (b) (4) as the primary manufacturer from the NDA (as of October 12, 2012 for NDA 022-110 and March 27, 2013 under NDA 022-407), and subsequently provided updated documentation for the proposal to add a new, alternate site for manufacturing at the following facility:

Hospira Worldwide, Inc. (Hospira McPherson)
1776 North Centennial Drive
McPherson, KS
USA

The Applicant has submitted a supplement as Changes Being Effected in 30 Days (CBE-30) pursuant to the approved comparability protocol. This NDA (022-407), for the new indication of HABP/VABP, relies upon the Applicant's CMC documentation submitted to NDA 022-110. Specifically, batch release data for the three process validation batches, Certificates of Analysis, and interim process validation summary report were submitted in support of the supplement (referencing supporting documents submitted under SDN's 230, 234, 235, 236, and 238A). Stability data derived from these lots will be submitted in subsequent NDA Annual Reports.

According to the review by ONDQA, "Release results for the three full-scale validation batches were examined; all results were within the approved acceptance criteria/limits". Overall, based on the updated CMC submissions, ONDQA recommended NDA 22-407 for approval. Please refer to the review by Joel Hathaway, Ph.D., dated May 29, 2013 (NDA 22110/S-006 Chemistry Review #1). Also of note, the Office of Compliance issued an Overall Recommendation of "Acceptable" for NDA 22-407 (reflected in the EES report).

Other minor changes, including additions to the reconstitution instructions under the Dosage and Administration section, of the package insert, were acceptable from the CMC perspective. These changes describe the potential for foaming and possible administration errors found in the 915 New Molecular Entity (NME) Post-market Safety Summary finalized on March 28, 2013. Please refer to the Labeling Section, Section 12, of this review for further details.

4. Nonclinical Pharmacology/Toxicology

There is no new nonclinical pharmacology/toxicology information provided in this submission.

5. Clinical Pharmacology/Biopharmaceutics

There is no new clinical pharmacology information provided in this submission.

6. Clinical Microbiology

There is no new clinical microbiology information provided in this submission.

7. Clinical/Statistical—Efficacy

There is no new clinical/statistical efficacy information provided in this submission.

8. Safety

The Applicant submitted no new safety findings in their review of available post-marketing data since the previous submission. In the recent 915 New Molecular Entity (NME) Post-market Safety Summary (finalized on March 28, 2013), however, the Agency discovered safety concerns identified since approval on September 11, 2009 that have new labeling implications. Adverse event profiles were identified; the cases and brief descriptions are listed below.

Anaphylaxis: There were at least three cases reported to AERS, including one case with a prior history of allergy to vancomycin.

- Case #7989617: “On 06JUN2011, a spontaneous report was received from a physician via an Astellas company representative regarding a 27 year old female who experienced severe anaphylaxis with shortness of breath and hives and serum creatinine over 2.0 with Vibativ (telavancin) therapy. On an unspecified date, she began telavancin for methicillin-resistant staphylococcal aureus (MRSA) infection, and urinary tract infection (UTI) (off label use). Prior to switching to telavancin, she experienced an allergic reaction to vancomycin that prevented the resolution of a MRSA infection. On an unspecified date she was switched to telavancin, and she experience severe anaphylaxis requiring Emergency Medical Services (EMS) support for shortness of breath and hives. Telavancin was discontinued and she was switched to daptomycin on day 3 of treatment. On an unspecified date, she also experienced an increase in serum creatinine to over 2.0 (units and reference range were not provided). The outcome of the events was not provided. Medical history included appendectomy, mild renal insufficiency, and an allergy to Levaquin (levofloxacin) and Zoloft (sertraline). Concomitant medications were not

provided. The reporting physician did not provide serious criteria or provide a causality assessment for the events and telavancin therapy. The Astellas medical reviewer assessed the events of anaphylaxis, shortness of breath and hives as medically significant and the event of increase in serum creatinine over 2.0 as non-serious. No additional information was provided.”

- Case #8064232: “On 25JUL2011, a spontaneous report was received from a pharmacist via an Astellas company representative regarding a 40 year old female who developed an anaphylactic reaction with the initial dose of Vibativ (telavancin) therapy. On 27JUN2011, she began telavancin for an unknown indication, with the assistance of a home infusion nurse. After an unspecified amount of time, she developed a severe anaphylactic reaction. When she first showed signs of the reaction, she was given a dose of Benadryl (diphenhydramine) but experienced no relief. The home infusion nurse called 911 and administered a dose of epinephrine. When the ambulance arrived, the epinephrine had taken effect and the patient refused transport to the hospital. The outcome of the event was not provided. Medical history and concomitant medications were not provided. The reporting pharmacist did not provide a seriousness or causality assessment for the event and telavancin therapy. An Astellas medical reviewer assessed the event as medically significant. No additional information was provided. ----- Additional information was received on 08AUG2011. Medical history included no known prior drug allergies. Concomitant medications included naproxen. The indication for telavancin therapy was a Methicillin-resistant Staphylococcus aureus (MRSA) infection of the right elbow. On 27JUN2011, after administration of telavancin, she developed anaphylaxis, a severe allergic reaction and difficult breathing. The events resolved after approximately 15 minutes, after she was treated with epinephrine. She did not receive further telavancin therapy. The reporting pharmacist assessed the events as probably related to telavancin therapy and did not provide a seriousness assessment for the events. An Astellas medical reviewer assessed the events as medically significant. No further information is expected.”
- Case #8159415: “On 20SEP2011, a spontaneous report was received from a nurse via an Astellas company representative regarding a patient who developed an anaphylactic reaction and may have been given too high of a dose with the use of Vibativ (telavancin) therapy. The patient was administered telavancin for an unspecified indication on an unspecified date. On an unknown date, the patient may have been given too high of a dose and developed an anaphylactic reaction. The outcome for the events was not provided. Medical history and concomitant medications were not provided. The nurse did not assess the seriousness or provide a causal relationship for the events and telavancin therapy. The Astellas medical reviewer assessed the events as medically significant. No additional information was received.”

Additionally, two cases were identified (listed as “medication errors” in AERS reports) that describe accidental exposure to the drug while preparing the product. During the preparation of telavancin, health care personnel were exposed to aerosolized drug substance, and afterwards, exhibited signs and symptoms such as swelling of the lips/throat and rash.

- Case #7281109v3: nurse was mixing Vibativ in the office mixing room, which did not have a vent hood, and subsequently she developed blisters on her lips, a sore throat and a cough. These events all resolved within 4 to 5 days with self-treatment. A second exposure to the drug occurred during product preparation, which resulted in a red face, a rash on her chest and neck (exposed areas), blisters on her lips and tongue, a sore throat, lip swelling and she lost her voice. The nurse's primary care physician assessed that she had an allergic reaction to the drug and treated her with steroids and antihistamines, which improved her symptoms. The nurse had no prior history of allergies.
- Case #7792506v1: describes a pharmacist who was exposed to Vibativ through cutaneous contact and thought she had an allergic reaction. The pharmacist was inspecting a vial of Vibativ and removed a piece at the top of the vial (unclear what piece) and a small amount, (described as less than 0.2 mL), spilled onto her hand. She washed her hands but the exposure resulted in lip swelling, chest tightness, hands turned red, welts on hands, scalp and back, and itching on hands and knees. The symptoms resolved in two days with self-treatment using diphenhydramine.

Medical Officer's comments: Taken together these cases are substantially consistent with drug-related hypersensitivity. Telavancin has previously been shown to cause similar reactions to vancomycin such as Red Man syndrome; however, these cases demonstrate reactions more consistent with hypersensitivity and anaphylaxis. Although, not as frequent, vancomycin has been shown to cause anaphylaxis as well. There is very little evidence, however, given the lack of clinical detail provided for the "allergic reaction" to vancomycin (as described in case # 7989617), that cross-reactive hypersensitivity will occur between glycopeptides such as telavancin and vancomycin.

9. Advisory Committee Meeting

The Anti-Infectives Advisory Committee (AIDAC) convened for the discussion of NDA 022-407 on November 29, 2012. The majority of the committee voted that approval should be limited for the treatment of nosocomial pneumonia due to MRSA, certain cases of MSSA (e.g., β -lactam allergy) and should also be limited to situations where alternative treatments are not available. The committee also strongly recommended labeling related to use of telavancin in renal dysfunction. Please refer to my February 1, 2013 review for further details.

10. Pediatrics

Theravance acknowledged the requirement for pediatric assessments of Vibativ.

The agreed upon pediatric studies as of January 23, 2013, are listed below:

- Conduct a single dose pharmacokinetic (PK) trial in patients ≥ 1 to 17 years old
- Conduct a single dose pharmacokinetic (PK) trial in neonates/infants 0 to < 1 year old
- Conduct a Phase 3, randomized, comparator-controlled trial of the safety and efficacy of telavancin in children from birth to 17 years old with Gram-positive infections

Of note, as part of this plan to further study PK in pediatric subjects, the Applicant had proposed to evaluate the PK of the solubilizing agent, hydroxypropyl- β -cyclodextrin. However, in an e-mail to the Division on April 14, 2013, the Applicant proposed not to include this evaluation in their study because pediatric PK data are available in subjects of ages 7 months to 17 years (based upon a single-dose study conducted by Johnson & Johnson with itraconazole by Abdel-Rahman *et al*). Since the dose and type of HP- β -cyclodextrin (0.1 g/kg) in telavancin are the same as the dose and type evaluated in the itraconazole study, the Applicant expects the PK to be similar. In addition, by not assaying HP- β -cyclodextrin, the required PK blood collection volume is reduced significantly.

Medical Officer's comments: *This reviewer agrees with the Applicant's rationale and proposal not to assay this agent in the PK study.*

11. Other Relevant Regulatory Issues

No other relevant regulatory issues.

12. Labeling

In addition to their proposed US label, the Applicant also provided current labels as approved outside of the US. In relation to the safety issue raised in the 915 NME Summary, and summarized in the Safety section of this review (Section 8), the following are contraindications as listed in the Canadian label: "contraindicated for use in patients who have known hypersensitivity to this drug or to other glycopeptides or to any ingredient in the formulation or component of the container", and in the EU label: "Hypersensitivity to the active substance or to any of the excipients."

Medical Officer's comments: *The U.S. Code of Federal Regulations, 201.57(c)(5)-(6), specifies that labeling contain a Contraindications section which describes situations where the risks are known and where the risks of use clearly outweigh any possible benefit. The Warnings and Precautions section is intended to describe clinically significant adverse reactions (including any that are potentially fatal, serious, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the*

pharmacologic class or those resulting from drug–drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). Although the cross-reactivity between glycopeptides such as telavancin and vancomycin is plausible, the evidence from these cases is still not well-described. For this reason, cautionary language regarding the history of hypersensitivity to vancomycin should be included in the Warnings and Precautions section, rather than the Contraindications section. These changes should also be added to the Medication Guide.

In order to address these hypersensitivity cases described in AERS, the following language was edited. The Applicant has agreed with these changes, as shown below (new text is shown in red and deleted text is shown in ~~red with strikethrough~~).

- Amendments to the **HIGHLIGHTS** section:

-----**CONTRAINDICATIONS**-----

(b) (4) Known hypersensitivity to VIBATIV. (4, 5.5, 6.2)

-----**WARNINGS AND PRECAUTIONS**-----

- Decreased efficacy among patients treated for skin and skin structure infections with moderate/severe pre-existing renal impairment: Consider these data when selecting antibacterial therapy for patients with baseline CrCl \leq 50 mL/min. (5.2)
 - Hypersensitivity reactions: Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin. (5.5, 6.2)
- Amendment to the **CONTRAINDICATIONS** section

4 CONTRAINDICATIONS

(b) (4) VIBATIV is contraindicated in patients with known hypersensitivity to telavancin.

- Additional section to the **WARNINGS AND PRECAUTIONS** section:

5.5 Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. Discontinue VIBATIV at first sign of skin rash, or any other sign of hypersensitivity. Telavancin is a semi-synthetic derivative of vancomycin; it is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-reactivity to telavancin. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin [see *Postmarketing Experience* (6.2)].

- Addition of Postmarketing Experience (6.2) to the **ADVERSE EVENTS** section:

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of VIBATIV. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious hypersensitivity reactions have been reported after first or subsequent doses of VIBATIV, including anaphylactic reactions. It is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-reactivity to telavancin. [see *Hypersensitivity Reactions (5.5)*].

The following was also recommended by DMEPA, due to reports of medication errors. The reports described foaming when the diluent was added to the vial or the product was further diluted into infusion bags. In one of these cases the foam caused the pump to interrupt the infusion, as it sensed air bubbles in the infusion tubing. The Applicant reviewed these edits and agreed with adding the following paragraph to preparation and administration instructions in the DOSAGE AND ADMINISTRATION section, (subsection 2.4):

2.4 Preparation and Administration

250 mg vial: Reconstitute the contents of a VIBATIV 250 mg vial with **15** mL of 5% Dextrose Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP. The resultant solution has a concentration of 15 mg/mL (total volume of approximately 17.0 mL).

750 mg vial: Reconstitute the contents of a VIBATIV 750 mg vial with **45** mL of 5% Dextrose Injection, USP; Sterile Water for Injection, USP; or 0.9% Sodium Chloride Injection, USP. The resultant solution has a concentration of 15 mg/mL (total volume of approximately 50.0 mL).

To minimize foaming during product reconstitution, allow the vacuum of the vial to pull the diluent from the syringe into the vial. Do not forcefully inject the diluent into the vial. Do not forcefully shake the vial and do not shake final infusion solution.

13. Recommendations and Risk-Benefit Assessment

13.1. Recommended Regulatory Action

The Applicant has fully addressed the CMC deficiencies as outlined in the Division's Complete Response letter on February 22, 2013. With the exception of new reports of hypersensitivity that were suspected to be due to telavancin and the need for clarification to dosing administration instructions to avoid the risk of medication errors associated with the product foaming, there are no new clinical or statistical issues. The newly proposed labeling contains new contraindications, warnings and precautions that adequately describe the risk of hypersensitivity and clarifying instructions to prevent foaming of the reconstituted product.

As recommended in my February 1, 2013 review, when accompanied by a boxed warning in the prescribing information, indicating an increased risk of nephrotoxicity and in patients treated for nosocomial pneumonia with moderate/severe renal impairment (creatinine clearance less than 50 mL/min) an increased risk of mortality, telavancin should be approved for use only when susceptible isolates of *Staphylococcus aureus* are strongly suspected or confirmed and alternatives are not available.

13.2. Risk/Benefit Assessment

For the new indication of HABP/VABP, when weighed against the potential safety risks of increased risk of nephrotoxicity and 28-day mortality in patients with baseline renal dysfunction compared to vancomycin, the use of telavancin should be reserved for use when MRSA is proven or suspected and other antibacterial agents are not suitable, or in certain cases of MSSA, such as when β -lactams cannot be used due to allergy.

13.3. Recommendation for Postmarketing Risk Evaluation and Management Strategies

In addition to merging the goals and objectives of NDA 022-110 and NDA 022-407 (the two indications would share the same USPI), the proposed goals should be amended to reflect a creatinine clearance of 50 mL/min, rather than 30 mL/min, below which increased mortality was observed and risk may outweigh the anticipated benefit. The REMS should also include an additional goal of reducing the risk of nephrotoxicity, and inform HCPs regarding the potential risks of nephrotoxicity, and the increased mortality that was observed, particularly in association with moderate/severe baseline renal insufficiency, congestive heart failure and the concomitant use of nephrotoxic agents.

13.4. Recommendation for other Postmarketing Requirements and Commitments

The Applicant has acknowledged previous postmarketing requirements and commitments. Once approved, depending on when the product becomes available, the Applicant will need to include an updated timetable for completion of the Pediatric Studies.

13.5. Recommended Comments to Applicant

No additional comments.

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

/s/

BENJAMIN D LORENZ
06/17/2013