

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022407Orig1s000

OTHER ACTION LETTERS



NDA 22-407

COMPLETE RESPONSE

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated January 23, 2009, received January 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 250 mg and 750 mg.

We acknowledge receipt of your amendments dated July 12, August 9 and 14, October 17, November 2, 9 and 16, December 5, 7, 14 and 19, 2012, January 4 (4), and 9 and February 7 (2), 10 and 20, 2013.

The July 12, 2012, submission constituted a complete response to our December 21, 2010, action letter.

This new drug application provides for the use of VIBATIV for the treatment of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates) when alternative treatments are not suitable.

We have completed our review of this application, as amended, and we have determined that, from a clinical and statistical perspective, the data submitted to the Agency are adequate to demonstrate the safety and efficacy of the product for the indication under review (Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia). The application is not approvable however, because it does not meet the standards for approval under Section 505 of the Federal Food Drug & Cosmetic Act (FD&C Act). Specifically, as provided in 505(d), the Agency will refuse to approve the application if “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity” of the product. See 21 CFR 314.110(a); 314.125(b)(1).

Your NDA indicates that [REDACTED] (b) (4) will manufacture telavancin at [REDACTED] (b) (4) facility in [REDACTED] (b) (4). FDA has determined that [REDACTED] (b) (4) has violated the FD&C Act by manufacturing, processing, packing, labeling, holding, and distributing drug products in violation of current good manufacturing practice (“CGMP”) at its [REDACTED] (b) (4) site.

On [REDACTED] (b) (4), United States District Court for the [REDACTED] (b) (4) approved a Consent Decree of Permanent Injunction against [REDACTED] (b) (4) that precludes [REDACTED] (b) (4) from, among other things, manufacturing, processing, packing, labeling, holding, or distributing non-medically necessary drugs until a remediation plan has been implemented and numerous conditions are met.

FDA is unable to approve an application in the absence of an adequate manufacturing facility and process. Before NDA 22-407 can be approved, it will be necessary for you to have a manufacturing facility that has methods, facility and controls that are adequate to preserve the drug's identity, strength, quality, purity, stability, and bioavailability.

LABELING

The attached draft labeling reflects the Agency's current assessment of your application. We note that the attached draft labeling, carton and immediate container labels and Medication Guide submitted by you are subject to revision until the application is otherwise approved. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Should this application be approved, we anticipate deferral of your pediatric studies for ages 0 to 16 years for this application because this product would be considered ready for approval for use in adults and pediatric studies would not have been completed.

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

Any additional specific details of these required pediatric studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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)].

We acknowledge receipt of your proposed REMS, included in your submissions dated January 9, and February 7, 2013, and amended on February 11, 2013, which contain a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for VIBATIV (telavancin), if it is approved, to ensure that the benefits of the drug outweigh the risk(s) of an increased risk of mortality seen in patients with HABP/VABP who had creatinine clearance \leq 50ml/min, and risk of fetal developmental toxicity. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,
{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
Draft Content of Labeling
Draft Medication Guide
Draft REMS

42 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/

KATHERINE A LAESSIG
02/22/2013



NDA 22-407

COMPLETE RESPONSE

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated January 23, 2009, received January 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIBATIV (telavancin) for injection, 250 mg and 750 mg.

We also acknowledge receipt of your amendments dated June 30, July 6 and 28, August 5, 11, 23 and 26, September 1, 9, 13, 28 and 30, October 8, November 1, 12, 19 and 30, and December 3, 2010.

The June 30, 2010, submission constituted a complete response to our November 23, 2009, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically:

1. The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia. While a substantial amount of missing mortality data has been recovered and provided for analysis, the analysis in the population of interest (i.e. patients with nosocomial pneumonia caused by Gram positive bacteria) in Study 0015 does not demonstrate

noninferiority of telavancin relative to vancomycin. When the same analysis population was assessed in Study 0019, the observed treatment difference in 28-day all-cause mortality rates is 2.0% (telavancin: 24.3%; vancomycin: 22.3%) and the upper bound of the 95% CI is 10.0%, (-6.1%, 10.0%), and does not provide sufficient evidence for the noninferiority of telavancin to vancomycin.

2. In addition, the method of selection of patients did not provide adequate assurance that they had the disease being studied due to uncertainties with respect to interpretations of chest radiographs and adequacy of respiratory tract specimens.
3. Your analysis method that compares the telavancin-treated patients from your Phase 3 trials to the historical studies of patients receiving inadequate, inappropriate, and delayed therapy is problematic. Specifically, the baseline characteristics of the patients in the telavancin trials patients are not comparable to those in the historical control groups.
4. The pooling of patients across the two Phase 3 trials is not appropriate because subjects in study 0015 had more potential risk factors for mortality (e.g., diabetes mellitus and renal impairment/failure) than the subjects in study 0019.
5. The inclusion of post-hoc selected prognostic risk factors for mortality in the analyses is not acceptable because they may bias the results.
6. The diagnosis of renal failure was left to the discretion of the investigator, and in some cases it was unclear whether some of the patients may have had acute as well as chronic renal failure. For patients with potential risk factors, renal status should have been more specifically defined by standardized measures at entry and followed more closely for at least 28 days.

Before the application can be approved, it will be necessary for you to perform at least two adequate and well-controlled studies to demonstrate the efficacy and safety of telavancin in patients with hospital-acquired bacterial pneumonia.

- The inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever > 38°C, leukocytosis or leukopenia, and purulent respiratory secretions.
- Chest radiograph interpretation should be performed by a qualified health care provider (i.e., radiologist, pulmonologist, intensive care physician) not involved in enrollment of patients in the trial.
- Uniform criteria should be applied to assess the quality of respiratory specimens for culture and subsequent pathogen identification.
- The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

- For patients with potential risk factors, renal status should be specifically defined by standardized measures at entry and followed more closely for at least 28 days.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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NDA 22-407
Page 4

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Reference ID: 2881952

Reference ID: 3335610

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

/s/

KATHERINE A LAESSIG
12/21/2010

Reference ID: 2881952

Reference ID: 3335610



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-407

COMPLETE RESPONSE

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

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We also acknowledge receipt of your amendments dated February 6, March 26, April 15 and 17, May 1, 6, 11, 13 (2) and 15, June 9, 10, 17 and 19, July 8, 15, 22, 24 and 29, and August 7, 12, 14, and 16, 2009.

We also acknowledge receipt of your amendments dated September 1, and October 5 and 29, 2009, which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia (NP). Both trials were designed and powered for a clinical response endpoint. However, as discussed at the FDA Anti-Infective Drugs Advisory Committee meeting for NDA 22-171 on July 16, 2008, the published scientific literature (identified to date) does not permit interpretation of non-inferiority studies of antibacterial drugs for NP and Ventilator-Associated Pneumonia (VAP) using clinical response as the primary endpoint due to the lack of scientific data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. Published historical evidence will only permit interpretation of non-inferiority trials for NP and VAP using all-cause mortality as the primary endpoint.

In this application, all-cause mortality was a secondary endpoint. The two submitted trials were of insufficient size and statistical power to identify a difference in all-cause mortality between telavancin and comparator-treated patient groups if such a difference existed. The submitted mortality data were incomplete and at this time, it is unclear whether an analysis of the all-cause mortality data derived by pooling the results of Studies 0015 and 0019 will be sufficient to determine the efficacy and safety of telavancin. Differences in the distribution of baseline prognostic factors for mortality across the two trials may preclude pooling; if, upon further review, pooling of the mortality data is determined to be acceptable, the collective all-cause mortality data may only be of sufficient size and statistical power to be considered analogous to one adequately sized trial with a mortality endpoint and additional evidence supporting safety and effectiveness would still be required.

In order to resolve these deficiencies:

1. Submit all available all-cause mortality data and account fully for any censored information. In addition, provide a listing of the patients by trial in which mortality status is not known up to the end of the mortality reporting window. The listing should include study number, subject ID, randomized treatment group, actual treatment group, and last Study Day that mortality status is known. A tabulation of the subjects whose mortality status is unknown should also be provided by trial and treatment group, as well as a summary that presents the distribution of the Study Day where censoring occurs by trial and treatment group.
2. Provide a scientific rationale for pooling all-cause mortality data across the two clinical trials. The rationale should address the consistency of the treatment difference for telavancin relative to vancomycin across the trials given the difference in the distribution of baseline prognostic factors for mortality between the two trials and the proportion of subjects whose mortality status is censored.
3. In design of the new clinical trials for the NP indication, consider the following:
 - a) The study population should contain patients with a high likelihood of having the disease of interest. Therefore, the inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever $> 38^{\circ}\text{C}$, leukocytosis or leukopenia, and purulent lower respiratory tract secretions.
 - b) Chest radiograph interpretation should be performed by a blinded healthcare provider, preferably a radiologist or pulmonologist, not directly involved in assessment of the patient for enrollment or during subsequent care.
 - c) Uniform criteria should be applied to identify the quality of sputum and endotracheal aspirate specimens for culture and subsequent pathogen identification.
 - d) The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

4. Data from the phase 3 trials conducted in support of this NDA, do not provide adequate information for the analysis of telavancin activity against penicillin non-susceptible isolates of *Streptococcus pneumoniae*. It is suggested that additional data from studies enriched to include subjects infected with penicillin non-susceptible isolates of *S. pneumoniae* be submitted.
5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.
6. In accordance with 21 CFR 314.55(b), a pediatric drug development plan for this indication, along with proposed timelines for submission of these studies must be submitted. A deferral has been requested in all pediatric age groups for this indication (NP/Hospital-Acquired Pneumonia (HAP)) pending FDA review and approval in adults. However, a pediatric plan for NP/HAP has not been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

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Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	ORIG-1	THERAVANCE INC	VIBATIV

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

/s/

KATHERINE A LAESSIG
11/23/2009