DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-407
NDA 22-110/S-003

NDA APPROVAL
SUPPLEMENT APPROVAL - REMS MODIFICATION

Theravance, Inc.
Attention: Rebecca Coleman, Pharm.D.
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 (FDCA) for VIBATIV (telavancin) for Injection, 250 mg and 750 mg.

We also acknowledge receipt of your amendments dated March 13 and 27, June 5, 11 (2), 12, 17 and 20, 2013, to NDA 22-407, and your risk evaluation and mitigation strategy (REMS) assessment dated June 18, 2013, submitted to NDA 22-110/S-003.

The March 13, 2013, submission constituted a complete response to our February 22, 2013, action letter for NDA 22-407.

NDA 22-407 provides for the use of VIBATIV (telavancin) 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 -resistant isolates) when alternative treatments are not suitable.

NDA 22-110, supplement 003, provides for a proposed modification to the approved risk evaluation and mitigation strategy (REMS) for VIBATIV (telavancin).

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide) Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the carton and immediate-container labels submitted on January 7, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-407**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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.

We are deferring submission of your pediatric studies for ages 0 to 17 years for this application until June 30, 2019, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These studies are listed below:

1995-001: Conduct a single dose pharmacokinetic (PK) trial in patients ≥1 to 17 years old.

Final Protocol Submission:	12/13
Trial Completion:	9/14
Final Report Submission:	3/15

1995-002: Conduct a single dose PK trial in neonates/infants 0 to <1 year old.

Final Protocol Submission:	12/14
Trial Completion:	9/15
Final Report Submission:	3/16

1995-003: Conduct a Phase 3, randomized, comparator-controlled trial of telavancin in children from birth to 17 years old with gram positive infections.

Final Protocol Submission:	12/15
Trial Completion:	12/18
Final Report Submission:	6/19

Submit the protocols to your IND 60,237, with a cross-reference letter to NDA 22-110.

Reports of these required pediatric postmarketing studies must be submitted as a supplement to NDA 22-110 with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for VIBATIV (telavancin) for injection was originally approved under NDA 22-110 on September 11, 2009, and a REMS modification was approved on July 27, 2011. Upon action, NDA 22-407 will be administratively closed and NDA 22-110 will be the primary application for VIBATIV (telavancin) for injection. Therefore, the proposed REMS submitted to NDA 22-407 constitutes a proposed modification to the approved REMS under NDA 22-110.

Your proposed modifications to the REMS consist of:

- Addition of a new goal to inform healthcare professionals about the increased risk of mortality associated with VIBATIV in patients with pre-existing creatinine clearance of ≤ 50 mL/min being treated for HABP/VABP.

- A revised Medication Guide that includes information about the risk of increased mortality seen in patients with HABP/VABP who had pre-existing creatinine clearance ≤ 50 mL/min.

- A revised Dear Healthcare Provider (DHCP) letter that includes information about the increased risk of mortality seen in patients with HABP/VABP who had pre-existing creatinine clearance ≤ 50 mL/min, the risk of nephrotoxicity, and risk of fetal developmental toxicity.

- The DHCP letter must be issued 60 days, 6 months, 1 and 2 years, following the date of the approval of this REMS modification.

Your proposed REMS, submitted on June 18, 2013, and appended to this letter, is approved. The modified REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments has been modified to be 18 months, 3 years, and 7 years from the date of the approval of this REMS modification.

The revised REMS assessment plan should include, but is not limited to, the following:

a. Surveys assessing healthcare professionals' and patients' understanding of the potential risk of fetal developmental toxicity if women are exposed to VIBATIV (telavancin) while pregnant.

b. Surveys assessing healthcare professionals' understanding of:

   1. the increased risk of mortality in VIBATIV (telavancin)-treated patients with pre-existing creatinine clearance of ≤ 50 mL/min being treated for hospital acquired bacterial pneumonia (HABP)/ ventilator-associated bacterial pneumonia (VABP).
   2. the need to monitor renal function (serum creatinine and creatinine clearance) prior to initiating therapy with VIBATIV (telavancin), during therapy (every 48 to 72 hours or more frequently if clinically indicated), and at the end of therapy.
   3. the need to perform a serum pregnancy test prior to initiating therapy with VIBATIV (telavancin) in Females of Reproductive Potential (FRP).
   4. the need to counsel FRP, including those being treated in the outpatient setting, about pregnancy prevention and use of effective contraception during VIBATIV (telavancin) use.

c. A summary and analysis of maternal and fetal outcomes for all reported pregnancies (from any data source) including:

    1. a cumulative number of all fetal exposures and outcomes reported for all reported pregnancies and;
    2. 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 the Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Since NDA 22-407 will be administratively closed, all REMS correspondences and submissions should be submitted to NDA 22-110.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-110 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 22-110 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-110
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-110
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

An authorized generic drug under NDA 22-110 must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Please submit all 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original **NDA 22-110** for this drug product, not to NDA 22-407. In the future, do not make submissions to NDA 22-407 except for the final printed labeling requested above.

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):
Content of Labeling
Medication Guide
REMS

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
06/21/2013