CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-110

NDA APPROVAL

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 December 6, 2006, received December 19, 2006, 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 submissions dated March 13 (2), 20 and 25, May 5 (2), 13 and 29, June 1, 10 and 12, July 6, 13, 15, 17, 27, 28, 29 (2) and 30, and August 6, 12, 17, 18, 25 (2), 27 (2) and 28, and September 2 and 4, 2009.

The March 13, 2009, submission constituted a complete response to our action letter dated February 20, 2009.

This new drug application provides for the use of VIBATIV (telavancin) for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for ages 0 to 17 years for this application until December 31, 2014, because this product is ready for approval for use in adults (b) (4)

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This study is listed below.

1529-001: Deferred pediatric study under PREA for the treatment of cSSSI in pediatric patients ages 0 to 17 years.

Final Report Submission: December 31, 2014

Submit final reports to this NDA. Use the following designator to prominently label all submissions:

"**Required Pediatric Assessment(s)**"

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)).

Your proposed REMS, submitted on September 4, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

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

a. A survey of healthcare providers and patients' understanding of the serious risks of VIBATIV (telavancin)

b. 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
    2. A root cause analysis to investigate the pregnancies reported with VIBATIV (telavancin) use in the U.S.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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 FDCA.

Prominently identify submissions containing 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:

- **NDA 022110 REMS ASSESSMENT**

- **NEW SUPPLEMENT FOR NDA 022110**
  PROPOSED REMS MODIFICATION
  REMS ASSESSMENT

- **NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022110**
  REMS ASSESSMENT
  PROPOSED REMS MODIFICATION (if included)

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

POSTMARKETING REQUIREMENT UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of serious risks of teratogenicity or bacterial resistance.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1529-002: A pregnancy registry must be established to evaluate the safety of this product in pregnant women and their offspring. You will be required to evaluate the safety of VIBATIV (telavancin) use during pregnancy by developing and maintaining a prospective, observational pregnancy exposure registry study conducted in the United States. The study should compare pregnancy and fetal/infant outcomes of women exposed to VIBATIV (telavancin) during pregnancy to an unexposed control population. The registry should identify and record major congenital anomalies, minor anomalies that occur in groups of three or more, spontaneous

abortions, stillbirths, elective terminations, functional deficits in the child, and any serious pregnancy outcomes. Infants should be assessed through at least the first year of life. For more information, please refer to the FDA Guidance for Industry on Establishing Pregnancy Exposure Registries (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf). Your proposed Pregnancy Registry protocol submitted August 12, 2009, should be implemented prior to product launch.

The timetable you submitted on August 28, 2009, states that you will conduct this study according to the following timetable:

Final protocol Submission:	by 8/2009 (completed)
Interim Report:	by 9/2010, then annually
Study completion date:	by 6/2019
Final Report Submission:	by 12/2019

1529-003: Conduct a prospective study over a five-year period after introduction of VIBATIV (telavancin) to the market to determine if decreased susceptibility to VIBATIV (telavancin) is occurring in the target population of bacteria that are in the approved VIBATIV (telavancin) package insert. Provide a detailed study protocol describing the study to the Agency for review and comment before commencing the study.

The timetable you submitted on August 28, 2009, states that you will conduct this study according to the following timetable:

Final protocol Submission:	by 1/2010
Interim Report Submission:	by 3/2011, then annually
Study Completion Date:	by 12/2014
Final Report Submission:	by 5/2015

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENT

We remind you of your postmarketing commitment in your submission dated August 28, 2009:

1529-004: In order to determine if there may be some effect of renal function on the biological activity of VIBATIV (telavancin) that may explain the decreased efficacy of telavancin in patients with renal impairment, you have agreed to conduct the following:

a. Compare results obtained with the current analytical assay for determining concentrations of telavancin in plasma to results obtained with a bioassay method for patients with normal renal function, severe renal impairment (creatinine clearance <30 mL/min), and end-stage renal disease receiving hemodialysis.
b. The bioassay is to be reproducible with appropriate controls developed to determine if the test is performing correctly at the time subject specimens are tested.
c. Subjects are to be dosed per the Phase 3 cSSSI clinical trial protocols.
d. Enroll sufficient subjects with normal renal function, severe renal impairment, and end-stage renal disease receiving hemodialysis in the trial to obtain data from 15 evaluable patients for each subject population.

Final protocol Submission:	by 1/2010
Trial Completion Date:	by 2/2011
Final Report Submission:	by 6/2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each trial. Prominently identify all submissions, including supplements, with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKETING COMMITMENT FINAL REPORT**
- **POSTMARKETING COMMITMENT CORRESPONDENCE**

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling submitted September 2, 2009, and Medication Guide submitted August 18, 2009. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-110**."

We request that the revised 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 container labels that are identical to the carton and immediate container labels submitted on July 13, 2009, 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 titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. 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 22-110**." 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.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

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

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Office Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: FDA Approved Labeling Text
Medication Guide
REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22110	ORIG-1	THERAVANCE INC	TELAVANCIN

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

/s/

EDWARD M COX
09/11/2009