CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	09/11/2009
From	Edward M. Cox, MD, MPH
Subject	Office Director Decisional Memo
NDA #	22-110
Applicant Name	Theravance, Inc.
Date of Submission	3/16/2009
PDUFA Goal Date	9/16/2009
Proposed Proprietary Name / Established (USAN) Name	Vibativ telavancin hydrochloride
Dosage Forms / Strength	lyophilized powder for injection
Proposed Indication	Treatment of complicated skin and skin structure infections
Action:	**Approval**

Telavancin is a lipoglycopeptide antibacterial agent derived from vancomycin studied in the treatment of complicated skin and skin structure infections (cSSSI). NDA 22-110 was initially submitted December 19, 2006, and received an approvable (AE) action on October 19, 2007. The deficiencies in the October 2007 AE letter included (1) deficiencies in cGMP identified in inspections of the Ben Venue facility in Bedford, Ohio, (2) financial disclosure forms that were not provided for three sub-investigators, (3) additional information on the benefit to risk ratio for telavancin including decreased cure rates in patients with decreased renal function and elderly patients, an imbalance in serious renal and vascular adverse events, effect on QTc interval, teratogenicity in animals, and insufficient information on dosing in patients with a creatinine clearance (CrCl) of less than 10 mL/min. The October 2007 AE letter also asked for available additional information on resistant organisms.

Theravance submitted a complete response on January 21, 2008. The application was scheduled to be presented to the Anti-Infective Drugs Advisory Committee on February 27, 2008, however, questions arose regarding inspectional findings from an inspection of one of the investigator sites in the first round of inspections and the clinical trial monitoring by a contract research organization (CRO) that could potential impact data integrity. The February 27, 2008, Advisory Committee meeting was cancelled just days before the meeting, pending further evaluation of these inspectional findings.

During the second cycle, the cGMP issues at the Ben Venue facility in Bedford, Ohio were addressed. The missing financial disclosure forms were provided and found to be acceptable. Some additional information on the noted safety issues and proposed labeling were provided.

The findings and questions from the first round of inspections of the clinical trials led to additional clinical trial site inspections. The total number of sites inspected by DSI for this application included 11 clinical trial sites, a CRO involved in the monitoring of the trial, and the applicant. The findings of non-compliance with GCP from the first round of inspections were either not seen or were found in only isolated instances in subsequent inspections. DSI's

recommendation is that overall, the inspectional findings support acceptable adherence to GCP for the pivotal clinical studies. The data that are considered unreliable are the efficacy data from site 38091, the two sites where the Applicant's audit revealed questions about monitoring (Sites 37004 and 38020) and ECG data from sites 38016 and 38163.

As noted in the Clinical and Statistical reviews from the second cycle, the data from the two phase 3 trials in cSSSI provide evidence of the noninferiority of telavancin to vancomycin in cSSSI. Additional analyses excluding patients with abscess, because of the uncertainty of treatment effect in patients with abscess, also found that the results support the finding of noninferiority.

Telavancin was presented to the Anti-Infective Drugs Advisory Committee meeting on November 19, 2008. The Committee voted that the safety and effectiveness of telavancin for the treatment of cSSSI had been demonstrated (Yes: 21, No 5). The Committee also recommended that the product labeling include information regarding the effect on the QT interval, renal toxicity, and teratogenic effects. On the question of whether there are clinical situations when the benefits of telavancin use in a pregnant woman would outweigh the risks, the Committee voted Yes 18, No 5, and abstain 3. The Committee also voted Yes 25, No 1, on the question of whether a risk management strategy was needed to prevent unintended use in pregnant women and described elements to consider in a program to manage risks.

Information in the complete response was provided for patients with renal adverse events from clinical trials in patients with hospital acquired pneumonia (HAP), however additional details were needed in order to assess renal function in patients who experienced these adverse events. Similarly, additional follow-up data were needed on patients who experienced a doubling of creatinine in the cSSSI trials. In order to manage and inform of the risks of telavancin, specifically including teratogenicity, a risk management program would need to be developed. Development of a program to manage the risks of telavancin is also consistent with the recommendations of the Advisory Committee.

For the second cycle, a complete response letter was issued on February 20, 2009, which cited the need for a Risk Evaluation and Mitigation Strategy that included a Medication Guide, a communication plan, and a timetable for assessing the program. Additional information on patients with serious renal adverse events needed to be provided for patients enrolled in the HAP trials and for patients who experienced a doubling of creatinine in the cSSSI trials. The complete response letter also requested that information on the risk of teratogenicity be incorporated in a boxed warning in product labeling and a warning regarding the potential for nephrotoxicity be included.

The applicant provided a response to the February 20, 2009, Complete Response letter received on March 16, 2009.

The review team has reviewed the issues in detail in their respective disciplines. For a detailed discussion of the third cycle reviews for NDA 22-110, the reader is referred to the individual discipline specific reviews and the Deputy Division Director's review and the Deputy Division Director for Safety's review, which summarize key issues in the NDA submission. In addition,

the reader is also referred to reviews from the previous cycles for NDA 21-110. This memorandum will focus on selected issues from the application from this cycle.

The evaluation from the Chemistry Manufacturing Controls standpoint for this review cycle recommends approval. As noted in the CMC review, the Ben Venue Laboratories facility, (Bedford, Ohio) is classified as Acceptable by the Office of Compliance.

The applicant provided additional information on renal adverse events from patients in the HAP studies. In one of the two HAP trials, renal adverse events led to discontinuation of study therapy more commonly in the telavancin arm of the study. Changes in serum creatinine (Cr) from baseline to a Cr $\geq$ 133 µmol/L and at least 50% greater than baseline in patients with normal Cr at baseline were more common in telavancin than comparator treated patients.

Additional follow-up information from some patients in the complicated skin trials who experienced renal adverse events has been provided. Follow-up information beyond the test-of-cure visit in patients who received telavancin 10 mg/kg and had an increase in creatinine 2 times baseline was available for 7 of the 19 patients who had such an increase. Two of the 7 had resolution of their increased creatinine. Five of the 7 did not have resolution of their increased creatinine during the time period of follow-up.

Information on renal adverse events has been incorporated in the product labeling, including a warning on nephrotoxicity. In addition, analysis of the cure rates by baseline renal function for the complicated skin studies is also incorporated in the product labeling.

A Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide, a communication plan in the form of a Dear Healthcare Provider Letter that will be distributed, prior to commercial launch, 6 months, 1 year and 2 years after product approval, and a timeline for submission of assessments of the REMS has been provided. The Medication Guide and product labeling has been reviewed by the Pregnancy and Maternal Health Team (PMHT), DDMAC, and DRISK. The product labeling, which includes a boxed warning regarding fetal risk, and the Medication Guide provide information describing the risks of telavancin.

As a postmarketing requirement the applicant is required to establish a pregnancy registry to evaluate the safety of telavancin in women and their offspring that are exposed to telavancin. The pregnancy registry protocol has been reviewed by the PMHT. Theravance should implement their pregnancy registry prior to product launch.

The approval also includes a postmarketing requirement to monitor rates of resistance among indicated bacteria on an annual basis for five years and a postmarketing commitment to further evaluate effects of renal function on the biological activity of telavancin.

DSI has also provided a clinical inspection summary of some additional clinical trial sites for the HAP trials in NDA [redacted] The DSI assessment of these inspections is that the data appear to be reliable and do not raise concerns that would have implications for the cSSSI trials. b(4)

Pediatric studies required in accordance with PREA are deferred at this time and a final report submission on these studies is expected by December 31, 2014.

Summary
I concur with the recommendations for approval from the review team and the Deputy Division Director. The safety and efficacy data evaluating Vibativ (telavancin) support an acceptable risk benefit profile for the treatment of complicated skin and skin structure infections (cSSSI). The product labeling and Medication Guide provide information on the benefits and risks of the telavancin. The approval includes requirements for a study of telavancin in cSSSI in the pediatric population under PREA, a REMS including a Medication Guide, a communication plan, and a timeline for submission of assessments of the REMS, postmarketing requirements for implementation of a pregnancy registry and a study to monitor rates of resistance among indicated pathogens. The approval also includes a postmarketing commitment to evaluate the effect of renal function on the biological activity of telavancin.

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/s/

EDWARD M COX
09/11/2009