CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 08-25-09

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

SUBJECT: Deputy Division Director's Summary Review Memo for NDA 22-110 Class II resubmission, telavancin lyophilized powder for reconstitution and injection (Proposed Tradename VIBATIV™)

1.0 Background/Regulatory History

The applicant, Theravance Inc., has submitted a complete response to an approvable letter for NDA 22-110 in support of telavancin for the requested indication of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram positive bacteria. This is the third review cycle for this application. The original NDA was submitted December 19, 2006, and received a 10-month standard review. The Agency issued an approvable letter on October 19, 2007. The deficiencies noted in the action letter for the first review cycle included deviations from cGMP of the Ben Venue manufacturing facility in Bedford, OH, missing financial disclosure information for three sub-investigators, and several issues that called into question the benefit-to-risk ratio of telavancin. A complete response was submitted by Theravance on January 21, 2008. Since the action date for the original application occurred after passage of the Food and Drug Administration Amendments Act (FDAAA) on September 27, 2007, a meeting of the Anti-infective Drugs Advisory Committee (AIDAC) was convened to discuss telavancin on November 19, 2008 as it is a new molecular entity. The proceedings of the AC meeting are discussed in the memo from the second review cycle. The applicant was issued another complete response on February 20, 2009. The Agency requested that the applicant:

1. Submit more comprehensive follow-up data and analyses performed on patients enrolled in the hospital acquired pneumonia trials (HAP), Studies 0015 and 0019, in whom adverse events (AE) related to renal impairment were observed.

2. Follow-up of patients enrolled in the complicated skin and skin structure infection studies (cSSSI), Studies 0017 and 0018, in whom elevation in serum creatinine (Cr) to greater than two times their baseline value was observed.
3. In accordance with provisions in the Food and Drug Administration Amendments Act of 2007, submission of a proposed Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of telavancin in treatment of cSSSI outweigh the risk of teratogenicity (seen only in nonclinical animal data, to date). The REMS submission was to include a Medication Guide as provided for by 21 CFR Part 208 and a communication plan for healthcare providers to provide for dissemination of information to patients in the form of a Dear Health Care Provider Letter.
4. Establish a pregnancy registry to identify any potential signal for teratogenicity in humans as a post-marketing requirement.
5. Updated draft product labeling in structured product labeling (SPL) format.

The remainder of this memo will outline the new information contained in the resubmission by discipline. Note that no new information was submitted for CMC, pharmacology/toxicology, clinical pharmacology, microbiology or efficacy.

2.0 Summary of Efficacy

Please refer to the summary memos from the two previous cycles, as well as the clinical and biometrics reviews of Dr. Janice Pohlman and Dr. Scott Komo, respectively, for additional information. Both reviewers have recommended this application for approval. Based on the deliberations of the November 2008 AIDAC meeting and our internal review of the evidence of treatment effect of antibacterials for cellulitis, erysipelas, and wound infections, a noninferiority margin of 10% is justified. However, no margin can be justified for major abscesses based on the limited information available in the literature. Since subjects with major abscesses constituted approximately 43% of study participants in both pivotal trials 0017 and 0018, a sensitivity analysis was performed by Dr. Komo that removed subjects with major abscess from the efficacy analysis populations. The lower bound of the 95% confidence interval for the co-primary populations of all-treated (AT) and clinically evaluable (CE) was less than -10% for all but the CE population of study 0018. The lower bound in that study was -12.3% and the point estimate was -5.0%. As Dr. Komo notes in his review, Study 0018 had low power (29%) to demonstrate noninferiority assuming the observed rates are the actual rates. The clinical and biometrics reviewers have previously determined that the Applicant has demonstrated the efficacy of telavancin for cSSSI, as have the AIDAC members at the November 2008 meeting.

An additional efficacy issue that was identified during the first review cycle was that of an apparent decline in efficacy with worsening renal function among

patients treated with telavancin. Similar findings were not noted among patients treated with vancomycin. Although the HAP application is still under review, in at least one of the phase 3 studies, there appears to be a correlation with worsening renal function and increased mortality. These cSSSI findings will be reported in the package insert with a statement that these data should be considered when selecting antibacterial therapy for patients with CrCl ≤ 50 mL/min.

3.0 Summary of Safety

Please refer to Dr. Pohlman's clinical review and Dr. Nambiar's Deputy Director for Safety memo for additional details. The majority of the deficiencies in the February 2009 CR letter were related to the findings of nephrotoxicity and the risk of teratogenicity in fetuses of pregnant women exposed to telavancin therapy. To address the first two deficiencies related to nephrotoxicity, the applicant included wording in the Warnings and Precautions section of the label. In addition, a summary of renal adverse events and laboratory abnormalities related to nephrotoxicity in the HAP trials, along with a cross-reference to the telavancin HAP NDA (NDA ( )) submitted by Theravance, Inc. on ( ) ( ) was cross-referenced to provide additional data on renal impairment observed in those studies. Information regarding the potential for nephrotoxicity with telavancin use, particularly in patients with underlying renal insufficiency or receiving concomitant nephrotoxic medications will be described in the package insert in the Warnings and Precautions section. The AIDAC members also expressed interest in some type of post-marketing study to evaluate the decline in efficacy among patients with renal insufficiency and nephrotoxicity. However, after extensive discussion internally, we were unable to conceive of a study design that would be informative. There was also concern that there may not be equipoise to study telavancin in subjects with underlying renal impairment who are known to be at a higher risk of telavancin-associated nephrotoxicity. The decrease in efficacy is also described in the Warnings and Precautions section of the package insert.

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As required by the CR letter, the Applicant submitted a Risk Evaluation and Mitigation Strategy (REMS) with the goal of reducing unintended exposure of pregnant women to telavancin. The purposes of the REMS are:

- To educate healthcare professionals (HCPs) and patients on the potential risk of fetal developmental toxicity if women are exposed to telavancin while pregnant
- To inform HCPs that a serum pregnancy test should be performed before initiating therapy with telavancin in women of childbearing potential
- To inform HCPs that women of childbearing potential, including those being treated in the outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during telavancin use

- To inform HCPs and patients about the pregnancy registry for patients exposed to telavancin during pregnancy

The components of the REMS include a Medication Guide that will be available for distribution with each telavancin prescription. In addition, there is a communication plan which consists of a Dear Healthcare Provider letter (DHCP), a description of the audience for the communication plan, and a schedule for when and how the DHCP letter will be distributed. The DHCP letter will also include information about the pregnancy registry. The communication plan will be distributed prior to commercial distribution, 6 months, 1 year, and 2 years after product approval. The Applicant will provide formal assessments of the REMS by 18 months, 3 years, and 7 years after approval. The pregnancy registry is a post-marketing requirement that will be useful to track any adverse fetal outcomes that result from exposure to telavancin in pregnant women. It will be a voluntary, prospective, observational cohort study of 300 women exposed to telavancin at any time during pregnancy. The study will be conducted in the U.S.

4.0 Summary of Other Regulatory Issues

DSI has stated that there are no new data integrity issues with the cSSSI application. There were 5 sites for which data integrity was questionable in the cSSSI studies, and that data has been excluded from all analyses. However, because a complaint was made to the Agency that the sponsor had manipulated data in the HAP NDA (

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) Dr. Mulinde's clinical inspection summary of the HAP trials concludes that the data in support of the HAP NDA appear reliable. The final classification for the CRO, ( ) is NAI, while for one of the six clinical sites, that of Dr. Lee, is VAI. The remaining classifications are preliminary, pending review of the EIRs. Notably, the preliminary classification for Theravance is NAI.

The proposed pediatric development plan was discussed with the Pediatric Research Committee (PeRC) on October 8, 2008. DMEPA and DDMAC have consulted on the proprietary name and concluded that it is not vulnerable to name confusion that could lead to medication errors, and is, therefore, acceptable.

5.0 Recommendation

I concur with the recommendations of the review team that the application may now be approved, as the Applicant has demonstrated substantial evidence of safety and efficacy for the requested indication and has adequately addressed the deficiencies from the February 2009 CR letter.

Katherine A. Laessig, M.D.

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/s/

KATHERINE A LAESSIG
09/10/2009