CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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MATERNAL HEALTH TEAM (MHT) REVIEW

Date: August 7, 2009 **Date Consulted:** July 22, 2009

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Anti-Infective and Ophthalmology Products (DAIOP)

Drug: NDA 22-110, Vibativ (telavancin) Injection

Subject: Pregnancy Registry Protocol

Materials Reviewed: Theravance July 16, 2009 response to FDA recommendations on Vibativ (telavancin) Pregnancy Exposure Registry Protocol

Consult Question: Please review Theravance's July 16, 2009 response to FDA recommendations on Vibativ (telavancin) Pregnancy Exposure Registry Protocol (Protocol 9809-CL-1409).

BACKGROUND

On March 13, 2009, Theravance submitted a response to the Division of Anti-Infective and Ophthalmology Product's (DAIOP) complete response action letter dated February 20, 2009, for Vibativ (telavancin) injection (NDA 22-110). Vibativ contains telavancin hydrochloride, a purified lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. Telavancin's proposed indication is for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible gram-positive pathogens.

In the March 13, 2009 submission, Theravance provided a pregnancy exposure registry protocol for review as requested by FDA in a postmarketing requirement. DAIOP consulted the Maternal Health Team (MHT) and requested review of the pregnancy exposure registry protocol submitted by the sponsor. The MHT reviewed the protocol and provided recommendations to the Division (see review dated May 9, 2009). On July 1, 2009, DAIOP communicated to the sponsor (via facsimile) FDA's recommendations on the pregnancy registry protocol.

On July 16, 2009, the sponsor submitted a response to FDA's recommendations and a revised protocol. DAIOP consulted the MHT and requested review of the sponsor's response. This review summarizes and comments on the sponsor's response to recommendations they received on the protocol from DAIOP and the MHT.

REVIEW OF SUBMITTED DATA

Provided below is the sponsors response to each FDA recommendation on the telavancin pregnancy exposure registry protocol. A reviewer comment regarding the acceptability of the sponsor's response follows.

1. **FDA Recommendation - Primary Objective**
   The sponsor should revise their primary objective to include women exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception).

   Sponsor Response
   The synopsis and Section 2.1.1 of the protocol have been revised to incorporate this recommendation.

   Reviewer comment
   Based on labeling negotiations with the sponsor and because the elimination half life ($t_{1/2}$) of telavancin is about eight hours, the sponsor should not enroll women who become pregnant within seven days after their last Vibativ dose since Vibativ will have been eliminated from the body. The sponsor should revise their primary objective to include only women exposed to Vibativ at any time during pregnancy.

2. **FDA Recommendation - Secondary Objective**
The sponsor's secondary objective is to evaluate the effect of fetal exposure to Vibativ on infant development and milestones through 12 months of age. The sponsor should revise this objective to evaluate the effect of fetal exposure to Vibativ on pregnancy and fetal/neonatal outcomes and infant development milestones through 12 months of age.

Sponsor Response
The synopsis and Section 2.1.2 of the protocol have been revised to incorporate this recommendation.

Reviewer comment
The MHT finds the sponsor's response acceptable.

3. **FDA Recommendation - Definitions**
The sponsor defines spontaneous abortions as a fetal loss occurring at <22 weeks gestation and stillbirth as fetuses born dead at > 22 weeks gestation. According to the American College of Obstetricians and Gynecologists (ACOG), a spontaneous abortion is a fetal loss occurring at ≤20 weeks gestation, and a stillbirth is a fetal death at >20 weeks gestation. The sponsor should adopt these definitions for the registry.

Sponsor Response
The definitions for spontaneous abortion and stillbirth in Appendix 1 of the protocol have been modified to reflect this recommendation.

Reviewer comment
The MHT finds the sponsor's response acceptable. The sponsor's revised definitions are provided below:

- *Spontaneous Abortion - any loss of a fetus due to natural causes at less than or equal to 20 weeks gestation as determined from the estimated date of conception or by ultrasound as spontaneous abortion. If available, data from gross or pathological examination of the abortus or fetus will be documented.*
- *Fetal Death/Stillborn - fetuses born dead at greater than 20 weeks gestation as estimated based on the estimated date of conception or by ultrasound or weighing >500 grams.*

4. **FDA Recommendation - Outcomes**
The sponsor should include preterm birth (< 37 weeks gestation) and low birth weight (< 2,500 grams) as a study outcome. The sponsor should explain the need for distinguishing between "early and late fetal loss." There does not appear to be a logical reason to make this distinction when gestational age descriptors are more informative.

Sponsor Response
Preterm birth and low birth weight were added as variables in the synopsis and as outcomes in Section 7.4.2 of the protocol. The definition of fetal death/stillbirth in Appendix 1 was also modified; no distinction between early and late fetal loss will be made. [See above, Section 2.3].

Reviewer comment
The MHT finds the sponsor's response acceptable.

5. **FDA Recommendation - Sample Size**
The sponsor plans to enroll 300 women from the U.S. or Canada into the registry. The sponsor should provide a rationale for the sample chosen for the registry based on the demographics of the populations. In addition, the registry should enroll an adequate sample to fully evaluate the risk of birth defects. In order to obtain data that can be generalizable to both populations of women, it is recommended that the sponsor evaluate the data obtained on the planned enrollment of 300 women. If one population is underrepresented, or if the sample size is too small to allow an evaluation of the risk of birth defects, the registry should continue enrollment to obtain more data.

Sponsor Response
The protocol has been revised to limit enrollment to U.S. patients only. Sample size justification is provided in Section 7.1 of the protocol. The text has not changed from the previous version (originally provided in Section 7.3 of the Protocol dated March 12, 2009).

Reviewer comment
The MHT finds the sponsor's response acceptable. The sponsor will only enroll women from the United States. However, if a pregnancy exposure is reported from a country outside the United States, the report will be added to the registry database, but analyzed separately.

6. **FDA Recommendation - Use of Verbal Consent**
The sponsor should consider whether use of verbal consent at the time of initial telephone contact followed by written consent (where allowed by IRB and by regulations) might enhance recruitment and retention efforts.

Sponsor Response
Section 3.2 of the protocol allows for patients to enter with verbal consent. Written approval to release information will be obtained after verbal consent is obtained.

Reviewer comment
The MHT finds the sponsor's response acceptable.

7. **FDA Recommendation - Registry Awareness Activities**
It is recommended that the sponsor implement all of their suggested registry awareness activities to help facilitate registry enrollment. In addition, the sponsor should provide the Vibativ pregnancy registry contact information to the Organization of Teratology Information Specialists (OTIS). OTIS is a teratogen service that answers calls from women who have been exposed to a drug during pregnancy and provides information on the effects of drug exposure. A woman may call OTIS after exposure to Vibativ during pregnancy, and the OTIS counselor can inform the patient about the pregnancy registry.

Sponsor Response
Reference to OTIS was added to Section 4.1 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

8. **FDA Recommendation - Inclusion of Retrospective Reports**
The sponsor should provide detailed information on how the registry will obtain and include retrospective reports in their data analysis. If retrospective reports will be included in the registry, the analysis of outcomes should be stratified by type of report (i.e., prospective or retrospective).

Sponsor Response
Pregnancies reported with a known outcome at the time of the initial contact will be collected as retrospective cases and analyzed separately. The collection and analysis of retrospective reports were added to the protocol in Sections 3.1, 4, and 7.

Reviewer comment
The MHT finds the sponsor's response acceptable.

9. **FDA Recommendation - Secondary Contacts**
The sponsor plans to collect the name, address, and telephone number of a secondary contact for the patient. The secondary contact will reside outside the patient's home. If the PRS is unable to reach the pregnant woman, the secondary contact will be contacted. If possible, a third contact should be identified to decrease the number of patients lost to follow-up.

Sponsor Response
Collection of contact information for one or more secondary contacts was added to Section 4.4 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable. The FDA recommended that the sponsor collect contact information from a third secondary contact. However, the sponsor revised the protocol to state that the name, address, and telephone number of one or more secondary

contacts (who reside outside the patient's home) will be collected. This revision is acceptable.

10. **FDA Recommendation - Visits with other Healthcare Providers other than Obstetrician**
The sponsor should determine if the patient was seen by someone other than her obstetrician, such as a geneticist or maternal/fetal medicine specialist. If so, the sponsor should obtain outcome data from those healthcare practitioners as well.

Sponsor Response
Collection of outcome data from other healthcare practitioners was added to Sections 4.6 and 4.7 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

11. **FDA Recommendation - Obstetrical Complications**
The sponsor should determine if the patient experienced any obstetrical complications during the pregnancy from the obstetric healthcare provider.

Sponsor Response
Collection of obstetrical complications was added to Sections 4.6 and 4.7 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

12. **FDA Recommendation - Head Circumference**
Head circumference should be included in the infant characteristics that the sponsor obtains from the pediatric healthcare provider.

Sponsor Response
Collection of head circumference was added to Section 4.7 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

13. **FDA Recommendation - Congenital Anomaly as a Serious Adverse Event**
According to 21 CFR 312.32, the sponsor must report to FDA any serious and unexpected adverse events within 15 calendar days. Per 21 CFR 314.80, the sponsor must consider any congenital anomaly within the definition of a serious adverse event. The sponsor's protocol should be revised to reflect these reporting requirements.

Sponsor Response
Section 5 of the protocol was updated to include reporting requirements. Congenital anomalies will be considered a serious adverse event and reported to the FDA as per CFR 21 312.32 and 314.80.

Reviewer comment
The MHT finds the sponsor's response acceptable.

14. **FDA Recommendation – Adverse Event Reporting**
The sponsor should report all adverse events that occur in the final report.

Sponsor Response
All adverse events will be summarized and reported in the final report as per Section 5 and 7.4.3 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

15. **FDA Recommendation - Agreement before Discontinuing the Registry**
Before discontinuing the registry, the sponsor must obtain agreement from FDA.

Sponsor Response
A statement was added to Section 6 of the protocol indicating the sponsor will obtain agreement with FDA before discontinuing the registry.

Reviewer comment
The MHT finds the sponsor's response acceptable.

16. **FDA Recommendation - Independent Data Monitoring Committee**
The sponsor is encouraged to have an independent data monitoring committee (DMC) as described in the Guidance for Industry, Establishing Pregnancy Exposure Registries: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071639.pdf to ensure scientific integrity and appropriate patient protection.

Sponsor Response
Section 10 of the protocol describes the use of an Independent Data Monitoring Committee (DMC). More specific information will be provided in a separate DMC charter.

Reviewer comment
The MHT finds the sponsor's response acceptable.

17. **FDA Recommendation - Additional Data for Live Births and Fetal Deaths/Stillbirths**
For live births and fetal deaths/stillbirths, the sponsor should include data on - multiple birth pregnancy, small for gestational age, preterm delivery, and any information on fetal outcomes including congenital anomalies or other fetal abnormalities.

Sponsor Response
Section 7.4.2 of the protocol was updated to include analyses of these additional parameters.

Reviewer comment
The MHT finds the sponsor's response acceptable.

18. **FDA Recommendation - Stratification**
All outcomes should by stratified by population type (i.e., U.S. or Canadian). If the populations are similar, a combined analysis can also be performed.

Sponsor Response
Enrollment into the protocol will be limited to patients in the U.S., therefore stratification will not be necessary.

Reviewer comment
The MHT finds the sponsor's response acceptable.

19. **FDA Recommendation - Comparing to an Automated Database**
The sponsor should compare U.S. registry data to a U.S. automated database that contains linked medical records for both inpatient and outpatient care including pharmacy data.

Sponsor Response
Section 7.5 of the protocol addresses comparisons to other U.S. registry data/automated databases, including the use of a population-based birth defects surveillance system, such as the Metropolitan Atlanta Congenital Defects Program.

Reviewer comment
The MHT finds the sponsor's response acceptable. The sponsor will compare registry data to reporting rates from the Metropolitan Atlanta Congenital Defects Program (MACDP). Data from other pregnancy registries will also be used as appropriate. In addition, the sponsor will compare registry data to a cohort of women of childbearing age who received intravenous antibiotics other than Vibativ. This cohort will be identified using a U.S. automated database that contains linked medical records for both inpatient and outpatient care including pharmacy data. The database will allow identification of women who are pregnant at the time of antibiotic administration, and will contain linked records for the patient's offspring.

20. FDA Recommendation - Adverse Infant/Fetal Outcomes

For individual cases where adverse infant/fetal outcomes occur, the sponsor should determine the duration of drug exposure and the gestational weeks of exposure for any specific adverse infant/fetal outcomes.

Sponsor Response

A statement was included in Section 7.4.2 of the protocol to address this recommendation.

Reviewer comment

The MHT finds the sponsor's response acceptable.

21. FDA Recommendation - Chromosomal Abnormalities

The sponsor should analyze chromosomal abnormalities separately from other adverse pregnancy outcomes or malformations.

Sponsor Response

A statement indicating chromosomal abnormalities will be analyzed separately was included in Section 7.4.2 of the protocol.

Reviewer comment

The MHT finds the sponsor's response acceptable.

22. FDA Recommendation - Grouping Minor Abnormalities

The sponsor states that clusters of 2 or more minor abnormalities will be included in their data analysis. However, the sponsor also states that the "Rule of Three" convention of grouping minor anomalies that occur in clusters of three or more will be used. The sponsor should evaluate minor anomalies that occur in groups of three for their data analysis.

Sponsor Response

Section 7.4.2 and Appendix 1 of the protocol were updated to evaluate minor abnormalities that occur in groups of 3 or more for data analysis, consistent with the "Rule of Three" convention.

Reviewer comment

The MHT finds the sponsor's response acceptable.

23. FDA Recommendation - Assessments of Birth Defects

The sponsor should include growth anomalies in their assessment of birth defects. For each identified birth defect, an expert on classifying birth defects (teratologist) should review the available description of the birth defect and suggest additional information to collect from the appropriate healthcare provider. Such additional information should include:

- details of the birth or birth defect
- details of any obstetric complications

- concomitant medication exposures during pregnancy that were not already identified
- known risk factors associated with the specific outcome reported (e.g., family history, specific medication exposure)
- if malformation, specific test(s) given, date of test(s), and test result(s)
- procedures or surgeries to date (including dates)
- other risk factors known to be associated with the specific birth defect or stillbirth
- other relevant information that can inform classification or etiology.

Sponsor Response
For infants with a birth defect, additional targeted data collection, as specified above, was added to Section 4.9 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

24. FDA Recommendation - Gestational Dating
The sponsor should use obstetrical ultrasound (US) to confirm or correct gestational dating based on the first date of the LMP (taking into account her usual menstrual cycle length). A first trimester obstetrical US is accurate within four to seven days (depending on gestational age at exam). US examinations performed later in pregnancy ate less accurate for establishing gestational age due to the wider normal range in fetal size. Ultrasound confirmation of gestational age is necessary and the sponsor needs to record the date of the ultrasound examination as well as the composite gestational age at the time of the exam.

Sponsor Response
The sponsor concurs that ultrasound data are useful to confirm or correct gestational dating. Data from ultrasound examination will be collected according to Section 4.4 of the protocol. For pregnancies in which ultrasound data are available, it will be used to confirm or correct the gestational age based on the first day of LMP (taking into account woman's usual menstrual cycle length) per Section 7.4.2 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable.

25. FDA Recommendation - Pregnancy Registry Report
If a safety signal is identified, the sponsor should submit a detailed pregnancy registry report that includes all information submitted in annual and semiannual reports as well as a detailed analysis and description of all cases that led to identification of the signal. In addition, the sponsor should submit a labeling supplement to NDA 22-110 that describes the safety signal in the Pregnancy subsection of labeling.

Sponsor Response
A detailed report will be provided if a signal is observed. This intent has been clarified in Section 8.4 of the protocol.

Reviewer comment
The MHT finds the sponsor's response acceptable. If a safety signal is identified, the sponsor will submit to FDA a detailed pregnancy registry report with analysis and description of all cases that led to identification of the signal. The protocol does not state that a labeling supplement will be submitted to NDA 22-110 upon identification of a safety signal. However, the registry protocol does not need to specify when a labeling supplement will be submitted.

DISCUSSION/CONCLUSIONS

The sponsor has responded to all FDA recommendations on the Vibativ pregnancy exposure registry protocol. However, based on recent labeling negotiations with the sponsor and because the elimination half life ($t_{1/2}$) of telavancin is about eight hours, the sponsor should not enroll women who become pregnant within seven days after their last Vibativ dose as Vibativ will have been eliminated from the body. Therefore, the sponsor should only enroll women exposed to Vibativ at any time during pregnancy.

RECOMMENDATIONS

The MHT's recommendations on the sponsor's pregnancy registry protocol are provided below.

1. The Division should inform the sponsor that because the elimination half life ($t_{1/2}$) of telavancin is about eight hours, the sponsor should revise their primary objective to only enroll women exposed to Vibativ at any time during pregnancy. Upon making this change and after FDA approval of Vibativ, the sponsor may proceed with the pregnancy registry.

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/s/

RICHARDAE T ARAOJO
08/10/2009

Karen B FEIBUS
08/10/2009
I agree with the content and recommendations contained in this review

LISA L MATHIS
08/10/2009
Concur with recommendations

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 6, 2009
To:	Wiley Chambers, MD, Acting Director Division of Anti-Infective and Ophthalmology Products
Through:	Denise Toyer, PharmD., Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Kristina C. Arnwine, PharmD, Team Leader Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	Vibativ (Telavancin) for Injection, 250 mg and 750 mg
Application Type/Number:	NDA 22-110
Supplement:	Theravance, Inc.
Applicant:	
OSE RCM #:	2009-644

CONTENTS

1 INTRODUCTION

This review was written to evaluate revisions to container labels and carton labeling submitted by the Applicant on July 14, 2009 and insert labeling submitted on July 6, 2009 for Vibativ (Telavancin) for Injection. These labels and labeling were submitted in response to comments provided by our Division in our OSE Review #2007-964 dated August 3, 2007.

2 METHODS AND MATERIALS

DMEPA reviewed the Applicant's revised container labels and carton and insert labeling submitted (See Appendices A through D) and our recommendations are provided below in Section 3.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation found that the majority of the recommendations provided in our OSE Review #2007-964 have been adequately implemented to the revised container labels and carton labeling submitted. However, we have noted additional areas that can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the review team's labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

3.1 COMMENTS TO THE DIVISION

Package insert, Section 2.3 Preparation and Administration

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3.2 COMMENTS TO THE APPLICANT

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Other 3

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/s/

KRISTINA C ARNWINE
08/06/2009

DENISE P TOYER
08/06/2009

CAROL A HOLQUIST
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MATERNAL HEALTH TEAM (MHT) REVIEW

Date: July 9, 2009 **Date Consulted:** March 13, 2009

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Anti-Infective and Ophthalmology Products (DAIOP)

Drug: NDA 22-110, Vibativ (telavancin) Injection

Subject: Label review

Materials Reviewed: Theravance proposed label for Vibativ (telavancin).

Consult Question: Please review the sponsor's proposed label for Vibativ (telavancin).

INTRODUCTION

On March 13, 2009, Theravance submitted a response to the Division of Anti-Infective and Ophthalmology Product's (DAIOP) complete response action letter dated February 20, 2009, for Vibativ (telavancin) injection (NDA 22-110). The proposed indication for Vibativ is for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following gram-positive microorganisms:

- Staphylococcus aureus (including methicillin-susceptible and -resistant isolates)
- Streptococcus pyogenes, Streptococcus agalactiae Streptococcus anginosus group (includes S. anginosus, S. intermedius and S. constellatus)
- Enterococcus faecalis (vancomycin-susceptible isolates only)

In the March 13, 2009 submission, Theravance provided a pregnancy exposure registry protocol and proposed Vibativ labeling (including a Medication Guide) for review. DAIOP consulted the Maternal Health Team (MHT) to review the sponsor's pregnancy registry protocol and proposed labeling on March 13, 2009. The MHT provided recommendations on the sponsor's pregnancy registry protocol in a review dated May 4, 2009. This review will provide the MHT's recommendations on the sponsors proposed labeling and Medication Guide.

BACKGROUND

Vibativ contains telavancin hydrochloride, a purified lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. Telavancin's proposed indication is for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible gram-positive pathogens. Therefore, it is highly likely to be used by women of childbearing potential. However, there are no human data on telavancin use during pregnancy. In addition, telavancin caused adverse developmental outcomes in three animal species at clinically relevant doses. This raises concerns about potential adverse developmental outcomes in humans (for detailed background information on Vibativ, see MHT review dated May 4, 2009).

DAIOP requested Theravance submit a Risk Evaluation and Mitigation Strategy (REMS), a pregnancy registry protocol, and revised labeling for telavancin. In addition, DAIOP plans to label telavancin as pregnancy category C and include a boxed warning that contains the following information: "Women of child-bearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in three animal species at clinically relevant doses, and this raises serious concerns about potential adverse developmental outcomes in humans."

This review will provide the MHT's recommendations on the sponsors proposed labeling and Medication Guide.

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Other 1

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/s/

Chardae Araojo
7/9/2009 09:28:27 AM
CSO

Karen Feibus
7/9/2009 09:39:07 AM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review.

Lisa Mathis
7/10/2009 04:17:29 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 10, 2009
To:	Wiley Chambers, M.D., Acting Division Director
	Division of Anti-infective and Ophthalmologic Products
Through:	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management
From:	LaShawn Grifffiths, MSHS-PH, BSN, RN
	Patient Product Information Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	VIBATIV (telavancin) for injection
Application Type/Number:	NDA 22-110
Applicant/sponsor:	Theravance, Inc.
OSE RCM #:	2009-542

1 INTRODUCTION

Theravance, Inc. submitted a New Drug Application (NDA 22-110) for Vibativ (telavancin) for injection on December 6, 2006. VIBATIV (telavancin) is an antibiotic indicated for the treatment of complicated skin and skin structure infections in adults. This review is written in response to a request from the Division of Anti-infective and Ophthalmologic Products for the Division of Risk Management to review the Applicant's proposed Medication Guide for Vibativ (telavancin) for injection.

FDA has determined that Vibativ (telavancin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Vibativ (telavancin). FDA has determined that Vibativ (telavancin) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use Vibativ (telavancin). FDA has also determined that Vibativ (telavancin) is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- VIBATIV Medication Guide (MG) submitted May 5, 2009
- VIBATIV Prescribing Information (PI) submitted December 6, 2006 and revised by the Review Division throughout the current review cycle

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the Applicant has a Flesch Kinkaid grade level of 7.7, and a Flesch Reading Ease score of 52.1%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the Applicant are acceptable.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss.* They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document

using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The Applicant uses both the terms "doctor," and "healthcare provider" in the proposed MG. We recommend that one term be used consistently throughout the MG. For this review we have used the term "healthcare provider".
2. In the "What is the most important information I should know about VIBATIV?" section:
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Please let us know if you have any questions.

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Risk 4

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/s/

LaShawn Griffiths
6/10/2009 02:27:03 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
6/11/2009 08:52:15 AM
DRUG SAFETY OFFICE REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: May 19, 2009

To: J. Christopher Davi, Senior Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Jeffrey Trunzo, RPh, MBA, Regulatory Review Officer
Sheila Ryan, Pharm.D., Group Leader

Subject: Vibativ (telavancin hydrochloride) for injection
NDA: 22-110

DDMAC has reviewed the proposed package insert (PI) for Vibativ™ (telavancin hydrochloride) for injection, dated May 11, 2009, and offers the following comments. Please feel free to contact me at (301) 796-2029 with any questions or clarifications.

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

- In accordance with the May 2007 Draft Guidance, Guidance for Industry and Review Staff, Labeling for Human Prescription Drugs – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information, please add the following information to this section:
    - Please add the pharmacological drug class to this section as outlined in the guidance.

USE IN SPECIFIC POPULATIONS

- Please specify here and/or in the INDICATIONS AND USAGE section that Vibativ has not been studied in pediatric patients < 18 years of age.

PATIENT COUNSELING INFORMATION

- Please revise the statement, "See 17 for PATIENT COUNSELING INFORMATION" to state, "See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE" and use bold type.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

b(4)

5. WARNINGS AND PRECAUTIONS

5.1 PREGNANCY

- Please see our comments under the Medication Guide section of this review regarding the inclusion of information regarding the risk of pregnancy for at least 1 month after the discontinuation of VIBATIV.

5.2 RENAL IMPAIRMENT

b(4)

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Other 3

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/s/

Jeffrey Trunzo
5/20/2009 04:47:42 PM
DDMAC PROFESSIONAL REVIEWER

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MATERNAL HEALTH TEAM (MHT) REVIEW

Date: May 4, 2009 **Date Consulted:** March 13, 2009

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Anti-Infective and Ophthalmology Products (DAIOP)

Drug: NDA 22-110, Vibativ (telavancin) Injection

Subject: Pregnancy Registry Protocol Review

Materials Reviewed: Vibativ (telavancin) Pregnancy Exposure Registry

Consult Question: Please review the Vibativ Pregnancy Exposure Registry Protocol (Protocol 9809-CL-1409).

EXECUTIVE SUMMARY

On March 13, 2009, Theravance submitted a response to the Division of Anti-Infective and Ophthalmology Product's (DAIOP) complete response action letter dated February 20, 2009, for Vibativ (telavancin) injection (NDA 22-110). Vibativ contains telavancin hydrochloride, a purified lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. Telavancin's proposed indication is for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible gram-positive pathogens. Therefore, it is highly likely to be used by women of childbearing potential. However, there are no human data on telavancin use during pregnancy and animal data raises serious concerns about potential adverse developmental outcomes in humans.

Therefore, DAIOP requested Theravance submit a Risk Evaluation and Mitigation Strategy (REMS) and conduct a pregnancy registry as a postmarketing requirement for telavancin.

In the March 13, 2009 submission, Theravance provided a pregnancy exposure registry protocol for review. DAIOP consulted the Maternal Health Team (MHT) to review the pregnancy exposure registry protocol submitted by the sponsor.

The Vibativ pregnancy registry will be a voluntary, prospective, observational cohort study of 300 women exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception). The registry will be conducted in the U.S. and Canada. Women can enroll themselves in the registry or be in enrolled by their healthcare provider. The study outcomes are:

- Spontaneous abortions - any fetal loss due to natural causes at < 22 weeks gestation
- Elective terminations
- Therapeutic terminations
- Fetal death/ stillbirth - fetuses born dead at ≥ 22 weeks gestation or weighing ≥ 500 grams. Fetal death occurring at ≥ 22 weeks, but ≤ 28 weeks gestation is considered an early fetal loss. Fetal death occurring at ≥ 28 weeks is considered a late fetal loss.
- Live birth (with and without birth defects)
- Other outcomes of interest are: ectopic pregnancy, maternal death, and neonatal death (a death occurring in a neonate prior to 28 days of life).

The sponsor's pregnancy registry protocol captures many of the elements needed to ensure adequate data collection. A detailed review of the registry protocol is provided on pages 4 to 17 of this review. In addition, the MHT has provided recommendations on the protocol to further enhance obtaining pregnancy and fetal outcomes from Vibativ exposure during pregnancy on pages 17 to 21 of this review.

INTRODUCTION

On March 13, 2009, Theravance submitted a response to the Division of Anti-Infective and Ophthalmology Product's (DAIOP) complete response action letter dated February 20, 2009, for Vibativ (telavancin) injection (NDA 22-110). The proposed indication for Vibativ is for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following gram-positive microorganisms:

- Staphylococcus aureus (including methicillin-susceptible and -resistant isolates)
- Streptococcus pyogenes, Streptococcus agalactiae Streptococcus anginosus group (includes S. anginosus, S. intermedius and S. constellatus)
- Enterococcus faecalis (vancomycin-susceptible isolates only)

In the March 13, 2009 submission, Theravance provided a pregnancy exposure registry protocol for review as requested by FDA in a postmarketing requirement. DAIOP consulted the Maternal Health Team (MHT) to review the pregnancy exposure registry protocol submitted by the sponsor.

BACKGROUND

Vibativ contains telavancin hydrochloride, a purified lipoglycopeptide antibacterial that is a synthetic derivative of vancomycin. Telavancin's proposed indication is for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible gram-positive pathogens. Therefore, it is highly likely to be used by women of childbearing potential. However, there are no human data on telavancin use during pregnancy and animal data raise serious concerns about potential adverse developmental outcomes in humans.

In reproductive and developmental toxicology studies, pregnant rats received intravenous telavancin during the period of organogenesis at exposures approximately 1.6 to 2.2 times the exposures observed in humans at the maximum recommended human dose (based on AUC). These doses produced signs of maternal toxicity. Fetal weights were reduced in exposed rat offspring, and there was a low, but increased, rate of brachymelia (shortened limb in two fetuses each in two telavancin treated groups among 322 fetuses in each group). In prenatal/perinatal development studies, pregnant rats received intravenous telavancin from early organogenesis through the end of lactation at the same doses used in the above studies. Offspring showed decreases in fetal body weight and an increase in the number of still-born pups.

When pregnant rabbits received telavancin during the period of organogenesis at a maternally toxic dose (systemic exposure 1.8 times higher than human systemic exposures at the recommended human dose), there were no adverse effects on fetal survival or body weights. However, one rabbit fetus of 156 fetuses in the high-dose group showed multiple abnormalities including brachymelia and a missing ulna.

When pregnant minipigs received telavancin during the period of organogenesis at systemic exposures 1 to 3 times the human exposure at the recommended human dose, there was an

increase in polydactyly and syndactyly among exposed offspring compared to offspring of concurrent and historical controls. This increased rate of digit malformations occurred in the low and mid dose groups, but not in the high dose group; therefore, it does not show an expected dose-response.

The animal data described above raises serious concerns about potential adverse developmental outcomes in humans. Therefore, DAIOP requested Theravance submit a Risk Evaluation and Mitigation Strategy (REMS) and a pregnancy registry protocol for telavancin. The REMS and pregnancy registry will be implemented upon approval of telavancin. In addition, DAIOP plans to label telavancin as pregnancy category C and include a boxed warning that contains the following information: "Women of child-bearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in three animal species at clinically relevant doses, and this raises serious concerns about potential adverse developmental outcomes in humans."

REVIEW OF PREGNANCY REGISTRY PROTOCOL

This consult reviews the submitted pregnancy registry protocol and provides recommendations on suggested protocol revisions.

Overview of Protocol and Study Design

The registry will be a voluntary, prospective, observational cohort study of women exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception). The registry will be conducted in the U.S. and Canada. The sponsor for the pregnancy registry will be Astellas Pharma Global Development, Inc. In addition, an independent Ethics Committee will review and approve the registry protocol.

The Pregnancy Registry Staff (PRS) will collect information from both the enrolling practitioner and the patient after the patient has provided verbal consent. The PRS will contact the patient at the time of registration and once per trimester. The patient's physician will be contacted at six to seven months of gestation for prenatal follow-up and within four weeks after the estimated delivery date (EDD) for pregnancy outcome follow-up. If a live birth is reported, the PRS will also contact the infant's health care provider when the infant is approximately three, six, nine, and 12 months of age to obtain follow up on the infant's health status.

Study Objectives and Outcomes

The study objectives are:

- Primary Objective
    - Evaluate the outcomes of pregnancy in women who were exposed to Vibativ at any time during pregnancy.

- Secondary Objective
  - Evaluate the effect of fetal exposure to Vibativ on infant development and milestones through 12 months of age.

The study outcomes are:

- Spontaneous abortions - any fetal loss due to natural causes at < 22 weeks gestation
- Elective terminations
- Therapeutic terminations
- Fetal death/ stillbirth - fetuses born dead at ≥ 22 weeks gestation or weighing ≥500 grams. Fetal death occurring at ≥ 22 weeks, but ≤ 28 weeks gestation is considered an early fetal loss. Fetal death occurring at ≥ 28 weeks is considered a late fetal loss.
- Live birth (with and without birth defects)
- Other outcomes of interest are: ectopic pregnancy, maternal death, and neonatal death (a death occurring in a neonate prior to 28 days of life).

Reviewer comments:

- *As described in the study design, women exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception) will be enrolled in the registry. However, the sponsor's primary objective is to evaluate the outcomes of pregnancy in women who were exposed to Vibativ at any time during pregnancy. It is recommended that the sponsor also include evaluating the outcomes of women who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception) as a primary objective.*

- *The secondary objective is to evaluate the effect of fetal exposure to Vibativ on infant development and milestones through 12 months of age. It is recommended that this objective be revised to evaluate the effect of fetal exposure to Vibativ on pregnancy and fetal/neonatal outcomes and infant developmental milestones through 12 months of age.*

- *The sponsor defines spontaneous abortions as a fetal loss occurring at <22 weeks gestation and stillbirth as fetuses born dead at ≥ 22 weeks gestation. According to the American College of Obstetricians and Gynecologists (ACOG), a spontaneous abortion is a fetal loss occurring at ≤ 20 weeks gestation and a stillbirth is a fetal death at >20 weeks gestation. It is recommended that the sponsor adopt these definitions for the registry.*

- *The sponsor should include preterm birth (< 37 weeks gestation) and low birth weight (<2,500 grams) as a study outcome. The sponsor should explain the need for distinguishing between "early and late fetal loss." There does not appear to be a logical reason to make this distinction when gestational age descriptors are more informative.*

Study Population

The registry will prospectively enroll 300 pregnant women exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ. Only pregnancies with an unknown outcome will be enrolled.

Inclusion Criteria

Inclusion Criteria: Prospective Pregnancies (U.S.)

Pregnant women are eligible for the study if all of the following apply:

1. Verbal informed consent is obtained at the time of enrollment. The PRS will send consented patients a Release of Medical Information for signature to allow the PRS to obtain medical records and contact other healthcare providers if necessary.

2. Female patients who were exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception). If exposure dates are unknown, the reporter must be able to specify or estimate trimester of exposure.

3. Outcome of pregnancy unknown at the time of enrollment.

Inclusion Criteria: Prospective Pregnancies (Canada)

Pregnant women are eligible for the study if all of the following apply:

1. Written informed consent is obtained at the time of enrollment. The PRS will send consented patients a Release of Medical Information for signature to allow the PRS to obtain medical records and contact other healthcare providers if necessary.

2. Female patients who were exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception). If exposure dates are unknown, the reporter must be able to specify or estimate trimester of exposure.

3. Outcome of pregnancy unknown at the time of enrollment.

Reviewer comments:

- *The sponsor plans to enroll 300 women from the U.S. or Canada into the registry. The sponsor should provide a rationale for the sample chosen for the registry based on the demographics of the populations. In addition, the registry should enroll an adequate sample to fully evaluate the risk of birth defects. In order to obtain data that can be generalizable to both populations of women, it is recommended that the sponsor evaluate the data obtained on the planned enrollment of 300 women. If one population is under-represented or if the sample size is too small to allow an evaluation of the risk of birth defects, the registry should continue enrollment to obtain more data.*

- *The sponsor should consider whether use of verbal consent at the time of initial telephone contact followed by written consent (where allowed by IRB and by regulations) might enhance recruitment and retention efforts.*

Patient Recruitment

As part of the U.S. Risk Evaluation and Mitigation Strategy (REMS) for Vibativ, a Communication Plan will be initiated and implemented with the approval of Vibativ. This will include displaying information regarding the Vibativ Pregnancy Registry in REMS educational materials, as well as in Vibativ professional labeling and the Medication Guide for patients.

The PRS will also use some or all of the following outreach options to make health care providers and patients in the U.S. and Canada aware of the registry:

- Information on Vibativ web site
- FDA pregnancy registry web site
- Toll-free telephone number printed on Vibativ Prescribing Information
- Toll-free telephone number printed in the Vibativ Medication Guide
- Discussion of the registry with female patients of childbearing potential who become pregnant while participating in Vibativ clinical trials

Reviewer comments:

- *The sponsor states that "some or all" of the patient outreach activities described above will be used to make patients aware of the registry. All activities described above should be implemented to help facilitate registry enrollment. In addition, the sponsor should provide the Vibativ pregnancy registry contact information to the Organization of Teratology Information Specialists (OTIS). OTIS is a teratogen service that answers calls from women who have been exposed to a drug during pregnancy and provides information on the effects of drug exposure. A woman may call OTIS after exposure to Vibativ during pregnancy and the OTIS counselor can inform the patient about the pregnancy registry.*

- *The sponsor's communication plan is under review by DAIOP and the Office of Surveillance and Epidemiology. As currently proposed by the sponsor, their plan includes communication tools to make healthcare professionals aware of the pregnancy registry including notification on healthcare professional websites, healthcare professional letters, and other required mailings.*

Study Enrollment and Procedures

A pregnant woman may enroll herself or be enrolled by her healthcare professional into the registry. In addition, the registry will accept reports from calls to the sponsors customer service line or secondary parties not involved in the patient's medical care. Women will be encouraged to enroll as early as possible and before prenatal testing has occurred. The PRS will maintain toll-free telephone lines and faxes to facilitate enrollment.

The PRS will contact the woman at the time of registration (enrollment) and once per trimester. The woman's physician will be contacted at six to seven months of gestation for the Prenatal Follow-Up and within four weeks after the EDD for the Pregnancy Outcome Follow-Up. If a live birth is reported, the PRS will also contact the infant's health care provider when the infant is approximately three, six, nine, and 12 months of age for Pediatric Follow-Up. In any country outside the U.S. and Canada in which Vibativ is marketed, spontaneous reports of pregnancy

exposure will be collected as per the sponsors safety and pharmacovigilance procedures. These reports will be added to the registry when they are considered complete. In the U.S. and Canada, pregnancy reports from Vibativ clinical trials that meet registry enrollment criteria will be included when the clinical trial follow-up is complete.

A summary of information collected at enrollment is provided below.

- Information collected from reporter
  - Contact information of pregnant woman and reporter
  - Medical specialty of reporter, if health care professional
- Patient
  - Date of birth, race and ethnic origin
  - Complete name and address, telephone number and e-mail address
  - Name, address, and telephone number of secondary contact. Secondary contact will reside outside the patient's home. If the PRS is unable to reach the pregnant woman the secondary contact will be contacted.
- Pregnancy history
  - Previous pregnancies
  - Complications in previous pregnancies
  - Previous pregnancy outcomes and any history of birth defects
  - Current pregnancy information
  - Date of last menstrual period
  - EDD
  - Method of pregnancy confirmation
  - Prenatal testing
  - Outcome (if retrospective report)
- Current medications
  - Vibativ exposure
  - Indication for use
  - Start date, dosage
  - Discontinuation date
  - Circumstances of exposure during pregnancy (e.g., woman known to be pregnant at time of exposure, inadvertent exposure)
  - Other anti-infective treatments (concurrent with Vibativ)
  - Other currently used medications (including OTC products, dietary supplements, prenatal vitamins, and supplemental vaccines)
- Possible risk factors
  - Smoking, caffeine, alcohol use, and/or recreational drug use
- History of skin and soft tissue infections or other serious infections

Reviewer comments:

- *The sponsor does not clearly specify how retrospective reports will be handled by the registry and how they will be obtained. The sponsor should provide detailed information on how the registry will obtain and include retrospective reports in their data analysis. If retrospective reports will be included in the registry, the analysis of outcomes should be stratified by type of report (i.e., prospective or retrospective).*

- *The sponsor plans to collect the name, address, and telephone number of a secondary contact for the patient. The secondary contact will reside outside the patient's home. If the PRS is unable to reach the pregnant woman the secondary contact will be contacted. The sponsor should also collect contact information for a third person who does not reside in the patient's home to ensure adequate mechanisms for reaching the patient and obtaining data.*

Table 1 below illustrates the registry's data collection schedule.

Table 1: Registry Data Collection (United States and Canada)

Data Collection	Enrollment	PRS Contact with Patient at each Trimester	PRS Contact with Practitioner(s) at Pregnancy Outcome Follow-up within 4 months after EDD	PRS Contact with Infant's Health Care Provider for Pediatric Follow-up, 3 months, 6 months, 9 months and 12 months
Consent	X			
Patient Demographics and Pregnancy History	X			
Contact Information	X	X		
VIBATIV Use	X	X	X	
Concomitant Medications	X			
Infection history	X			
Pregnancy Status/ Outcome		X	X	
Pediatric History and Examinations			X	X
Adverse Events	X	X	X	X

Note: There are no mandated visits for this Registry. Medical data will be collected based on the HCP's practice for patient care.

In addition, the following information will be collected at pregnancy outcome (within 4 weeks after the EDD) or from the infant's healthcare provider if a live birth:

- Outcome of pregnancy, e.g. live birth, stillbirth, fetal loss, therapeutic termination, or elective termination
- Infant characteristics: Gestational age, sex, weight, length, birth order (when reporting multiple births), Apgar scores, and any birth defect noted, including description and attribution
- If live birth, the following information will be collected from the infant's healthcare provider at approximately three, six, nine, and 12 months:
    - Developmental milestones
    - Evidence of any abnormalities in development, including functional deficits.

Reviewer comments:

- *The PRS will contact the patient's health care provider when any adverse pregnancy outcome, therapeutic termination, or birth defect is reported.*

- *The sponsor should determine if the patient was seen by someone other than her obstetrician such as a geneticist or maternal/fetal medicine specialist. If so, the sponsor should obtain outcome data from those healthcare practioners as well.*

- *The sponsor should determine if the patient experienced any obstetrical complications during the pregnancy from the obstetric healthcare provider.*

- *Head circumference should be included in the infant characteristics that the sponsor obtains from the pediatric healthcare provider.*

To obtain follow-up information, the PRS will contact the healthcare providers using multiple mechanisms (i.e., mail, fax, telephone, or e-mail) based on prior success and/ or healthcare provider preference to minimize the occurrence of missing data. If the PRS is unable to obtain pregnancy outcome information from the healthcare provider, the sponsor will contact the patient for the information.

Reviewer comments:

- *The sponsor will summarize losses to follow-up in the Registry Interim Report; however they will not be included in the statistical analysis.*

- *If the PRS is unable to obtain pregnancy outcome information from the healthcare provider, the sponsor will contact the patient. When contacting the patient, the sponsor should not only collect information verbally but should also ask the patient to request their records for the sponsors review.*

Each patient or her legal representative has the right to withdraw consent (for the woman and infant) from the registry at any time. A woman's participation will terminate immediately upon her request. Any termination of the woman's participation will also terminate the infant's participation.

Study Duration and Sample Size

The sponsor will continue the registry until one or more of the following occur:

- Sufficient information has accumulated to meet the scientific objective of the registry
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or loss to follow-up (if this situation arises, the sponsor will consult the FDA to determine if the registry should be discontinued), and/or
- Other methods of gathering appropriate information become achievable or are deemed preferable.

Reviewer comment:

- *This pregnancy registry will be conducted as a postmarketing requirement mandated by the FDA. Before discontinuing the registry, the sponsor must obtain agreement from FDA.*

The registry will have a targeted sample size of approximately 300 women. The sponsor states this sample size was chosen based on the ability to detect an increase in the rate of birth defects among women exposed to Vibativ as compared to general population background rates. The sponsor estimates that up to 10 % of women may be lost to follow up, or in the case of some early spontaneous abortions, pathologic specimens may not be available for analysis. Therefore, 300 pregnant women will be enrolled in the registry in order to have at least 270 evaluable pregnancy outcomes. Table 2 shows the sample size requirements to achieve 80% power for study outcomes. All calculations will be based on 80% power and an alpha of 0.05 with two sided significance testing for the specified study outcomes.

Table 2: Sample Size Requirements to Achieve 80% Power for Specified Effect Sizes for Selected Endpoints

Endpoint	Background Rate	Relative Risk	Exposed Pregnancies Needed
Spontaneous Abortion	15%	2	266
Low Birth Weight (<2500 g)	10%	2	261
Fetal Death or Stillbirth	3%	3	236
Any Major Birth Defect	3%	3	236

All calculations are based on 80% power, alpha of 0.05 and two-sided significance testing

Adverse Event Reporting

The registry will report only serious adverse events (SAE) related to the pregnancy and pregnancy outcomes. If the patient's practitioner identifies a pregnancy related SAE, it must be reported to the PRS as soon as possible (within one business day) by phone or fax. The registry requires the reporting practitioner to assess the relationship of the pregnancy-related SAE to Vibativ on the reporting form. The sponsor's definitions for SAEs and their relationship to Vibativ therapy are described below.

An SAE is any event that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect
- Is a medically important event or reaction (see Table 3 below)

Table 3. Relatedness of Event to Drug Exposure

Not related	An event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease(s) provide plausible explanations.
Possible	An event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	An event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

An SAE may also be any other medically important event that, in the opinion of the reporting health care provider, may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. In addition, the sponsor will summarize and stratify reported SAEs by pregnancy outcome as well as by the earliest trimester of exposure to Vibativ.

Reviewer comments:

- *According to 21 CFR 312.32, the sponsor must report to FDA any serious and unexpected adverse events within 15 calendar days. Per 21 CFR 314.80, the sponsor must consider any congenital anomaly within the definition of a serious adverse event. It is recommended that the registry protocol be revised to reflect these reporting requirements.*

- *The sponsor states that SAEs will be reported, however no information is provided on how the sponsor will report adverse events that occur regardless of a perceived association with telavancin exposure. The sponsor should report all adverse events that occur in the final report.*

Evaluation of Outcomes

The registry adopted the term "birth defect" for an abnormality usually referred to as a "congenital abnormality" and defines birth defect according to the following criteria:

1. "any major structural or chromosomal defect diagnosed with signs/symptoms, using the Centers for Disease Control and Prevention (CDC) MACDP classification of birth defects

2. on a case-by-case basis, through evaluator review and agreement from external advisors (if required), clusters of 2 or more minor abnormalities that might in combination constitute a birth defect, even if the outcome of each event alone would not constitute a birth defect according to the CDC MACDP classification

3. on a case-by-case basis, through evaluator review and agreement from external advisors (if required), any structural or chromosomal defect (that satisfy criterion 1 or 2) detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant will be included, if available, to increase the sensitivity of Pregnancy Registry monitoring."

Only cases meeting the CDC MACDP criteria and those with two or more minor defects will be included in the sponsor's analysis. The registry will attempt to assess all outcomes for the presence of birth defects (major congenital anomalies, minor anomalies that occur in groups of three or more) and functional deficits[1] in the infant up to 12 months of age. The "Rule of Three" convention of grouping minor anomalies that occur in clusters of three or more specifies that when three or more individual birth defects appear to be the same both structurally and physically and the same exposure is detected, they will be flagged for immediate review.[2] These findings will be evaluated in comparison to other available data sources describing the frequency of major and minor anomalies.

Reviewer comments:

- *Chromosomal abnormalities are often not due to drug exposure during pregnancy. Chromosomal abnormalities should be analyzed separately from other adverse pregnancy outcomes or malformation.*

- *The sponsor states that clusters of 2 or more minor abnormalities will be included in their data analysis. However the sponsor also states that the "Rule of Three" convention of grouping minor anomalies that occur in clusters of three or more will be used. MHT recommends that the sponsor evaluate minor anomalies that occur in groups of three for their data analysis.*

The registry will classify pregnancy outcomes into one of the following categories:

- spontaneous abortions - any loss of a fetus due to natural causes at < 22 weeks gestation
- elective terminations
- therapeutic terminations
- fetal death/ stillbirth - refers to fetuses born dead at ≥ 22 weeks gestation or weighing ≥ 500 grams. Fetal death occurring at ≥ 22 weeks, but ≤ 28 weeks gestation is considered an early fetal loss. Fetal death occurring at ≥ 28 weeks is considered a late fetal loss.
- live birth (with and without birth defects)
- Other outcomes of interest are: ectopic pregnancy, maternal death, and neonatal death (a death occurring in a neonate prior to 28 days of life).

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[1] Functional deficit is defined by the registry as functional abnormalities, including neurobehavioral and other peripheral organ system deficits, as well as postnatal cancer which may not be apparent as gross structural alterations.

[2] Covington DL, Tilson H, Eilder J, et al. Assessing teratogenicity of antiretroviral drugs: Monitoring and analysis plan of the Antiretorviral Pregnancy Registry. Pharmacoepidemiology and Drug Safety 2004; 13:537-545.

Reviewer comments:

- *The sponsor defines spontaneous abortions as a fetal loss occurring at <22 weeks gestation and stillbirth as fetuses born dead at ≥ 22 weeks gestation. According to the American College of Obstetricians and Gynecologists (ACOG), a spontaneous abortion is a fetal loss occurring at ≤ 20 weeks gestation and a stillbirth is a fetal death at >20 weeks gestation. MHT recommends that the sponsor adopt these definitions for the registry.*

- *The sponsor should include growth anomalies in their assessment of birth defects.*

All cases will be reviewed based on earliest exposure to Vibativ. The registry will calculate gestational weeks beginning the first day of the last menstrual period. If the date of the last menstrual period is not available, the EDD may be used. If the gestation week is inconsistent with exposure dates and/or the dates of outcome (outside + 1 week of the first trimester, outside + 2 weeks for the second and third trimesters) a corrected EDD will be used for gestational weeks calculations. The registry defines the second trimester as beginning at week 14, and the third trimester beginning at week 28.

A valid report of a pregnancy will be considered "closed" by the registry when clear information on the exposure and pregnancy outcome has been obtained. Otherwise the case will be considered pending. A report will be closed as "lost to follow-up" after repeated attempts to obtain outcome information are unsuccessful. Only data from closed reports of pregnancies with known outcomes will be analyzed. In addition, the numbers of reports considered pending and "lost to follow-up" will be provided by the sponsor in all reports.

In addition, the sponsor will consult experts in relevant specialties (teratology, maternal and fetal medicine, infectious disease medicine, epidemiology, etc.), if deemed necessary, for evaluation of birth defects and other significant findings throughout the registry.

Reviewer comments:

- *For each identified birth defect, an expert on classifying birth defects (teratologist) should review the available description of the birth defect and suggest additional information to collect from the appropriate healthcare provider. Such additional information should include:*
    - *details of the birth or birth defect*
    - *details of any obstetric complications*
    - *concomitant medication exposures during pregnancy that were not already identified*
    - *known risk factors associated with the specific outcome reported (e.g., family history, specific medication exposure)*
    - *if malformation, specific test(s) given, date of test(s), and test result(s)*
    - *procedures or surgeries to date (including dates)*
    - *other risk factors known to be associated with the specific birth defect or stillbirth*
    - *other relevant information that can inform classification or etiology.*

- *The sponsor states that they will consult experts in relevant specialties if deemed necessary, for evaluation of birth defects and other significant findings from the registry. As described in the Guidance for Industry, Establishing Pregnancy Exposure Registries (http://www.fda.gov/cder/guidance/3626fnl.htm#_Toc3015017) it is recommended that the sponsor institute an independent data monitoring committee, similar to those used for clinical studies, to ensure scientific integrity of the registry. Members of the committee should include a broad presentation of clinic expertise including at a minimum a pediatrician, an expert in obstetrics, maternal/fetal medicine, teratology, epidemiology, embryology, and infectious disease in pregnancy. The committee should assist in the review of data, classification of any birth defects, and the dissemination of information to ensure that results are interpreted and reported accurately. In addition, the duties of the committee should be specified in the registry protocol.*

- *The protocol states that the registry will calculate gestational age based on the first day of the last menstrual period, and if the date of the last menstrual period (LMP) is not available, an EDD will be used. However, it is important that the basis for the EDD is known and documented, since gestational dating is critical to establishing both the timing of fetal drug exposure and interpreting any gestational age dependent pregnancy outcomes.*

  Obstetrical ultrasound (US) should confirm or correct gestational dating based on the first day of the LMP (taking into account her usual menstrual cycle length). A first trimester obstetrical US is accurate within four to seven days (depending on gestational age at exam). US examinations performed later in pregnancy are less accurate for establishing gestational age due to the wider normal range in fetal size. Ultrasound confirmation of gestational age is necessary and the sponsor needs to record the date of the ultrasound examination as well as the composite gestational age at the time of exam.

Data Analysis

The registry's primary population for analysis will be prospective reports of Vibativ exposed pregnancies with unknown outcomes and not lost to follow-up. All other reports with known outcomes at the time of enrollment (retrospective reports) or initial contact will be analyzed separately from the prospective reports.

For data analysis, pregnancy and infant outcomes will be analyzed cumulatively from the beginning of the registry. All analyses will be stratified by earliest trimester of exposure. If sufficient numbers are obtained, the sponsor will stratify the data according to maternal age, gestational age at enrollment, and by other important risk factors determined by the sponsor. Demographic information, clinical characteristics, and other factors that may affect pregnancy outcome will be also described. In addition, the sponsor's analysis will include the following:

- Number of women enrolled in the registry
- Number and proportion of:
  - Spontaneous abortions, fetal losses, or ectopic pregnancies
    - By gestational age at enrollment

- Premature infants (delivered before 37 weeks from last menstrual period)
- Elective or therapeutic termination
- Live-born infants:
  - Normal outcomes
  - Small for gestational age
  - With any major malformations
  - With two or more minor malformations
- Number of pregnancies with outcomes pending
- Number of women lost to follow-up

Reviewer comments:

- *For live births and fetal deaths/stillbirths the sponsor should include data on - multiple birth pregnancy, small for gestational age, preterm delivery, and any information on adverse fetal outcomes including congenital anomalies or other fetal abnormalities.*

- *The registry allows both physician and patient enrollment. The sponsor should determine if duplicate reports exist and if so, duplicate reports should not be included in the analysis.*

- *All outcomes should by stratified by population type, i.e., U.S. or Canadian. If the populations are similar, a combined analysis can also be performed.*

- *For individual cases where adverse infant/fetal outcomes occur, the sponsor should determine the duration of drug exposure and the gestational weeks of exposure for any specific adverse infant/fetal outcomes.*

- *The sponsor should include growth anomalies in their evaluation of birth defects.*

Descriptive statistics will be used for the registry's primary analysis. Prevalence ratios and 95% confidence intervals will be calculated. The registry will assess the presence or absence of risk from pregnancy exposures to Vibativ by comparing registry data to data from pregnancies exposed to other intravenous antibiotics and general population data for birth defects and spontaneous abortions. Therefore, the registry will use the following comparison groups to review prospective data for teratogenicity signals.

1. Comparison group 1:
   A sample of women of childbearing age who have received a course of intravenous antibiotics, other than Vibativ. This cohort of women will be identified using an automated database that contains linked medical records for both inpatient and outpatient care including pharmacy data, and will include those who receive a course of intravenous antibiotics (other than Vibativ) that are used to treat serious gram-positive infections (such as linezolid, nafcillin, vancomycin, cefazolin, clindamycin, daptomycin, and tigecycline). The database will also contain linked records for the offspring of the women.

2. Comparison group 2:
   Reporting rates from the registry will be compared to background rates from population-based birth defects surveillance systems such as MACDP in the U.S. and the Canadian Perinatal Surveillance System in Canada. The sponsor will use data from other pregnancy registries as appropriate.

Reviewer comment:

- *For comparison group #1, it is recommended that U.S. registry data be compared to a U.S. automated database that contains linked medical records for both inpatient and outpatient care including pharmacy data.*

Submission of Annual Reports
The sponsor states that data from the registry will be assessed annually and reports will be submitted to FDA as part of their REMS assessments.

Reviewer comment:

- *If a safety signal is identified, the sponsor should submit a detailed pregnancy registry report that includes all information submitted in annual and semiannual reports as well as a detailed analysis and description of all cases that led to identification of the signal. In addition, the sponsor should submit a labeling supplement to NDA 22-110 that describes the safety signal in the Pregnancy subsection of labeling.*

DISCUSSION/CONCLUSIONS

Vibativ is an antibacterial for the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible gram-positive pathogens. Therefore, it will likely be used by women of childbearing potential. However, there are no human data on Vibativ use during pregnancy and animal data raise serious concerns about potential adverse developmental outcomes in humans. Therefore, FDA is requiring the sponsor to establish a Vibativ pregnancy registry. The submitted protocol captures many of the elements needed to ensure adequate data collection. However, the MHT provides recommendations below to further enhance collection of pregnancy and fetal outcomes from Vibativ exposure during pregnancy.

RECOMMENDATIONS

The MHT recommendations on the sponsor's pregnancy registry protocol are provided below.

1. The sponsor should revise their primary objective to include women exposed to Vibativ at any time during pregnancy or those who become pregnant within seven days after their last dose of Vibativ (based on estimated date of conception).

2. The sponsor's secondary objective is to evaluate the effect of fetal exposure to Vibativ on infant development and milestones through 12 months of age. The sponsor should revise

this objective to evaluate the effect of fetal exposure to Vibativ on pregnancy and fetal/neonatal outcomes and infant developmental milestones through 12 months of age.

3. The sponsor defines spontaneous abortions as a fetal loss occurring at <22 weeks gestation and stillbirth as fetuses born dead at ≥ 22 weeks gestation. According to the American College of Obstetricians and Gynecologists (ACOG), a spontaneous abortion is a fetal loss occurring at ≤ 20 weeks gestation and a stillbirth is a fetal death at >20 weeks gestation. The sponsor should adopt these definitions for the registry.

4. The sponsor should include preterm birth (< 37 weeks gestation) and low birth weight (<2,500 grams) as a study outcome. The sponsor should explain the need for distinguishing between "early and late fetal loss." There does not appear to be a logical reason to make this distinction when gestational age descriptors are more informative.

5. The sponsor plans to enroll 300 women from the U.S. or Canada into the registry. The sponsor should provide a rationale for the sample chosen for the registry based on the demographics of the populations. In addition, the registry should enroll an adequate sample to fully evaluate the risk of birth defects. In order to obtain data that can be generalizable to both populations of women, it is recommended that the sponsor evaluate the data obtained on the planned enrollment of 300 women. If one population is under-represented or if the sample size is too small to allow an evaluation of the risk of birth defects, the registry should continue enrollment to obtain more data.

6. The sponsor should consider whether use of verbal consent at the time of initial telephone contact followed by written consent (where allowed by IRB and by regulations) might enhance recruitment and retention efforts.

7. It is recommended that the sponsor implement all of their suggested registry awareness activities to help facilitate registry enrollment. In addition, the sponsor should provide the Vibativ pregnancy registry contact information to the Organization of Teratology Information Specialists (OTIS). OTIS is a teratogen service that answers calls from women who have been exposed to a drug during pregnancy and provides information on the effects of drug exposure. A woman may call OTIS after exposure to Vibativ during pregnancy and the OTIS counselor can inform the patient about the pregnancy registry.

8. The sponsor should provide detailed information on how the registry will obtain and include retrospective reports in their data analysis. If retrospective reports will be included in the registry, the analysis of outcomes should be stratified by type of report (i.e., prospective or retrospective).

9. The sponsor plans to collect the name, address, and telephone number of a secondary contact for the patient. The secondary contact will reside outside the patient's home. If the PRS is unable to reach the pregnant woman the secondary contact will be contacted. The sponsor should also collect contact information for a third person who does not reside in

the patient's home to ensure adequate mechanisms for reaching the patient and obtaining data.

10. The sponsor should determine if the patient was seen by someone other than her obstetrician such as a geneticist or maternal/fetal medicine specialist. If so, the sponsor should obtain outcome data from those healthcare practioners as well.

11. The sponsor should determine if the patient experienced any obstetrical complications during the pregnancy from the obstetric healthcare provider.

12. Head circumference should be included in the infant characteristics that the sponsor obtains from the pediatric healthcare provider.

13. If the PRS is unable to obtain pregnancy outcome information from the healthcare provider, the sponsor will contact the patient. When contacting the patient, the sponsor should not only collect information verbally but should also ask the patient to request their records for the sponsors review.

14. According to 21 CFR 312.32, the sponsor must report to FDA any serious and unexpected adverse events within 15 calendar days. Per 21 CFR 314.80, the sponsor must consider any congenital anomaly within the definition of a serious adverse event. The sponsor's protocol should be revised to reflect these reporting requirements.

15. The sponsor should report all adverse events that occur in the final report.

16. Before discontinuing the registry, the sponsor must obtain agreement from FDA.

17. As described in the Guidance for Industry, Establishing Pregnancy Exposure Registries (http://www.fda.gov/cder/guidance/3626fnl.htm#_Toc3015017) the sponsor should institute an independent data monitoring committee, similar to those used for clinical studies, to ensure scientific integrity of the registry. Members of the committee should include a broad presentation of clinic expertise including at a minimum a pediatrician, an expert in obstetrics, maternal/fetal medicine, teratology, epidemiology, embryology, and infectious disease in pregnancy. The committee should assist in the review of data, classification of any birth defects, and the dissemination of information to ensure that results are interpreted and reported accurately. In addition, the duties of the committee should be specified in the registry protocol.

18. For live births and fetal deaths/stillbirths the sponsor should include data on - multiple birth pregnancy, small for gestational age, preterm delivery, and any information on fetal outcomes including congenital anomalies or other fetal abnormalities.

19. The registry allows both physician and patient enrollment. The sponsor should determine if duplicate reports exist and if so, duplicate reports should not be included in the analysis.

20. All outcomes should by stratified by population type, i.e. U.S. or Canadian. If the populations are similar, a combined analysis can also be performed.

21. The sponsor should compare U.S. registry data to a U.S. automated database that contains linked medical records for both inpatient and outpatient care including pharmacy data.

22. For individual cases where adverse infant/fetal outcomes occur, the sponsor should determine the duration of drug exposure and the gestational weeks of exposure for any specific adverse infant/fetal outcomes.

23. The sponsor should analyze chromosomal abnormalities separately from other adverse pregnancy outcomes or malformations.

24. The sponsor states that clusters of 2 or more minor abnormalities will be included in their data analysis. However the sponsor also states that the "Rule of Three" convention of grouping minor anomalies that occur in clusters of three or more will be used. The sponsor should evaluate minor anomalies that occur in groups of three for their data analysis.

25. The sponsor should include growth anomalies in their assessment of birth defects. For each identified birth defect, an expert on classifying birth defects (teratologist) should review the available description of the birth defect and suggest additional information to collect from the appropriate healthcare provider. Such additional information should include:
    - details of the birth or birth defect
    - details of any obstetric complications
    - concomitant medication exposures during pregnancy that were not already identified
    - known risk factors associated with the specific outcome reported (e.g., family history, specific medication exposure)
    - if malformation, specific test(s) given, date of test(s), and test result(s)
    - procedures or surgeries to date (including dates)
    - other risk factors known to be associated with the specific birth defect or stillbirth
    - other relevant information that can inform classification or etiology.

26. The sponsor should use obstetrical ultrasound (US) to confirm or correct gestational dating based on the first day of the LMP (taking into account her usual menstrual cycle length). A first trimester obstetrical US is accurate within four to seven days (depending on gestational age at exam). US examinations performed later in pregnancy are less accurate for establishing gestational age due to the wider normal range in fetal size. Ultrasound confirmation of gestational age is necessary and the sponsor needs to record the date of the ultrasound examination as well as the composite gestational age at the time of exam.

27. If a safety signal is identified, the sponsor should submit a detailed pregnancy registry report that includes all information submitted in annual and semiannual reports as well as a detailed analysis and description of all cases that led to identification of the signal. In addition, the sponsor should submit a labeling supplement to NDA 22-110 that describes the safety signal in the Pregnancy subsection of labeling.

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/s/

Chardae Araojo
5/4/2009 02:33:04 PM
CSO

Karen Feibus
5/6/2009 09:00:00 AM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review

Lisa Mathis
5/12/2009 09:04:51 AM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: April 30, 2009

To: Sumanthi Nambiar, MD
Deputy Director for Safety
DAIOP

Christopher Davi, MS
Senior Regulatory Project Manager
DAIOP

CC: Mary Dempsey
Project Management Officer
OSE, DRISK

Jodi Duckhorn
Lead Social Science Analyst
OSE, DRISK

From: Sharon Watson, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Drug: Vibativ (telavancin hydrochloride) for injection
NDA: 22-110

DDMAC has reviewed the proposed Medication Guide (Med Guide) for VIBATIV and we offer the following comments.

If you have any questions or concerns regarding these comments, please contact Sharon Watson.

- **TITLE**

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X § 552(b)(4) Trade Secret / Confidential

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/s/

Jeffrey Trunzo
5/21/2009 11:20:23 AM
DDMAC PROFESSIONAL REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Maternal Health Team Addendum

Date: December 16, 2008

From: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Anti-infectives and Ophthalmology Products

Drug: Vibativ (telavancin)

Subject: Pregnancy labeling and preventing fetal exposure

Materials Reviewed:

This is an addendum to the Maternal Health Team Consult review on televancin dated May 31, 2007.

INTRODUCTION

This review addendum summarizes the Maternal Health Team's interpretation of the animal reproductive toxicology data for telavancin hydrochloride and its potential clinical relevance for pregnancy labeling. It discusses potential options for pregnancy labeling and pregnancy category based on regulatory definitions and available data. In addition, it explores the need for either pregnancy surveillance as part of a REMS program or a prospective pregnancy registry as a postmarketing requirement as defined under FDAAA.

BACKGROUND

Reproductive toxicology data on telavancin hydrochloride submitted to FDA and reviewed by the Division of Anti-infective and Ophthalmology Products (DAIOP) demonstrated teratogenic effects in rats, rabbits, and minipigs. On February 20, 2007, DAIOP consulted the Maternal

Health Team (MHT) to obtain input on drug labeling for use in pregnant and nursing women and the need for a pregnancy registry and/or a risk minimization action plan.

Telavancin is a semi-synthetic, lipoglycopeptide antibiotic that exhibits bactericidal activity against most gram-positive bacteria. The telavancin molecule core is identical to vancomycin and its antimicrobial coverage is similar. The current NDA application is for marketing telavancin as an antimicrobial to treat complicated skin and skin structure infections (cSSSI). Based on data review by both the DAIOP microbiologist and medical officer, telavancin is equivalent to, but not superior to, vancomycin for this indication.

REVIEW OF DATA

Reproductive toxicology studies show similar teratogenic effects and increased post-implantation pregnancy loss in rats, rabbits, and Göttingen minipigs at non-maternotoxic doses of drug (see Appendix A) While the presence or absence of teratogenic effects in any one animal species does not necessarily predict teratogenicity in developing humans, the occurrence of increased post-implantation loss and skeletal (limb) malformations across all three species at animal exposures 1-15 times the human therapeutic dose is highly concerning. In addition, the minipig study showed a lower fecundity ratio than that seen in either historical database, and male fertility studies in rats showed decreased sperm motility and increased abnormal sperm morphology.

There were potential confounding factors in the minipig study. Many of the minipigs were treated with other antimicrobial agents (three topical ointments and three systemic agents)[1], but these animals were evenly distributed among treatment groups and these types of malformations were not seen in animal studies with these other drugs. Dr. Peters, the pharmtox reviewer who reviewed the studies following submission, found the minipig pregnancy rates unusually low, especially in the placebo (36%) and high dose telavancin (36%) groups.[2] Pregnancy rates were 64% in the low-dose group and 57% in the mid-dose group. Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies. There were an increased number of litters with late resorptions noted in the mid dose (mean = 0.6) and high dose (mean = 0.8) groups compared to historical controls (maximum mean = 0.4).

Reviewer comment:
While the aberrations in the conduct of the minipig study may undermine the strength of the finding, the results should be considered. The post-implantation loss increased by more than 100% in the high dose treatment group compared with the placebo and diluent treatment groups. Increased pregnancy loss and skeletal anomalies occurred at increased rates in all three species of animal studied.

DISCUSSION

Labeling and Pregnancy Category

[1] According to the pharmacologist, this is very unusual among toxicology studies submitted for regulatory review.
[2] Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies.

Based on preclinical developmental toxicity studies in animals, telavancin is a multi-species teratogen. Its classification with regard to use in pregnancy should be based on both its potential risk to mother and fetus as well as its potential clinical benefits above other available therapies. The regulatory definitions for pregnancy categories of teratogenic risk are provided in Appendix C.

Currently, there are eight antimicrobial agents FDA approved for the treatment of cSSSI (see Appendix B). Vancomycin remains first-line therapy for severe infections possibly caused by MRSA. Based on current labeling for these approved cSSSI antimicrobial therapies, telavancin does not offer broader or better antimicrobial coverage and has a larger, more consistent safety signal for teratogenic potential in humans. Telavancin should be assigned pregnancy category X for the proposed indication of cSSSI based on risk that exceeds potential benefit given the availability of other safer therapies.

There are reasons to consider pregnancy category C for telavanin based on potential clinical benefit to a pregnant woman (and indirect benefit to her fetus) despite positive animal developmental studies in three species. In the noninferiority trials, telavancin was noninferior, but not superior, to vancomycin for the treatment of CSSSI caused by MRSA or by other organisms. While vancomycin is often considered the "gold standard" comparator for treatment of these infections, the relative efficacy of telavancin compared to other approved therapies for CSSSI is technically not known. Under IND, there were two patients treated successfully with telavancin who failed therapy with vancomycin. However, this fact does not change the outcomes or conclusions from the clinical trials in CSSSI patients that demonstrated that telavancin was noninferior (and not superior) to vancomycin and offered no unique antimicrobial coverage. .

Prevention of Human Fetal Exposure

When a drug is a suspected human teratogen, the goal is to prevent fetal exposures to the drug. Women of childbearing potential get infections, and it is likely that telavancin will be used in this population. Thus, there is a risk of fetal exposure.

Preventing fetal exposure to telavancin may be more challenging than with other potential teratogens because of its indication, route of administration, and clinical settings of use. The following is a list of points to consider from a risk management perspective:

- Route of administration:
  - Intravenous
- Indication for use:
  - Complicated skin and skin structure infections (requires timely initiation of therapy)
- Potential settings for use:
  - Hospitals, chronic care facilities, physician offices, and homes with instruction or home care assistance.
- Avoiding fetal exposure to a highly suspected human teratogen:

- For all women of childbearing potential, same day documentation of a negative serum pregnancy test should be required prior to starting telavancin treatment.

- It is important to note that while one serum pregnancy test will detect most established pregnancies, it will not detect pregnancies within a few days of conception. However, with telavancin, the acute need for therapy eliminates the ability to require two negative pregnancy tests over an interval of time or the use of highly effective contraception for one month before treatment initiation.

- Additional questions:
  - Will healthcare practitioners check for a negative pregnancy test prior to telavancin administration? Should there be a role for the dispensing pharmacy?

  - For therapy in the outpatient setting, should there be contraceptive requirements and how can these requirements be defined to suit telavancin treatment scenarios?

CONCLUSIONS

Based on available data and alternative approved therapies for the treatment of CSSSI, telavancin does not appear to offer an efficacy advantage that would justify the teratogenic risk suggested by preclinical animal studies. The once daily dosing, while convenient, does not offer substantial advantages in terms of patient compliance because the drug is administered intravenously and most often in a healthcare provider-assisted setting. Based on relative risk and benefit for treatment of CSSSI and the risk management concerns cited above, the Maternal Health Team recommends a pregnancy category "X" . However, the MHT recognizes that there are some unknown factors that hold out a potential for clinical benefit that may be recognized in the future either for this indication or for others. When and if that occurs, then a pregnancy category C could be considered.

The pregnancy category designation for telavancin use during pregnancy should help determine whether postmarketing fetal exposures should be tracked as part of a REMS program or whether a postmarketing requirement (PMR) for a prospective pregnancy registry should be considered to collect additional data on human outcomes following televanin use during pregnancy. A highly suspected human teratogen that carries a contraindication for use during pregnancy (Category X) should have a risk evaluation and mitigation strategy (REMS) program that includes a pregnancy surveillance registry. Such a registry would track pregnancy outcomes when fetal exposure does occur despite the contraindication to use during pregnancy.

If telavancin is approved for marketing and labeled with a pregnancy category C based on a theoretical potential for maternal benefit that could outweigh the teratogenic risk to the fetus, then a different approach may be appropriate. In this situation, use of telavancin during pregnancy would not be contraindicated and use in pregnant women may be more likely to occur. Based on the safety signal in more than one animal and a lack of data in human pregnancy, the MHT recommends a postmarketing requirement for the sponsor to conduct a prospective pregnancy registry. This registry would be a cohort study of pregnant women

treated with telavancin for therapeutic reasons. Title IX of FDAAA supports requirement of such a study in this situation.

RECOMMENDATIONS

If telavancin hydrochloride is approved, the Maternal Health Team recommends the following:

1. Boxed warning informing prescribers (and patients) that telavancin caused congenital anomalies and increased pregnancy loss in rats, rabbits, and minipigs and is, therefore, a suspected teratogen in humans that should not be used in women of childbearing potential.

2. Pregnancy category X (based on no increased benefit over current therapies and the potential for greater risk based on data from studies in three animal species). Even if the minipig study is not considered, the signal consistency from the remaining two species may represent a greater risk.

3. Indicated populations should include adult men, adult women who are not of childbearing potential, and women of child-bearing potential who have an extremely low risk of recent conception. It will be important to define this group of women of child-bearing potential. This group might include women who are never sexually active by lifestyle choice (e.g. nuns), and women using highly reliable, non-user dependent contraceptive methods (e.g. tubal sterilization, IUDs, hormone implants or injections).

4. Restricted distribution at the pharmacy level that requires documentation of age and gender of the patient. If the patient is female, documentation of menopause, other evidence of non-childbearing potential, and/or contraceptive use and pregnancy status should be required.

5. A REMS program should include a pregnancy surveillance registry.

6. If telavancin hydrochloride is approved as a pregnancy category C drug, then a prospective pregnancy registry should be required in the post-marketing setting.

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Appendix A: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Telavancin Hydrochloride				
Species	**Study Type**	**Treatment Groups**	**Treatment Duration**	**Positive Findings**
Rabbit	Developmental toxicity Phase I and II AMI CSN: 02-001-03	5% dextrose Placebo (diluent?) 12.5 mg/kg/d telavancin 25 mg/kg/d telavancin 45 mg/kg/d telavancin By slow IV bolus daily Phase I: 20 females per group Phase II: satellite groups Toxicokinetics N=4 Recovery: N=4 Amniotic fluid: N=10	Gestational days 7-20	Two does in the 25 mg/kg/d group aborted and were removed from the study. In all telavancin-dosed groups, there was a drug-related increase in post-implantation losses. This did not appear to be dose-related An increase in dilated lateral ventricles of the brain and missing intermediate lung lobes occurred in feti from all three telavancin dose groups. This increase was statistically signficant for both anomalies at the highest dose and for dilated ventricles in the low and medium dose groups. There was incomplete ossification of the 5^{th} and 6^{th} sternebrae in the high dose telavancin feti but this was not a statistically significant finding. Maternal NOAEL = 45 mg/kg/d Fetal NOAEL = not clear
Rabbit	Developmental toxicity AMI CSN: 02-001-015	Placebo (diluent?) 60 mg/kg/d telavancin 75 mg/kg/d telavancin By slow IV bolus daily Main study: 20 females per group Toxicokinetics: N=4 Amniotic fluid: N=10	Gestational days 7-20	Only one animal had telavancin levels detected in amniotic fluid. This suggests limited fetal exposure to drug or that the drug was rapidly metabolized. Overall, telavancin treated animals had skeletal variations including an increased incidence of unilateral 13^{th} ribs and presacral vertebrae. In the telavancin 75 mg/kg/d group: ▪ One fetus from each of five litters had various skeletal malformations including: absent ulna, fusion of sternebrae, adactyly, and vertebral anomalies. ▪ Additional abnormalities noted were: one fetus with brachymelia, adactyly, and gastroschisis; one fetus with umbilical hernia; and one fetus with diaphragmatic hernia and gall bladder agenesis (the latter two conditions have been seen in historical controls) NOAEL for developmental toxicity – 60mg/kg/d. The Pharmtox reviewer stated that the evel of concern is quite high given "enormity of the effects."

Appendix A: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Telavancin Hydrochloride				
Species	**Study Type**	**Treatment Groups**	**Treatment Duration**	**Positive Findings**
Rat	Fertility and Early embryonic development to implantation AMI CSN: 02-001-05	Diluent control Placebo 50 mg/kg/d telavancin 75 mg.kg.d telavancin 100 mg/kg/d telavancin By slow IV bolus daily 20 males and 20 females in each group	Males dosed for at least 28 days before mating Females dosed from at least 14 days before mating until gestation day 7.	Males: Decreased sperm motility Increased abnormal morphology These effects were also seen in the placebo group but less often and to a smaller degree. The effects were dose dependent in the telavancin treated groups.
Rat	Pre- and post-natal development, Including maternal function AMI CSN: 02-001-07	5% dextrose Placebo 50 mg/kg/d telavancin 100 mg/kg/d telavancin 150 mg/kg/d telavancin By slow IV bolus daily 25 females per group	Gestational day 6 to Lactation day 20	Telavancin treated F_0 dams in the two higher dose groups had decreased mean maternal body weights, mean body weight changes, and food consumption. Total litter death in 3 F_0 dams: 1 placebo, 2 high dose. There was a dose-related increase in the number of stillborn pups and the number of dams with stillborn pups. F_1 pups in the high dose group were cyanotic (2 litters), swollen (2 litters), and anophthalmic (3 litters), and one pup had brachymelia (limited use of a forelimb). These findings were consistent with those a previous study. Compared to controls, mean F_1 pup weights were decreased at 50 mg/kg/d. On necropsy, all F_1 pups treated with telavancin had dilated renal pelvices compared with 1 control female pup. NOAEL for F_0 maternal effects = 50 mg/kg/d NOAEL for F_1 fetal/pup effects = 100 mg/kg.d

Appendix A: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Telavancin Hydrochloride				
Species	**Study Type**	**Treatment Groups**	**Treatment Duration**	**Positive Findings**
Minipig	Embryo-fetal development	Diluent (5% dextrose) Placebo 25 mg/kg/d telavancin 50 mg.kg/d telavancin 75 mg/kg/d telavancin By slow IV bolus daily 14 females per treatment group	Gestational days 11-35 Toxicokinetic satellite groups (3 animals/group) dosed gestational days 11-16 only and then euthanized	Number of and reasons for dams sacrificed *in extremis* were similar by treatment group. ▪ Many of these animals were treated with other antimicrobial agents(3 topical ointments, 3 systemic agents)[3] ▪ Pregnancy rates seemed unacceptably low to the review pharmacologist, especially in the placebo (36%) and high dose telavancin (36%) groups[4] ▪ There were an increased number of late resorptions noted in the mid and high dose groups compared to historical controls ▪ There was a > 100% increase in post-implantation loss in the high dose treatment group compared with placebo and diluent ▪ 45% of telavancin-treated litters had feti with external and soft tissue abnormalities compared to 14% of litters and 20% of litters in the diluent and placebo groups respectively. ▪ Among 58 feti from the placebo and diluent treated groups, the sponsor noted 1 fetus with retained testes and 1 with retained testes and polydactyly[5] ▪ Among 84 feti from the telavancin treated groups, the sponsor noted the following findings: 9 feti with polydactyly (3 on two limbs), 1 fetus with diaphragmatic hernia, one with discolored diaphragm, one with syndactyly, and one with retained testes In addition, the pharmacology reviewer noted: a low dose fetus with defomred head and a misshapen digit; a mid-dose fetus with "legs turned inward"; a mid-dose fetus with multiple absent ossification sites and bilateral absence of tarsal bones; a mid-dose fetus with absent ossification sites distal to the metacarpi; a mid-dose fetus with exophthalmos; a mid-dose fetus with anencephaly; a high-dose fetus with deformed head, forelegs, and snout (very autolytic); and a high dose fetus with a deformed hind leg.

[3] According to the pharmacologist, this is very unusual among toxicology studies submitted for regulatory review. These animals were evenly distributed among treatment groups but call the validity of the study into question.

[4] Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies.

[5] The historical Danish database shows that the incidence of syndactyly is ≤ 0.4% and the incidence of pentadactyly was ≤2.3% for the past five years. However, after a change from line breeding to a population based breeding program in November 2004, these rates declined to <0.2% and <0.7% respectively. The historical Japanese database shows a 1.4% incidence of polydactyly among newborn piglets, a preimplantation loss rate of 11.7%, and a post-implantation loss rate of 15.6%.

Appendix B: Comparison of Reproductive Toxicology Data and Antimicrobial Coverage for Telavancin and Anti-microbial Drugs Approved For the Treatment of Complicated Skin and Skin Structure Infections			
Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Telavancin	?	Reproductive studies in rats, rabbits, and minipigs showed increased post-implantation losses and increased skeletal malformations including limb abnormalities and absent or decreased ossification centers. There effects occurred at doses 1 – 15 times the human therapeutic dose. In rats, sperm motility was decreased and abnormal sperm morphology was increased.	cSSSI caused by susceptible strains of the following gram positive organisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible isolates only)
Daptomycin	B	Studies performed in rats and rabbits at doses up to 2 and 4 times the human dose showed no evidence of fetal harm. There are no adequate and well-controlled studies in women.	cSSSI caused by susceptible isolates of the following gram positive organisms: *Staphylococcus aureus* (including methicillin resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis*, and *Enterococcus faecalis* (vancomycin susceptible isolates only)
Piperacillin/ Tazobactam	B	Piperacillin: Reproduction and teratology studies in mice and rats have not revealed impaired fertility or harm to the fetus at 0.5 to 1 times the maximum human dose. Tazobactam: Reproduction studies in rats revealed no evidence of impaired fertility at up to 3 times the maximum human dose. There are no adequate and well-controlled studies in women.	Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections, caused by piperacillin-resistant β–lactamase producing strains of *Staphylococcus aureus*
Ertapenum	B	Mice and rats given three times and 1.2 times the equivalent human dose respectively showed no evidence of developmental fetal toxicity. In mice, there was a slight decrease in mean fetal weight and an associated decrease in the average number of ossified sacrocaudal vertebrae. There are no adequate and well-controlled studies in women.	cSSSI, including diabetic foot infections without osteomyelitis, due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia*
Meropenem	B	Reproductive studies in the rat (1.8 times the human dose) and cynomolgus monkeys (3.7 times the human dose) revealed no evidence of impaired fertility or harm to the fetus due to meropenem. There were slight changes in fetal body weight at 0.4 times the human dose. There are no adequate and well-controlled studies in women.	cSSSI due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species

Appendix B: Comparison of Reproductive Toxicology Data and Antimicrobial Coverage for Telavancin and Anti-microbial Drugs Approved For the Treatment of Complicated Skin and Skin Structure Infections			
Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Levofloxacin	C	Not teratogenic in rats at doses up to 9.4 times the oral human dose and 1.9 times the IV dose. The higher doses caused reduced fetal weights and increased fetal mortality. No teratogenic effects were seen in rabbits at doses 0.5 to 1.1 times the human dose. There are no adequate and well-controlled studies in women.	cSSSI due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Enterococcus faecalis*, *Streptococcus pyogenes*, or *Proteus mirabilis*
Linezolid	C	Not teratogenic in mice, rats, or rabbits at doses of 0.6 to 6 times the human therapeutic dose. However, embryo and fetal toxicities occurred. There are no adequate and well-controlled studies in women.	cSSSI, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicilin susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*
Vancomycin	C	No reproductive animal studies were conducted. There are no adequate and well-controlled studies in women. One small study of pregnant women using vancomycin in the second and third trimesters was published. This study evaluated the potential ototoxic and nephrotoxic effects of vancomycin on infants following maternal exposure. No sensorineural hearing loss or nephrotoxicity was attributed to vancomycin. The number of patients studied was limited. No other fetal/neonatal effects were reported.	cSSSI caused by susceptible strains of methicillin-resistant staphylococci
Tigecycline	D*	Not teratogenic in the rat or the rabbit. Slight reductions in fetal weight and an increased incidence of minor skeletal anomalies (delays in bone ossification) occurred at 5 times and 1 time the human daily dose. Doses equivalent to the human dose were materno-toxic in rabbits and resulted in an increased incidence of fetal loss in rats and rabbits. There are no adequate and well-controlled studies in women.	cSSSI caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (including methicillin resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus pyogenes*, and *Bacteroides fragilis*

Appendix C: Regulatory Definitions of Pregnancy Categories for Teratogenic Risk	
Pregnancy Category	**Assessment of Teratogenicity**
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal reproduction studies show an adverse fetal effect but adequate but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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/s/

Karen Feibus
12/17/2008 03:22:16 PM
MEDICAL OFFICER
This is an addendum to the May 31, 2007 review from the Maternal Health Team by Karen Feibus

Lisa Mathis
12/19/2008 10:51:00 AM
MEDICAL OFFICER

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M E M O R A N D U M

Date: May 31, 2007 **Date Consulted:** February 20, 2007

From: Karen B. Feibus, M.D.
Team Leader, Pediatric and Maternal Health Staff

Through: Sandra Kweder, MD
Deputy Director, Office of New Drugs

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Anit-Infective and Ophthalmology Products (DAIOP)

NDA: **22-110**

Drug: Telavancin hydrocloride

Subject: Determination of pregnancy category and need for pregnancy exposure registry and/or risk minimization action plan (RiskMAP)

Materials Reviewed: Pharmacology/Toxicology Review and other relevant documents submitted to IND 60,237 and NDA 22-110

Consult Question:
Telavancin has exhibited consistent teratogenic effects in rats, rabbits, and minipigs, which represents a significant safety concern. The Division is requesting a PMHS consultation in the determination of appropriate labeling (i.e. pregnancy category) and pregnancy exposure registry considerations. In addition, we would like PMHS's opinion on the necessity of any pregnancy prevention risk management programs, and an assessment of fetal safety following in-utero drug exposure. The following documents are attached for your review:

1. DAIOP Pharmacology/Toxicology review of related IND 60,237 serial submission 171
2. A copy of the (sponsor's) proposed labeling for telavancin (NDA 22-110).

EXECUTIVE SUMMARY

Telavancin is a semi-synthetic, lipoglycopeptide antibiotic that exhibits bactericidal activity against most gram-positive bacteria. The telavancin molecule core is identical to vancomycin and its antimicrobial coverage is similar. The current NDA application is for marketing telavancin as an antimicrobial to treat complicated skin and skin structure infections (cSSSI). Based on data review by both the DAIOP microbiologist and medical officer, telavancin is equivalent to, but not superior to, vancomycin for this indication. In addition, reproductive toxicology studies show similar teratogenic effects and increased post-implantation pregnancy loss in rats, rabbits, and Göttingen minipigs at non-maternotoxic doses of drug. While the presence or absence of teratogenic effects in any one animal species does not necessarily predict teratogenicity in developing humans, the occurrence of increased post-implantation loss and skeletal (limb) malformations across all three species at 1 – 15 times the human therapeutic dose is highly concerning. In addition, the minipig study showed a lower fecundity ratio than that in either historical database, and male fertility studies in rats showed decreased sperm motility and increased abnormal sperm morphology.

Televancin is a multi-species teratogen. Its classification with regard to use in pregnancy should be based on both its potential risk to mother and fetus as well as its potential clinical benefits above other available therapies. Currently, there are eight antimicrobial agents FDA approved for the treatment of cSSSI. Vancomycin remains first-line therapy for severe infections possible caused by MRSA. Based on current labeling for these approved cSSSI antimicrobial therapies, televancin does not offer broader or better antimicrobial coverage and has a much larger, consistent, and concerning animal safety signal for teratogenic potential in humans.

For the proposed indication of cSSSI, televancin, if approved, should be assigned pregnancy category X because of a consistent teratogenic signal in three animal species combined with a lack of evidence of clinical benefit over eight other approved therapies for this indication. It is possible that data submitted for a different clinical indication in the future could support pregnancy category C if some direct benefit to mother or fetus was demonstrated. However, for the indication of cSSSI, there is no data to support such a benefit.

A RiskMAP that includes education and reminders alone will not adequately safeguard against televancin use in pregnant women, and a RiskMAP with a performance-linked access system is probably not feasible for this drug, which will be used in acute care situations to treat acute infections.

If televancin hydrochloride is approved, the Maternal Health Team recommends the following:

1. Boxed warning informing prescribers (and patients) that televancin caused congenital anomalies and increased pregnancy loss in rats, rabbits, and minipigs and is, therefore,

a suspected teratogen in humans that should not be used in women of childbearing potential.

2. Pregnancy category X (based on no increased benefit over current therapies and the potential for greater risk based on consistent teratogenic and pregnancy loss safety signals in three animal species)

3. Indicated populations should include adult men and adult women who are not of childbearing potential.

4. Restricted distribution at the pharmacy level that requires documentation of age and gender of the patient. If the patient is female, documentation of menopause or other evidence of non-childbearing potential should be required.

INTRODUCTION

On December 19, 2007, Theravance, Inc. submitted NDA 22-110 for Telavancin, an antimicrobial indicated for the treatment of adults with complicated skin and skin structure infections. The Telavancin drug development program is ongoing and focuses on treatment of adult patients with the following infections caused by susceptible strains of gram positive microorganisms:

- Hospital-acquired pneumonia, including cases with concurrent bacteremia
- Complicated skin and skin structure infections (cSSSI), including cases with concurrent bacteremia.

Reproductive toxicology data submitted under IND 60,237 and reviewed by the Division of Anti-infective and Ophthalmology Products (DAIOP) demonstrate teratogenic effects in rats, rabbits, and minipigs. On February 20, 2007, DAIOP consulted the Maternal Health Team to obtain input on drug labeling for use in pregnant and nursing women and the need for a pregnancy registry and/or a risk management action plan.

BACKGROUND

Telavancin is a semi-synthetic, lipoglycopeptide antibiotic that exhibits bactericidal activity against most gram-positive bacteria. The telavancin molecule core is identical to vancomycin. The addition of a N-decaaminoethyl group provides a functional lipid tail that improves microbiological activity, and a phosphonomethyl aminoethyl group improves the pharmacokinetic profile to allow once daily dosing. Telavancin's antimicrobial activity is concentration dependent, and the inhibition of cell wall synthesis and disruption of the bacterial cell wall phospholipids are the primary mechanisms of action.

To document the in-vitro activity of telavancin, the applicant conducted 19 studies with more than 12,000 bacterial isolates from 165 centers worldwide. Telavancin demonstrated in-vitro activity against: staphylococci and β-hemolytic streptococci (the principal species involved with cSSSI), and all other Gram-positive species considered human pathogens. Isolates resistant to

oxacillin/methicillin, linezolid, clindamycin, fluoroquinolones, or trimethoprim/ sulfamethoxazole and staphylococci resistant to daptomycin or with reduced susceptibility to vancomycin were susceptible to telavancin. Telavancin has potent and consistent activity against methicillin-resistant staphylococcus aureus (MRSA).

The applicant states that telavancin exhibited rapid bactericidal action in time-kill studies and suggests that this rapid killing action reduces that potential development of antimicrobial resistance. In-vitro resistance emergence testing with three staphlococcal strains found no resistant isolates. Resistant variants did occur with vancomycin-resistant enterococci (*E. faecalis* and *E. faecium*). Bactericidal activity against staphylococci [including methicillin sensitive S. *aureus* (MSSA), MRSA, vancomycin-intermediate S. *aureus*, and coagulase negative staphylococci] was concentration-dependent and superior to most comparator antimicrobial agents. Telavancin was bactericidal at low concentrations against streptococci, including β-hemolytic streptococci and *Streptococcus pneumoniae* isolates. At low multiples of the MIC (minimum inhibitory concentration), telavancin did not achieve a 3-log reduction in colony forming units of vancomycin-susceptible and non-vanA-type vancomycin-resistant enterococci but was bactericidal at concentrations of 16 – 32 μg/mL. The applicant states that in-vitro, telavancin was superior to vancomycin against the majority of enterococcal isolates studied. However, Fred Marsik, Ph.D., microbiology team leader for DAIOP, noted in his reviews dated 05/31/2006 and 06/26/2004 that telavancin activity against vancomycin-resistant enterococci (VRE) is dramatically decreased in the presence of human sera. It is not clear how these conflicting results predict telavancin's clinical activity in humans with VRE infection, but the current indication of sCCCI and the ongoing studies for hospital acquired pneumonia do not require the treatment of VRE.

Animal model studies show that telavancin is active in-vivo against MRSA in both immunocompetent and immunocompromised models. In the mouse subcutaneous abscess (MSA) model, televancin was 3-fold more potent than vancomycin and linezolid against MRSA. For MRSA, the telavancin ED_{50} in the MSA model and the mouse neutropenic thigh model were similar. In contrast, the vancomycin and linezolid ED_{50}'s were 10 and 34 times higher in the immunocompromised model than in the immunocompetent MSA model. The applicant concluded that telavancin efficacy was comparable or superior to vancomycin and/or linezolid for the treatment of clinically relevant Gram-positive pathogens including: MSSA, MRSA, ( ) *S. aureus*, ( ) ( ) b(4)

Based on preliminary review of the NDA submission, the review team made the following observations (as presented at the mid-cycle meeting on May 08, 20007:

- Preclinical Pharmacology/Toxicology
  - There are signs of liver toxicity in animal studies conducted in rats and dogs at televancin doses equivalent to 1 – 2 times the therapeutic human dose. These findings included elevations of liver transaminases and mild hepatocellular degenerative changes.

- There are signs of renal toxicity in rats and dogs including renal tubular degeneration. Elevations in blood urea nitrogen and creatinine occurred with occult blood and amorphous crystals in the urine.

- Reproductive toxicology studies have positive findings in three species: rat, rabbit, and minipig. In Segment I studies in rats, televancin reduced sperm motility and increased abnormal sperm morphology. In Segment II studies, skeletal malformations occurred in all three species at doses that did not cause maternal toxicity.

- Microbiology
  - In-vitro and in-vivo testing suggest that televancin is bactericidal against the organisms responsible for complicated skin and skin structure infections. However, there are no data to support superiority of this drug for treatment of cSSSI.

  - No treatment emergent resistance occurred in-vitro or in clinical studies. Microbiology reviewers are awaiting data from the sponsor that can address the potential for development of hetero-resistance to televancin and the effectiveness of televancin against organisms with hetero-resistance to vancomycin.

- Clinical Pharmacology
  - The applicant initially studied televancin at doses of 7.5 mg/kg. They increased the dose to 10 mg/kg early in Phase III of the drug development programs after Phase II study anaylysis demonstrated a 15% increase in microbiological cure rates at the higher dose. However, the increase in clinical cure rate was only 5%. It is not clear how this increase in dose affects the incidence or degree of renal toxicity.

  - Results of a skin blister study suggests that televancin achieves adequate tissue levels in the skin to treat complicated skin and skin structure infections.

- Clinical
  - Clinical trials show a renal safety signal consistent with preclinical findings, but a hepatic safety signal is not evident on initial review.

  - Using a non-inferiority margin of 10%, the Phase III trials demonstrated non-inferiority of televancin to vancomycin for the treatment of cSSSI caused by Gram positive organisms.

  - The Phase III pooled study data did not demonstrate statistical superiority of televancin over vancomycin for the treatment of cSSSI caused by MRSA. (The team statistician stated that it was not even close.)

REVIEW OF DATA

The following materials were submitted for review with the DAIOP consult:

- Pharmacology/toxicology review of IND 60,237, N171 (03/10/2006) by Terry S. Peters, D.V.M (dated 04/06/2006)

- Four published resources supporting the use of the Göttingen minipig as an animal model in teratogenic studies

  - Earl FL, Miller E, Van Loon EJ. Teratogenic research in beagle dogs and miniature swine. (This research was conducted at the FDA laboratories at Beltsville, MD)

  - Jørgensen KD. Minipig in Reproduction Toxicology. Scand J Lab Anim Sci. 1998; 25, supple 1: 63-75.

  - Misawa J, Kanda S, Kokue E, Hayama T, Teramoto S, Aoyama H, Kaneda M, Iwasaki T. Teratogenic activity of pyrimethamine in Göttingen minipig. Toxicol Letters 1982; 10: 51-54.

  - Palludan B. The Teratogenic effect of Thalidomide in Pigs. Limb Development and Deformity: Problems of Evaluation and Rehabilitation. 1969. Charles C. Thomas, publisher. pp 199-202.

Other materials reviewed include:

- Pharmacology/toxicology review of IND 60,237, N014 (04/19/2003) by Terry S. Peters, D.V.M (dated 08/21/2003)

- Pharmacology/toxicology review of IND 60,237, N025 (11/19/2003) by Terry S. Peters, D.V.M (dated 12/10/2003)

- Reproductive and developmental toxicity sections of the toxicology written summary submitted to NDA 22-110. Specific studies were reviewed when needed.

The Division used the submitted publications to support their request for the reproductive study in the Göttingen minipig. The historical information for this species provides baseline malformation rates against which to compare the incidences of various malformations among study animals in the televancin reproductive toxicology study. Dr. Terry Peters, the pharmacology/toxicology reviewer for IND 60,237 reviewed the study report on the minipig study upon its initial submission (see review of submission N171 dated 04/06/2006). Currently, Dr. Zhou Chen, the pharmacology/toxicology reviewer for NDA 22-110, is reviewing this study as part of the NDA submission.

Table 1 on the next page summarizes the outcomes from five reproductive toxicology studies of televancin in three species:

- Rabbit: two segment I and II studies of televancin doses of 12.5 – 75 mg/kg/d administered on gestational days 7-20

- Rat: one fertility and early embryonic (segment I) study and one pre-and post-natal development study (segment II and III) at televancin doses of 50-150 mg/kg/d

- Minipig: embryo-fetal development (segment II) at doses of 25-75 mg/kg/d

Table 1: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Televancin Hydrochloride				
Species	**Study Type**	**Treatment Groups**	**Treatment Duration**	**Positive Findings**
Rabbit	Developmental toxicity Phase I and II AMI CSN: 02-001-03	5% dextrose Placebo (diluent?) 12.5 mg/kg/d televancin 25 mg/kg/d televancin 45 mg/kg/d televancin By slow IV bolus daily Phase I: 20 females per group Phase II: satellite groups Toxicokinetics N=4 Recovery: N=4 Amniotic fluid: N=10	Gestational days 7-20	Two does in the 25 mg/kg/d group aborted and were removed from the study. In all televancin-dosed groups, there was a drug-related increase in post-implantation losses. This did not appear to be dose-related An increase in dilated lateral ventricles of the brain and missing intermediate lung lobes occurred in feti from all three televancin dose groups. This increase was statistically signficant for both anomalies at the highest dose and for dilated ventricles in the low and medium dose groups. There was incomplete ossification of the 5th and 6th sternebrae in the high dose televancin feti but this was not a statistically significant finding. Maternal NOAEL = 45 mg/kg/d Fetal NOAEL = not clear
Rabbit	Developmental toxicity AMI CSN: 02-001-015	Placebo (diluent?) 60 mg/kg/d televancin 75 mg/kg/d televancin By slow IV bolus daily Main study: 20 females per group Toxicokinetics: N=4 Amniotic fluid: N=10	Gestational days 7-20	Only one animal had televancin levels detected in amniotic fluid. This suggests limited fetal exposure to drug or that the drug was rapidly metabolized. Overall, televancin treated animals had skeletal variations including an increased incidence of unilateral 13th ribs and presacral vertebrae. In the televancin 75 mg/kg/d group: ▪ One fetus from each of five litters had various skeletal malformations including: absent ulna, fusion of sternebrae, adactyly, and vertebral anomalies. ▪ Additional abnormalities noted were: one fetus with brachymelia, adactyly, and gastroschisis; one fetus with umbilical hernia; and one fetus with diaphragmatic hernia and gall bladder agenesis (the latter two conditions have been seen in historical controls) NOAEL for developmental toxicity – 60mg/kg/d. The Pharmtox reviewer stated that the evel of concern is quite high given "enormity of the effects."

Table 1: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Televancin Hydrochloride				
Species	**Study Type**	**Treatment Groups**	**Treatment Duration**	**Positive Findings**
Rat	Fertility and Early embryonic development to implantation AMI CSN: 02-001-05	Diluent control Placebo 50 mg/kg/d televancin 75 mg.kg.d televancin 100 mg/kg/d televancin By slow IV bolus daily 20 males and 20 females in each group	Males dosed for at least 28 days before mating Females dosed from at least 14 days before mating until gestation day 7.	Males: Decreased sperm motility Increased abnormal morphology These effects were also seen in the placebo group but less often and to a smaller degree. The effects were dose dependent in the televancin treated groups.
Rat	Pre- and post-natal development, Including maternal function AMI CSN: 02-001-07	5% dextrose Placebo 50 mg/kg/d televancin 100 mg/kg/d televancin 150 mg/kg/d televancin By slow IV bolus daily 25 females per group	Gestational day 6 to Lactation day 20	Televancin treated F_0 dams in the two higher dose groups had decreased mean maternal body weights, mean body weight changes, and food consumption. Total litter death in 3 F_0 dams: 1 placebo, 2 high dose. There was a dose-related increase in the number of stillborn pups and the number of dams with stillborn pups. F_1 pups in the high dose group were cyanotic (2 litters), swollen (2 litters), and anophthalmic (3 litters), and one pup had brachymelia (limited use of a forelimb). These findings were consistent with those a previous study. Compared to controls, mean F_1 pup weights were decreased at 50 mg/kg/d. On necropsy, all F_1 pups treated with televancin had dilated renal pelvices compared with 1 control female pup. NOAEL for F_0 maternal effects = 50 mg/kg/d NOAEL for F_1 fetal/pup effects = 100 mg/kg.d

Table 1: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Televancin Hydrochloride				
Species	**Study Type**	**Treatment Groups**	**Treatment Duration**	**Positive Findings**
Minipig	Embryo-fetal development	Diluent (5% dextrose) Placebo 25 mg/kg/d televancin 50 mg.kg/d televancin 75 mg/kg/d televancin By slow IV bolus daily 14 females per treatment group	Gestational days 11-35 Toxicokinetic satellite groups (3 animals/group) dosed gestational days 11-16 only and then euthanized	Number of and reasons for dams sacrificed *in extremis* were similar by treatment group. ▪ Many of these animals were treated with other antimicrobial agents(3 topical ointments, 3 systemic agents)[1] ▪ Pregnancy rates seemed unacceptably low to the review pharmacologist, especially in the placebo (36%) and high dose televancin (36%) groups[2] ▪ There were an increased number of late resorptions noted in the mid and high dose groups compared to historical controls ▪ There was a > 100% increase in post-implantation loss in the high dose treatment group compared with placebo and diluent ▪ 45% of televancin-treated litters had feti with external and soft tissue abnormalities compared to 14% of litters and 20% of litters in the diluent and placebo groups respectively. ▪ Among 58 feti from the placebo and diluent treated groups, the sponsor noted 1 fetus with retained testes and 1 with retained testes and polydactyly[3] ▪ Among 84 feti from the televancin treated groups, the sponsor noted the following findings: 9 feti with polydactyly (3 on two limbs), 1 fetus with diaphragmatic hernia, one with discolored diaphragm, one with syndactyly, and one with retained testes In addition, the pharmacology reviewer noted: a low dose fetus with defomred head and a misshapen digit; a mid-dose fetus with "legs turned inward"; a mid-dose fetus with multiple absent ossification sites and bilateral absence of tarsal bones; a mid-dose fetus with absent ossification sites distal to the metacarpi; a mid-dose fetus with exophthalmos; a mid-dose fetus with anencephaly; a high-dose fetus with deformed head, forelegs, and snout (very autolytic); and a high dose fetus with a deformed hind leg.

[1] According to the pharmacologist, this is very unusual among toxicology studies submitted for regulatory review. These animals were evenly distributed among treatment groups but call the validity of the study into question.

[2] Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies.

[3] The historical Danish database shows that the incidence of syndactyly is ≤ 0.4% and the incidence of pentadactyly was ≤2.3% for the past five years. However, after a change from line breeding to a population based breeding program in November 2004, these rates declined to <0.2% and <0.7% respectively. The historical Japanese database shows a 1.4% incidence of polydactyly among newborn piglets, a preimplantation loss rate of 11.7%, and a post-implantation loss rate of 15.6%.

Both the sponsor and Dr. Terry Peters, FDA pharmacology reviewer, acknowledge potential confounding factors in the minipig study; however, they disagree about their impact on study result interpretation and application. Many of the minipigs were treated with other antimicrobial agents(3 topical ointments, 3 systemic agents)[4], but these animals were evenly distributed among treatment groups. Dr. Peters found the minipig pregnancy rates unusually low, especially in the placebo (36%) and high dose televancin (36%) groups.[5] Pregnancy rates were 64% in the low-dose group and 57% in the mid-dose group. Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies. There were an increased number of litters with late resorptions noted in the mid dose (mean = 0.6) and high dose (mean = 0.8) groups compared to historical controls (maximum mean = 0.4).

Reviewer comment:

While these aberrations in the minipig study should not be discounted, the study findings are still very worrisome. The post-implantation loss increased by more than 100% in the high dose treatment group compared with the placebo and diluent treatment groups. Increased pregnancy loss and skeletal anomalies occurred at increased rates in all three species of animal studied. These similarities should not be attributed to coincidence and confounding alone.

Table 2 summarizes the main fetal findings from the reproductive toxicology studies conducted using televancin in rats, rabbits, and minipigs. In addition, it includes details about televancin's antimicrobial coverage for the proposed indication, complicated skin and skin structure infections (cSSSI).

Table 2: Summary of Televancin's Reproductive Toxicology Data and Antimicrobial Coverage for cSSSI Indication

Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Televancin	?	Reproductive studies in rats, rabbits, and minipigs showed increased post-implantation losses and increased skeletal malformations including limb abnormalities and absent or decreased ossification centers. There effects occurred at doses 1 – 15 times the human therapeutic dose. In rats, sperm motility was decreased and abnormal sperm morphology was increased.	cSSSI caused by susceptible strains of the following gram positive organisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible isolates only)

This information can be compared and contrasted with the reproductive toxicology study information included in the pregnancy section of labeling for all anti-microbials approved by the FDA for the treatment of cSSSI. This information is shown in Table 3 on following pages.

[4] According to the pharmacologist, this is very unusual among toxicology studies submitted for regulatory review.
[5] Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies.

Table 3: Anti-microbial Drugs Approved For the Treatment of Complicated Skin and Skin Structure Infections			
Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Daptomycin	B	Studies performed in rats and rabbits at doses up to 2 and 4 times the human dose showed no evidence of fetal harm. There are no adequate and well-controlled studies in women.	cSSSI caused by susceptible isolates of the following gram positive organisms: *Staphylococcus aureus* (including methicillin resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis*, and *Enterococcus faecalis* (vancomycin susceptible isolates only)
Piperacillin/ Tazobactam	B	Piperacillin: Reproduction and teratology studies in mice and rats have not revealed impaired fertility or harm to the fetus at 0.5 to 1 times the maximum human dose. Tazobactam: Reproduction studies in rats revealed no evidence of impaired fertility at up to 3 times the maximum human dose. There are no adequate and well-controlled studies in women.	Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections, caused by piperacillin-resistant β–lactamase producing strains of *Staphylococcus aureus*
Ertapenum	B	Mice and rats given three times and 1.2 times the equivalent human dose respectively showed no evidence of developmental fetal toxicity. In mice, there was a slight decrease in mean fetal weight and an associated decrease in the average number of ossified sacrocaudal vertebrae. There are no adequate and well-controlled studies in women.	cSSSI, including diabetic foot infections without osteomyelitis, due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia*
Meropenem	B	Reproductive studies in the rat (1.8 times the human dose) and cynomolgus monkeys (3.7 times the human dose) revealed no evidence of impaired fertility or harm to the fetus due to meropenem. There were slight changes in fetal body weight at 0.4 times the human dose. There are no adequate and well-controlled studies in women.	cSSSI due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species
Levofloxacin	C	Not teratogenic in rats at doses up to 9.4 times the oral human dose and 1.9 times the IV dose. The higher doses caused reduced fetal weights and increased fetal mortality. No teratogenic effects were seen in rabbits at doses 0.5 to 1.1 times the human dose. There are no adequate and well-controlled studies in women.	cSSSI due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Enterococcus faecalis*, *Streptococcus pyogenes*, or *Proteus mirabilis*
Linezolid	C	Not teratogenic in mice, rats, or rabbits at doses of 0.6 to 6 times the human therapeutic dose. However, embryo and fetal toxicities occurred. There are no adequate and well-controlled studies in women.	cSSSI, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicilin susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*

Table 3: Anti-microbial Drugs Approved For the Treatment of Complicated Skin and Skin Structure Infections			
Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Vancomycin	C	No reproductive animal studies were conducted. There are no adequate and well-controlled studies in women. One small study of pregnant women using vancomycin in the second and third trimesters was published. This study evaluated the potential ototoxic and nephrotoxic effects of vancomycin on infants following maternal exposure. No sensorineural hearing loss or nephrotoxicity was attributed to vancomycin. The number of patients studied was limited. No other fetal/neonatal effects were reported.	cSSSI caused by susceptible strains of methicillin-resistant staphylococci
Tigecycline	D	Not teratogenic in the rat or the rabbit. Slight reductions in fetal weight and an increased incidence of minor skeletal anomalies (delays in bone ossification) occurred at 5 times and 1 time the human daily dose. Doses equivalent to the human dose were materno-toxic in rabbits and resulted in an increased incidence of fetal loss in rats and rabbits. There are no adequate and well-controlled studies in women.	cSSSI caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (including methicillin resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus pyogenes*, and *Bacteroides fragilis*

There are no adequate and well-controlled studies in pregnant women for any of the eight antibiotics approved for the treatment of cSSSI. Four of these drugs have reproductive toxicology studies in two species negative for teratogenic effects (pregnancy category B drugs). Linezolid is pregnancy category C due to embryo-fetal toxicities (not clear if this refers to increased post-implantation loss) but no teratogenic effects were seen in mice, rats, or rabbits. Similarly, levofloxacin is pregnancy category C due to increased fetal mortality and reduced fetal weights, but no teratogenic effects were seen in rats or rabbits. Tigecycline has a pregnancy category D but this category does not appear to be supported by the reproductive toxicology data included in the label. There are no adequate and well-controlled studies in women. There was an increased incidence of minor skeletal anomalies (delays in bone ossification). An increased incidence of fetal loss in rabbits occurred at materno-toxic doses.

Compared to FDA-approved antimicrobial agents indicated for the treatment of cSSSI, televancin does not offer any unique antimicrobial coverage. Televancin is a drug for intravenous administration, so its once daily dosing, while convenient, would not offer substantial advantages in terms of patient compliance.

DISCUSSION

Telavancin is a semi-synthetic, lipoglycopeptide antibiotic that exhibits bactericidal activity against most gram-positive bacteria. The telavancin molecule core is identical to vancomycin and its antimicrobial coverage is similar. The current NDA application is for marketing televancin as an antimicrobial to treat complicated skin and skin structure infections (cSSSI). Based on data review by both the DAIOP microbiologist and medical officer, televancin is equivalent to, but not superior to, vancomycin for this indication. In addition, reproductive toxicology studies show similar teratogenic effects and increased post-implantation pregnancy loss in rats, rabbits, and Göttingen minipigs at non-maternotoxic doses of drug. While the presence or absence of teratogenic effects in any one animal species does not necessarily predict teratogenicity in developing humans, the occurrence of increased post-implantation loss and skeletal (limb) malformations across all three species at 1 – 15 times the human therapeutic dose is highly concerning. In addition, the minipig study showed a lower fecundity ratio than that in either historical database, and male fertility studies in rats showed decreased sperm motility and increased abnormal sperm morphology.

Televancin is a multi-species teratogen. Its classification with regard to use in pregnancy should be based on both its potential risk to mother and fetus as well as its potential clinical benefits above other available therapies. Currently, there are eight antimicrobial agents FDA approved for the treatment of cSSSI. Vancomycin remains first-line therapy for severe infections possible caused by MRSA. Based on current labeling for these approved cSSSI antimicrobial therapies, televancin does not offer broader or better antimicrobial coverage and has a much larger, consistent, and concerning animal safety signal for teratogenic potential in humans.

If approved, televancin would require a risk management action plan (RiskMAP) that could prevent use by pregnant women and provide for responsible outcomes tracking for those who

do become pregnant. Televancin is administered intravenously. It would potentially be used with direct or indirect healthcare practitioner supervision in hospitals, chronic care facilities, physician offices, and homes with instruction or home care assistance. However, unlike a teratogen that is used to treat a chronic condition (like isotretinoin), televancin would be used to treat severe skin and skin structure infections in acute care situations. Use in acute care situations and settings makes it more difficult to ensure that a woman of reproductive age is not pregnant prior to drug exposure. One negative serum pregnancy test is not adequate. Prior to initiating drug therapy, the iPLEDGE program for isotretinoin requires documented use of two forms of contraception for one month and two serum or highly sensitive urine pregnancy tests performed 19 days apart. These results must be documented and reviewed in an electronic database system before the pharmacist will dispense drug. These sorts of safeguards are not feasible with an acute infection that requires immediate antimicrobial therapy.

CONCLUSIONS

For the proposed indication of cSSSI, televancin, if approved, should be assigned pregnancy category X because of a consistent teratogenic signal in three animal species combined with a lack of evidence of clinical benefit over eight other approved therapies for this indication. It is possible that data submitted for a different clinical indication in the future could support pregnancy category C if some direct benefit to mother or fetus was demonstrated. However, for the indication of cSSSI, there is no increase in benefit to offset the increase in risk for a pregnant patient.

A RiskMAP that includes education and reminders alone will not adequately safeguard against televancin use in pregnant women, and a RiskMAP with a performance-linked access system is probably not feasible in acute care situations to treat acute infections.

RECOMMENDATIONS

If televancin hydrochloride is approved, the Maternal Health Team recommends the following:

1. Boxed warning informing prescribers (and patients) that televancin caused congenital anomalies and increased pregnancy loss in rats, rabbits, and minipigs and is, therefore, a suspected teratogen in humans that should not be used in women of childbearing potential.

2. Pregnancy category X (based on no benefit over current therapies combined with a consistent teratogenic and pregnancy loss safety signal in three species).

3. Indicated populations should include adult men and adult women who are not of childbearing potential. The following definitions may be used:

   Females not of Child-Bearing Potential (non-FCBP) - Female patients who are not physically capable of becoming pregnant. This includes pre-pubertal females (Tanner Stages 1 and 2) and females who have undergone surgical (i.e., removal of the ovaries and/or the uterus) or natural menopause (see definition of menopause below). The risk

management plan should require confirmation of menopausal status and detail the procedure(s) providers will use for documenting and verifying non-FCBP patient status (e.g. by obtaining copies of surgical records or conducting blood tests – see below).

Menopause is the permanent cessation of menstruation following the loss of ovarian activity. Women pass through a transition from the reproductive stage of life to the post menopausal years, a period marked by waning ovarian function. This commonly occurs over a few years. The median age of menopause in the United States is 51.5 years. [6] A provider may assume that a woman is in menopause when there is:

- Appropriate medical documentation of prior complete bilateral oophorectomy, which results in surgically-induced menopause at the time of the procedure, or
- Permanent cessation of menses (no menses for 12 months or longer) as a result of ovarian failure. Hormonal changes consistent with ovarian failure should be properly documented in the case of suspected spontaneous menopause as follows[7,8]:
  - If age >54 years and normal menses are absent: Elevated serum FSH (Follicle Stimulating Hormone) level in the post-menopausal range based on the laboratory reference range where the hormonal assay is performed.
  - If age <54 years and normal menses are absent: Negative serum or urine β-HCG with concurrently elevated serum FSH (Follicle Stimulating Hormone) level in the post-menopausal range, depressed estradiol (E_2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

4. Restricted distribution at the pharmacy level that requires documentation of age and gender of the patient. If the patient is female, documentation of menopause or other evidence of non-childbearing potential should be required.

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[6] Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility, Chapter 18, 5th ed. 1994. Williams & Wilkins.

[7] Midlife Transitions: A Guide to Approaching Menopause 2003 [AP013] ACOG Patient Education Pamphlet. Available at: http://www.acog.org/publications/patient_education/ab013.cfm, accessed April 22, 2005.

[8] http://www.ipledgeprogram.com

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REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anti-Infective and Ophthalmology Products (DAIOP)

Application Number: 22-110

Name of Drug: Telavancin (telavancin hydrochloride)

Applicant: Theravance, Inc.

Material Reviewed:

Submission Date(s): December 6, 2006

Receipt Date(s): December 19, 2006

Submission Date of Structure Product Labeling (SPL): December 6, 2006

Type of Labeling Reviewed: Word and SPL versions

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following editorial issues have been identified in the proposed labeling in the sections listed:

HIGHLIGHTS OF PERSCRIBING INFORMATION:

1. The HIGHLIGHTS OF PERSCRIBING INFORMATION section should not exceed ½ page in length (8 point font).

2. [redacted] b(4)

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Other 2

4.

b(4)

FULL PERSCRIBING INFORMATION:

1.

2.

3.

b(4)

RECOMMENDATIONS:

The above listed review issues will be conveyed to the Sponsor via facsimile, and a copy of the facsimile will be placed in the division file system (DFS).

J. Christopher Davi, MS
Regulatory Project Manager
DAIOP

Supervisory Comment/Concurrence:

Frances V. Lesane
Chief, Project Management Staff
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Drafted: J. Christopher Davi (2/28/07)
Revised/Initialed: Frances LeSane (3/1/07)
Finalized: J. Christopher Davi (3/1/07)
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

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3/1/2007 01:58:15 PM
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