CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

CHEMISTRY REVIEW(S)

Revised specification which was previously reviewed and found acceptable.

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

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/s/

BALAJEE SHANMUGAM
09/10/2009

MEMORANDUM

Date: September 8, 2009

To: NDA 22-110

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-110, Vibativ (televancin hydrochloride) for injection

I have assessed the ONDQA reviews of NDA 22-110 and concur with the approval recommendation from a CMC perspective.

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

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/s/

ELAINE M MOREFIELD
09/08/2009
Tertiary review

NDA 22-110

VIBATIV™
(telavancin hydrochloride)
For Injection

Theravance, Inc.

Balajee Shanmugam, Ph.D
Division of Pre-Marketing Assessment, Branch IV
ONDQA

Chemistry Review Data Sheet

1. NDA 22-110

2. REVIEW #: 3

3. REVIEW DATE: 10-June-2009

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	13-March-2009
Amendment	05-May-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Theravance, Inc.
Address:	901 Gateway Boulevard, South San Francisco, CA 94080.
Representative:	Rebecca Coleman, PharmD
Telephone:	650-808-6076

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: VIBATIV™
b) Non-Proprietary Name (USAN): telavancin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile lyophilized powder for injection

12. STRENGTH/POTENCY: 250 and 750 mg

13. ROUTE OF ADMINISTRATION: Intravenous infusion

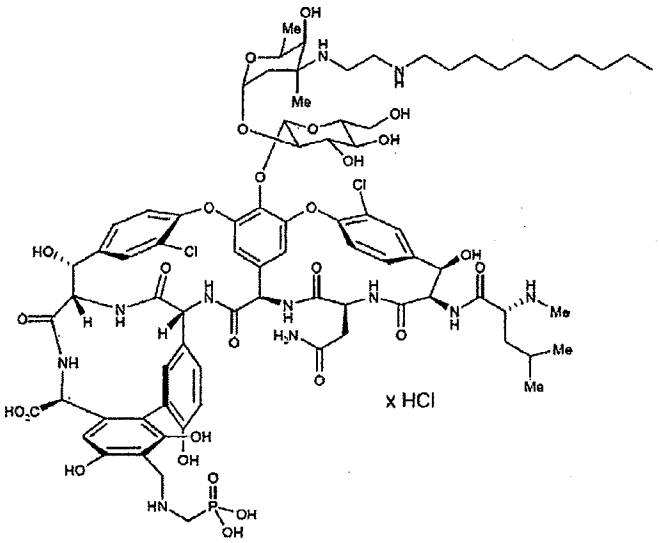
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Vancomycin, N3″ [2 (decylamino) ethyl] 29 [[(phosphono-methyl) amino] methyl] hydrochloride.
Molecular formula: $C_{80}H_{106}Cl_2N_{11}O_{27}P$. xHCl (where x= 1-3)
Molecular weight: 1755.63 (free base)
CAS: 380636-75-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a	n/a	n/a
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
DMETS			
EA			
Microbiology			

The Chemistry Review for NDA 22-110

The Executive Summary

Recommendation and Conclusion on Approvability

All chemistry review issues have been successfully negotiated with the company. While all significant labeling issues have been addressed, there remains one minor labeling issue that remains to be negotiated with the company. However, this will not negatively impact the overall quality of the NDA application. Therefore, the application is recommended Approval from the chemistry, manufacturing and controls perspective.

Chemistry Assessment

Please refer to chemistry review 1and 2 by this reviewer for details on the drug substance and drug product.

The original submission (dated 06-Dec-2006) was issued an Approvable on 19-Oct-2007. One of the deficiencies cited in the Action Letter was the non-compliance with cGMP of the drug product (contract) manufacturer Ben Venue (BVL) in Bedford, Ohio. The facility was later recommended Acceptable by the Office of Compliance on 04-June-2008.

The company was issued a Complete Response (CR) on 20-Feb-2009. The CR had no chemistry deficiencies. In response to the CR, Theravance submitted a response on 13-March-2009 (receipt date 16-March-2009).

Update on Drug Product Stability Data

Theravance submitted an update to the stability of the drug product on 05-May-2009. This submission provided for [redacted] months data and the company requested an extension of the expiration dating period from [redacted] months to 48-months for drug product stored at the proposed storage condition of 5°C. Tables 1 and 2 provide a summary of the stability data of the 250 mg and 750 mg strengths. Analysis of the data showed no significant change in values of the quality attributes tested, nor was any trend apparent. The company has also used regression analysis to justify the requested extension to [redacted] months. Details of this study are presented in Report DVR530 (version 3.). Based on the stability data presented, the request for extension of expiration dating from [redacted] months to 48-months for drug product stored at 5°C is acceptable.

Table 1. Stability Results for 4 Lots of 250 mg/vial Registration Stability Lots at Time Zero and 24-months.

Tests	Methods	Commercial Specifications	Initial Time Point	Data At 36 Months	
				5°C	25°C/60% RH
Appearance of Lyophilized Dosage Form	QCT095	White to slightly colored.	Complies	Complies	Complies
Reconstitution time (minutes)	QCT095	NMT			
Appearance of Constituted Solution	QCT095	Conforms to USP <1>	Complies	Complies	Complies
pH of Constituted Solution Dosage Form	QCT095	4.0 - 5.0			
HPLC Assay (%LC)	QCT081				
Degradation Products by HPLC (%w/w)	QCT081	Specified Degradants Degradant A NMT Degradant B NMT Total Degradation Products NMT			
Water Content (%w/w)	QCT038	NMT			
Sterility	USP <71>	Sterile	Complies	Complies	Complies
Particulate Matter (particules per container)	USP <788>	NMT NMT			

b(4)

b(4)

b(4)

b(4)

Table 2. Stability Results for 2 Lots of 750 mg/vial Registration Stability Lots at Time Zero and 18-months.

Tests	Methods	Commercial Specifications	Initial Time Point	Data At 36 Months	
				5°C	25°C/60% RH
Appearance of Lyophilized Dosage Form	QCT095	White to slightly colored,	Complies	Complies	Complies
Reconstitution time	QCT095	NMT			
Appearance of Constituted Solution	QCT095	Conforms to USP <1>	Complies	Complies	Complies
pH of Constituted Solution Dosage Form	QCT095	4.0 - 5.0			
HPLC Assay (%LC)	QCT081				
Degradation Products by HPLC (%w/w)	QCT081	Specified Degradants Degradant A NMT Degradant B NMT Total Degradation Products NMT			
Water Content (%w/w)	QCT038	NMT			
Sterility	USP <71>	Sterile	Complies	Complies	Complies
Particulate Matter (particules per container)	USP <788>	NMT NMT			

b(4)

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b(4)

Labeling

We had recommended revision of the dilution scheme (to prepare various dosing strengths) and provide the details in a table for the package insert. Instead, the company has provided the formula to calculate this amount. This is acceptable.

The minor issue that is currently under negotiation is about the total volume of the reconstituted solution. After reconstitution, the total volume is ( ) ml which at present is not mentioned in the package insert. Inclusion of this information may avoid any possible confusion. However, this issue will not negatively impact labeling or cause any errors in preparing the dosing solution. Therefore, from CMC perspective, this application is recommended Approval.

b(4)

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/s/

Balajee Shanmugam
6/10/2009 10:52:52 AM
CHEMIST
CMCReview3

Norman Schmuff
6/11/2009 08:10:48 AM
CHEMIST

NDA 22-110

VIBATIV™
(telavancin hydrochloride)
For Injection

Theravance, Inc.

Balajee Shanmugam, Ph.D
Division of Pre-Marketing Assessment, Branch IV
ONDQA

Chemistry Review Data Sheet

1. NDA 22-110

2. REVIEW #: 2

3. REVIEW DATE: 05-SEPTEMBER-2008

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	21-Jan-2008
Amendment	12-Feb-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Theravance, Inc.
Address:	901 Gateway Boulevard, South San Francisco, CA 94080.
Representative:	Rebecca Coleman, PharmD
Telephone:	650-808-6076

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: VIBATIV™
b) Non-Proprietary Name (USAN): telavancin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile lyophilized powder for injection

12. STRENGTH/POTENCY: 250 and 750 mg

13. ROUTE OF ADMINISTRATION: Intravenous infusion

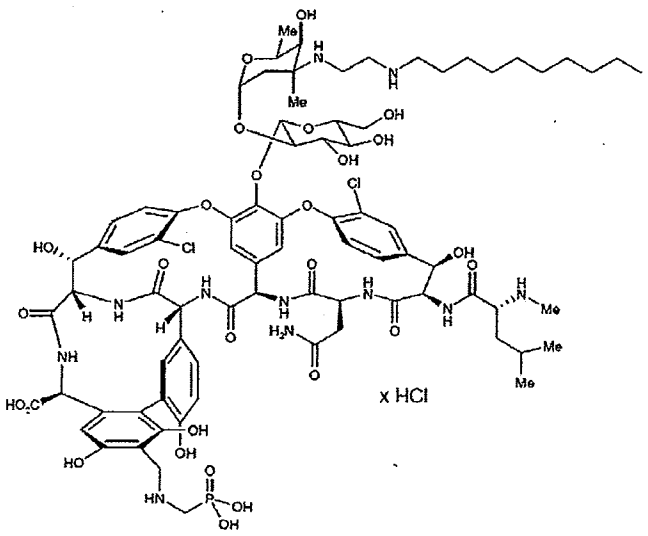
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Vancomycin, N3″ [2 (decylamino) ethyl] 29 [[(phosphono-methyl) amino] methyl] hydrochloride.
Molecular formula: $C_{80}H_{106}Cl_2N_{11}O_{27}P$. xHCl (where x= 1-3)
Molecular weight: 1755.63 (free base)
CAS: 380636-75-9



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6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a	n/a	n/a
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
DMETS			
EA			
Microbiology			

Chemistry Assessment Section

The Chemistry Review for NDA 22-110

The Executive Summary

Recommendation and Conclusion on Approvability

The application is recommended Approval from the chemistry, manufacturing and controls perspective. The cGMP non-compliance deficiency of the BenVenue facility which manufactures the drug product was one of the reasons for Approvable of the original submission. Office of Compliance has now recommended Acceptable of this facility indicating that the facility now conforms to cGMP operations. All chemistry review issues have been successfully negotiated with the company and resolved and it is only some minor labeling issues that remain to be negotiated with the company.

Chemistry Assessment

Please refer to chemistry review 1 by this reviewer for details on the drug substance and drug product.

The original submission (dated 06-Dec-2006) was issued an Approvable on 19-Oct-2007. One of the deficiencies cited in the Action Letter was the non-compliance with cGMP of the drug product (contract) manufacturer Ben Venue (BVL) in Bedford, Ohio. When Theravance submitted its response (21-Jan-2008) to the Action Letter, a request in EES was made by this reviewer to the Office of Compliance (OC) for their evaluation and recommendation of BVLs Bedford facility. A recommendation of Acceptable of the facility was issued by OC on 04-June-2008 which indicates that the facility is now in conformance with cGMP operations.

The deficiency has been resolved.

Update on Drug Product Stability Data

Theravance provided an update to the stability of the drug product and requested an extension of the expiration dating period from / months to / months for drug product stored at the proposed storage condition of 5 °C. The update provides 24-month data for the 250 mg strength registration lots, 18-month data for the 750-mg strength registration lots and 24-month data for the drug substance. Tables 1 and 2 provide a summary of the stability data of these strengths. Analysis of the data showed no significant change in values of the quality attributes tested, nor was any trend apparent. The company has also used regression analysis to justify the requested extension to / months. Details of this study are presented in Report DVR530. Regression analysis of degradant B (best predictor of stability of the drug product) and assay data of individual lots is presented in Figures 1 and 2, respectively. Based on the stability data presented, the request for extension of expiration dating from / -months to / -months for drug product stored at 5 °C is acceptable.

b(4)

Table 1. Stability Results for 4 Lots of 250 mg/vial Registration Stability Lots at Time Zero and 24-months.

Tests	Methods	Commercial Specifications	Initial Time Point	Data At 24 Months	
				5°C	25°C/60% RH
Appearance of Lyophilized Dosage Form	QCT095	White to slightly colored,	Complies	Complies	Complies
Reconstitution time (minutes)	QCT095	NMT			
Appearance of Constituted Solution	QCT095	Conforms to USP <1>	Complies	Complies	Complies
pH of Constituted Solution Dosage Form	QCT095	4.0 - 5.0			
HPLC Assay (%LC)	QCT081				
Degradation Products by HPLC (%w/w)	QCT081	Specified Degradants Degradant A Degradant B Total Degradation Products NMT			
Water Content (%w/w)	QCT038	NMT			
Sterility	USP <71>	Sterile	Complies	Complies	Complies
Particulate Matter (particules per container)	USP <788>	NMT NMT			

b(4)

b(4)

b(4)

b(4)

a See discussion on downward trend in stability data (Section 2.3).

Table 2. Stability Results for 2 Lots of 750 mg/vial Registration Stability Lots at Time Zero and 18-months.

Tests	Methods	Commercial Specifications	Initial Time Point	Data At 18 Months	
				5°C	25°C/60% RH
Appearance of Lyophilized Dosage Form	QCT095	White to slightly colored,	Complies	Complies	Complies
Reconstitution time	QCT095	NMT			
Appearance of Constituted Solution	QCT095	Conforms to USP <1>	Complies	Complies	Complies
pH of Constituted Solution Dosage Form	QCT095	4.0 - 5.0			
HPLC Assay (%LC)	QCT081				
Degradation Products by HPLC (%w/w)	QCT081	Specified Degradants Degradant A Degradant B Total Degradation Products NMT			
Water Content (%w/w)	QCT038	NMT			
Sterility	USP <71>	Sterile	Complies	Complies[c]	Complies[c]
Particulate Matter (particules per container)	USP <788>	NMT NMT			

b(4)

b(4)

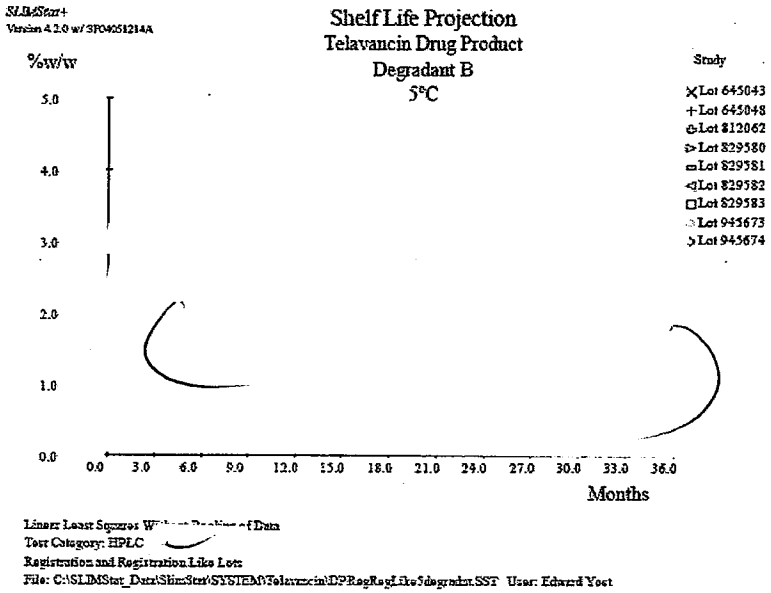
b(4)

a This value for water content is from the 13 month time point, because water content was not tested per the stability protocol at the 18 month time point.

b This value for particulate matter is from the 13 month time point, because particulate matter was not tested per the stability protocol at the 18 month time point.

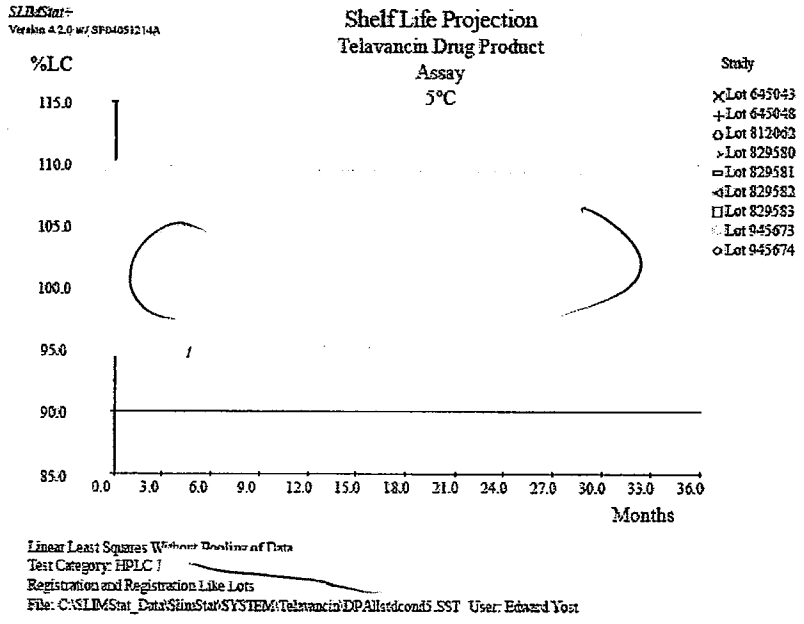
c This result is from the 12 month time point, because sterility was not tested per the stability protocol at the 18 month time point.

Figure 1. Combined Individual Regression Analysis of Degradant B Data for Drug Product Registration and Registration Like Lots.



b(4)

Figure 2. Combined Individual Regression Analysis of Assay Data for Drug Product Registration and Registration Like Lots.



b(4)

Labeling

While a significant part the PI and container/carton label is adequate, some minor issues (revised carton/container label with new Trade name) are currently being negotiated with the company. Should it be deemed necessary, a memo documenting significant chemistry related revisions to the label, if any, will be filed.

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/s/

Balajee Shanmugam
10/29/2008 08:33:24 AM
CHEMIST
NDA22-110

Norman Schmuff
11/18/2008 09:26:21 AM
CHEMIST

MEMORANDUM

Date: October 16, 2007

To: NDA 22-110

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-110, Vibativ (televancin hydrochloride) for injection

I have assessed the ONDQA review of NDA 22-110 and concur with the approvable recommendation from a CMC perspective. I support the overall not approvable action.

ONDQA has suggested the following wording for the action letter to cover the CMC issues: "FDA inspection of the Ben Venue facility in Bedford, Ohio revealed significant deviations from the Current Good Manufacturing Practice regulations. A satisfactory resolution of these violations is required before this application can be approved."

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/s/

Elaine Morefield
10/16/2007 01:48:16 PM
CHEMIST

NDA 22-110

VIBATIV™
(telavancin hydrochloride)
For Injection

Theravance, Inc.

Balajee Shanmugam, Ph.D
Division of Pre-Marketing Assessment, Branch IV
ONDQA

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Chemistry Review Data Sheet

1. NDA 22-110

2. REVIEW #: 1

3. REVIEW DATE: 18-JUNE-2007

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-Dec-2006
IR Response	21-Dec-2006
IR Response	06-Feb-2007
IR Response	08-May-07
IR Response	22-May-07
IR Response	07-June-07
IR Response	25-July-07
IR Response	07-August-07

7. NAME & ADDRESS OF APPLICANT:

Name:	Theravance, Inc.
Address:	901 Gateway Boulevard, South San Francisco, CA 94080.
Representative:	Rebecca Coleman, PharmD
Telephone:	650-808-6076

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: VIBATIV™

b) Non-Proprietary Name (USAN): telavancin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile lyophilized powder for injection

12. STRENGTH/POTENCY: 250 and 750 mg

13. ROUTE OF ADMINISTRATION: Intravenous infusion

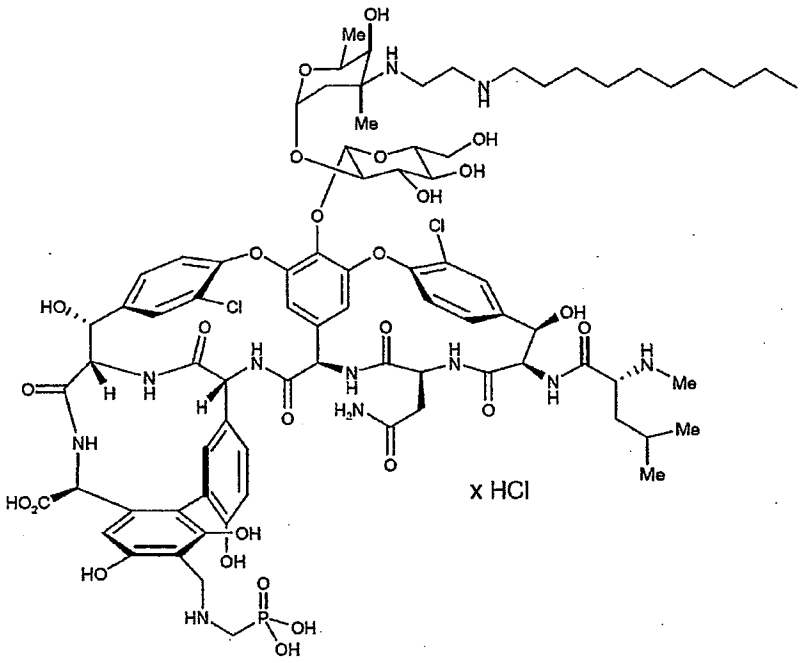
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Vancomycin, N3″ [2 (decylamino) ethyl] 29 [[(phosphono-methyl) amino] methyl] hydrochloride.
Molecular formula: $C_{80}H_{106}Cl_2N_{11}O_{27}P$. xHCl (where x= 1-3)
Molecular weight: 1755.63 (free base)
CAS: 380636-75-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	15-May-2006	N/A
	III			3, 4	Adequate	15-June-2007	N/A
	V			3, 4	Adequate	10-May-2007	N/A
	III			3, 4	Adequate	17-Aug-2006	N/A
	III			3, 4	Adequate	23-Dec-2002	N/A
	V	Ben Venue Laboratories	Manufacturing-Sterilization	4, 7	Adequate	20-April-2007	Microbiology review

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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B. Other Documents:

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a	n/a	n/a
EES	Pending	13-AUG-07	
Pharm/Tox	Acceptable	28-JUN-07	Dr. Zhou Chen
Biopharm	n/a	-	
LNC	n/a	-	
Methods Validation	Not requested	-	
DMETS			
EA	Categorical exclusion	31-JUL-2007	B. Shanmugam
Microbiology	Acceptable	18-JUNE-2007	Dr. John Metcalfe

The Chemistry Review for NDA 22-110

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended Approvable from the chemistry, manufacturing and controls perspective, pending recommendation from Office of Compliance (OC). The BenVenue facility which manufactures the drug product has been cited for non-compliance with GMP which prompted a "Withhold" recommendation by OC. All chemistry review issues have been successfully negotiated with the company and resolved and it is only labeling that remains to be negotiated with the company.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

While no recommendations for Phase 4 CMC commitments are made, the firm should, as committed in the submission, continue to monitor the stability of the drug product.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Telavancin is formulated as a sterile, preservative-free white to slightly colored lyophilized
containing either 250 mg or 750 mg of telavancin fee base for intravenous use following reconstitution with 5% dextrose injection or 0.9% sodium chloride injection. The inactive ingredients are hydroxypropylbetadex, Ph. Eur (hydroxypropyl-beta-cyclodextrin) (2500 mg per 250 mg telavancin, 7500 mg per 750 mg telavancin), mannitol (312.5 mg per 250 mg telavancin, 937.5 mg per 750 mg telavancin) and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment. The reconstituted solution is clear to slightly colored solution with a pH of 4.5 (4.0-5 . The drug product stability data provided for the 250 mg and 750 mg dosage strengths supports the requested expiration date of months when stored refrigerated at 5°±3° C. b(4)

The drug substance telavancin hydrochloride is a semi-synthetic purified lipoglycopeptide antibacterial agent derived from the modification of vancomycin. Telavancin acts by inhibiting bacterial cell wall biosynthesis and disruption of the functional integrity of the bacterial plasma membrane. Telavancin hydrochloride is vancomycin, *N*3"-[decylamino)ethyl-29-[[phosphonomethyl)amino]methyl]-hydrochloride. The drug substance occurs as an off-white to slightly colored solid. The solubility of telavancin in water is classified as soluble slightly soluble) and very slightly soluble above pH 4.5. One of the key starting materials in the synthesis of telavancin is vancomycin) Because of the) vancomycin and as agreed with the Agency for this reason, the company referenced DMF) for vancomycin. A LOA from the DMF holder) authorizing the Agency to refer to the DMF has been submitted. The DMF was previously reviewed by Dr. Maria Shih (review dated 2/24/2006) and found to be adequate. b(4)

B. Description of How the Drug Product is Intended to be Used

Vibativ™ is indicated for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible strains of select Gram positive bacteria. The intended dosing for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to 14 days. Telavancin for injection will be available in 250 mg and 750 mg strengths. The requested expiration date of \ months for product stored refrigerated at 5°±3°C is supported by adequate stability data. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The original submission and the subsequent amendments submitted by the firm have provided adequate information describing the CMC for Vibativ™ (telavancin HCl) for injection.

The DMF for vancomycin HCl, one of the key structural entities of the drug substance was previously and found to be adequate. The drug substance has been well characterized and the manufacturing process is well documented. The specification will ensure adequate control of the quality attributes and stability of the drug substance justifies the proposed retest date. The acceptance criteria for some of the quality attributes have been successfully negotiated with the applicant, the details of which are provided in Section S.4.1.

The manufacture of the drug product has been adequately described. The sterility part of the manufacturing process was reviewed by Dr. John Metcalfe, OPS/NDMS, HFD-805 and was found to be adequate in his review dated June 18, 2007. All issues regarding the drug product specifications have been adequately negotiated with the applicant. The company has established key process parameters in the manufacture of the drug product. The applicant will continue to monitor the stability of the drug substance and drug product. The BenVenue facility which manufactures the drug product was issued a 483 for non-compliance with cGMP which has prompted a "Withhold" recommendation by the Office of Compliance.

In accordance to 21 CFR 314.50, the application provides adequate information on manufacturing and packaging procedures, in-process controls, methods, and specifications.

III. Administrative

A. Reviewer's Signature

{see Electronic Signature Page}

B. Endorsement Block

Balajee Shanmugam/
Norman Schmuff/Date
Christopher Davi/Date

C. CC Block

110 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Balajee Shanmugam
9/5/2007 06:42:26 AM
CHEMIST
NDA22-110

Norman Schmuff
9/5/2007 08:53:25 AM
CHEMIST