

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206334Orig1s000**

**CHEMISTRY REVIEW(S)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Hitesh Shroff, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)  
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**FROM:** FDA

Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
645 S Newstead Avenue  
St. Louis, MO 63110  
Phone: (314) 539-3815

**Through:** John Kauffman, Deputy Director  
Phone: (314) 539-2168

**SUBJECT:** Methods Validation Report Summary

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Application Number: 206334

Name of Product: Orbactiv (oritavancin) for injection

Applicant: The Medicines Company

Applicant's Contact Person: Ketna Patel

Address: 8 Sylvan Way, Parsippany, NJ 07054

Telephone: (973) 290-6031 Fax: (862) 207-6031

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Date Methods Validation Consult Request Form Received by DPA: Jan-22-2014

Date Methods Validation Package Received by DPA: Jan-22-2014

Date Samples Received by DPA: Feb-6-2014

Date Analytical Completed by DPA: Jun-19-2014

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments: See analyst's attached memo for comments and summary of results.



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3815

Date: June 19, 2014  
To: Hitesh Shroff, CMC Reviewer  
Office of New Drug Quality Assessment  
Through: John F. Kauffman, Deputy Director, Division of Pharmaceutical Analysis  
From: Larry Revelle, Chemist  
Subject: Methods Validation for NDA 206334  
Orbactiv (oritavancin) for injection  
The Medicines Company

The following methods were evaluated and are acceptable for quality control and regulatory purposes with modification:

1. RTM.0560900 Assay and Related Substances by HPLC for Oritavancin
2. Quantification of Impurities in Oritavancin for Injection by HPLC

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods.

- Method 1: Addition of a table of relative retention times and an example chromatogram are necessary to identify and label the impurity peaks. An example chromatogram was provided in the validation data but is not provided in the method. DPA suggests that the method be modified to include a table of impurities with relative retention times, and an example chromatogram with identified impurities.
- Method 2: The applicant provided an ID standard and instructions regarding how to prepare ID standard material in the methods. The applicant's reference ID standard material, which was provided, was acceptable. However, an ID standard prepared following the instructions to (b) (4) and was not acceptable. DPA suggests that the instructions regarding preparation of the (b) (4) drug substance be clarified with respect the specific conditions required.

The following method was evaluated and is acceptable for quality control and regulatory purposes:

3. Assay and Identification for Oritavancin for Injection by HPLC

Analyst's work sheets and chromatograms are available at  
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88072648f>

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/s/  
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MICHAEL L TREHY  
06/19/2014

JOHN F KAUFFMAN  
06/19/2014

**NDA 206334****Orbactiv (oritavancin) for injection  
400 mg per vial****The Medicines Company****Hitesh Shroff, Ph.D.**

Review Chemist

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch V****CMC Review of NDA 206334  
For the Division of Anti-Infective Products  
(HFD-520)**

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# Chemistry Review Data Sheet

1. NDA 206334
2. REVIEW:#1
3. REVIEW DATE: 05-May-2014
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	06-Dec-2013
Amendment	21-Mar-2014
7. NAME & ADDRESS OF APPLICANT

Name:	The Medicines Company
Address:	8 Sylvan Way Parsippany, NJ 07054
Representative:	Ketna Patel Director, Regulatory Affairs
Telephone:	973-290-6031
Email:	ketna.patel@themedco.com
8. DRUG PRODUCT NAME/CODE/TYPE:
  - a) Proprietary Name: Orbactiv
  - b) Non-Proprietary Name (USAN): Oritavancin diphosphate
  - b) Code Name/# (ONDQA only): None
  - c) Chem. Type/Submission Priority (ONDQA only):
    - Chem. Type: 1
    - Submission Priority: P
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Antibacterial
11. DOSAGE FORM: Injection, powder lyophilized, for solution
12. STRENGTH/POTENCY: 400 mg Oritavancin per vial



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	11-Apr-2014	See P.7
	III			4			

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:** N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	Jan 10, 2014	Sharp, T.
Pharm/Tox	N/A		
Biopharm	Pending		Mahayni, Houda
LNC	N/A		
Methods Validation	Pending		Trehy, Michael L.
DMEPA	N/A		
EA	Claim for categorical exclusion		Hitesh Shroff
Microbiology	Pending		Pawar, Vinayak B.

# The Chemistry Review for NDA 206344

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The product quality microbiology review is pending as of the date of this review. All other CMC information in the NDA is sufficient to assure the identity, strength, purity and quality of the drug product.

An overall “Acceptable” recommendation for the facilities involved in this application from the Office of Compliance has been made as of this review.

The labeling issues and product quality microbiology recommendations are pending as of the date of this review. Therefore, from the ONDQA perspective, this NDA is *not* ready to recommend for approval in its present form until the pending issues are satisfactorily resolved.

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

*No* recommendations at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

##### (1) Drug Substance

Orbactiv contains oritavancin diphosphate as an active ingredient. It is a white to (b) (4) and it is manufactured by (b) (4)

Oritavancin diphosphate is a semi-synthetic lipoglycopeptide. The production of nucleus factor B involves classical fermentation using a strain of the bacterium *Kibdelosporangium aridum*. (b) (4)

The drug substance is characterized by mass spectroscopy, NMR spectroscopy methods and correlation with structurally related glycopeptides.

The drug substance specification includes appearance, identification, assay, impurities, water content, residual solvents, heavy metals and microbial contamination. The drug substance specification is deemed adequate to assure the identity, strength, purity, and quality of the drug substance.

The proposed retest period of (b) (4) months at (b) (4) is supported by the long term stability and accelerated stability data.

## (2) Drug Product

Orbactiv (oritavancin) for injection is a sterile, lyophilized white to off-white (b) (4) powder. It is supplied in a single use 50 ml USP/EP type I clear glass vial fitted with 20 mm gray (b) (4) rubber stoppers and sealed with 20 mm (b) (4) over seals. Each vial contains 449 mg of oritavancin diphosphate salt equivalent to 400 mg of oritavancin free base and (b) (4) of mannitol. A (b) (4) phosphoric acid solution is used to adjust the pH of the bulk solution (b) (4). Sterility is acquired by (b) (4). The acceptability of sterility and endotoxin are being reviewed by the product quality microbiology reviewer. The review is pending as of this date. The drug product is manufactured by (b) (4) and (b) (4) is performed at (b) (4).

The long term stability up to 36 months at 25°C/60% RH and accelerated stability at 40°C/75% RH up to 6 months of the drug product in to-be marketed container closure are ongoing. The stability studies of two drug product registration batches manufactured at (b) (4) (400 mg/vial), three registration batches manufactured at (b) (4) (400 mg/vial) and six batches of drug product for supportive stability studies manufactured at (b) (4) were performed in accordance with ICH Q1A (R2) guidance.

The proposed release specification of the finished product includes appearance, identification, assay of the active ingredient, impurities, dose uniformity, pH, particulate matter, sterility and microbial limits. The proposed specification is deemed adequate to assure the identity, strength, purity, and quality of the drug product.

Based on the stability data from the registration and supportive batches of drug product at long term ( up to 36 months) and accelerated (6 months) conditions, the proposed 36 months expiration dating period, when stored at room temperature, is granted.

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

Orbactiv (oritavancin) for injection is indicated for treatment of acute bacterial skin and skin structure infection. Orbactiv is available as a sterile, lyophilized white to off-white (b) (4) powder in single use vial for intravenous use.

Orbactiv is intended for intravenous administration after reconstitution with sterile water for injection followed by dilution with 5% Dextrose Injection USP to a concentration of 1.2 mg/ml prior to injection. There is a 1.25% oritavancin free base overfill (405 mg/vial) for vial retention to ensure the labeled content (400 mg oritavancin) is withdrawn.

Three Orbactiv vials need to be reconstituted and diluted to prepare a single 1200 mg IV dose. Each vial is reconstituted with 40 ml sterile water for injection and shaken gently to mix the drug product completely. Then 40 ml from each of reconstituted vials are added to D5W IV bag to bring the bag volume to 1000 ml.

Orbactiv must not be reconstituted or diluted with normal saline for dilution as this may cause precipitation. Therefore other IV substances, additives or other medications mixed in normal saline should not be added to orbactiv single-use vials or infused simultaneously through the same IV line. Oritavancin has been found to be incompatible with many commonly coadministered intravenous drugs. Also the intravenous drugs formulated at a basic or neutral pH may be incompatible with the drug product.

The reconstituted solution must be used in (b) (4) and the diluted IV solution in the infusion bag should be used within 6 hours at room temperature (b) (4) or within 12 hours when refrigerated (2°-8°C). Based on the stability data provided the storage conditions for reconstituted and diluted solutions are acceptable from CMC perspective. However, the micro review is not completed yet so the final storage conditions are not recommended at the time of this review.

### C. Basis for Approvability and Not-Approval Recommendation

The applicant has provided sufficient information regarding raw materials, manufacturing processes and process controls, specifications for assuring identity, purity, strength and quality of the drug substance and drug product. Sufficient drug substance and drug product stability study data is submitted to assure the strength, purity and quality during the retest period of the drug substance and the drug product expiration dating period. The drug substance and drug product manufacturing facilities have received acceptable recommendation from the Office of Compliance. However, at the time of this review the labeling issues and product quality microbiology recommendations are pending. Therefore, from the ONDQA perspective, this NDA is recommended for approval upon satisfactory resolution of pending issues.

**III. Administrative****A. Reviewer's Signature**

Hitesh Shroff, Ph.D./ 05-May-2014

**B. Endorsement Block**

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division II

**C. CC Block**

Dorota Matecka, Ph.D.

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/s/  
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HITESH N SHROFF  
05/07/2014

RAPTI D MADURAWA  
05/08/2014