CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206334 SUPPL # HFD # 520

Trade Name ORBACTIV

Generic Name oritavancin diphosphate for injection

Applicant Name The Medicines Company

Approval Date, If Known August 6, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

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d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

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NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

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summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

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If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

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GAIN Exclusivity Summary

NDA#: 206334

Product Name: Orbactiv (oritavancin diphosphate) for injection

Sponsor: The Medicines Company

1. Does this product have Qualified Infectious Disease Product (QIDP) designation?

YES	NO
X	

2. Is the indication(s) approved in this NDA or supplement the same as the indication(s) identified in the QIDP designation letter?

YES	NO
X	

3. Has this product or any product containing this drug previously received a 5-year GAIN exclusivity extension?

YES	NO
	X

There are no currently approved products containing oritavancin diphosphate and no products containing oritavancin diphosphate that have received an exclusivity extension under GAIN.

Name of person completing form: Naseya Minor, MPH

Title: Regulatory Project Manager

Date: *<see electronic signature>*

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH

Title: Director

Date: *<see electronic signature>*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASEYA N MINOR
08/06/2014

SUMATHI NAMBIAR
08/07/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206334 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Orbactiv Established/Proper Name: oritavancin diphosphate Dosage Form: 400 mg		Applicant: The Medicines Co. Agent for Applicant (if applicable):
RPM: Naseya Minor		Division: Division of Anti-Infective Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is August 6, 2014	☒ AP
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): IP
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Reference ID: 3606209

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	August 6, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included December 6, 2013
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	N/A
• Original applicant-proposed labeling	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptable March 4, 2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: July 1, 2014 DMEPA: May 19, 2014 DMPP/PLT (DRISK): May 12, 2014 OPDP: June 4, 2014 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	April 4, 2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC June 11, 2014 If PeRC review not necessary, explain: N/A	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	Emails included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	June 27, 2013
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	March 18, 2014
• Late-cycle Meeting *(indicate date of mtg)*	June 3, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	August 6, 2014
Division Director Summary Review *(indicate date for each review)*	August 6, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	July 9, 2014
PMR/PMC Development Templates *(indicate total number)*	7
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See primary review
• Clinical review(s) *(indicate date for each review)*	May 8, 2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

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❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	 N/A N/A May 12, 2014
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Letters May 14, 2014 (2) Reviews June 3, 2014
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	See primary review
Clinical Microbiology Review(s) *(indicate date for each review)*	June 21, 2014
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	See primary review
Statistical Review(s) *(indicate date for each review)*	May 27, 2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	See primary review
Clinical Pharmacology review(s) *(indicate date for each review)*	May 16, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	See primary review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	May 2, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	See primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	May 7, 2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	July 7, 2014 N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	May 8, 2014
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: May 8, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: N/A ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	☒ N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Reference ID: 3606209

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NASEYA N MINOR
08/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206334

GAIN Exclusivity

The Medicines Company
Attention: Ketna Patel, Pharm.D
Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Patel

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (FDCA) ORBACTIV (oritavancin diphosphate) sterile, lyophilized powder for injection 400 mg/vial for the treatment of Acute Bacterial Skin and Skin Structure Infections. We also refer to the letter, dated August 6, 2014, granting approval of this NDA.

We also refer to our correspondence dated October 31, 2013 to your Investigational New Drug (IND) Application 051292 in which we granted Qualified Infectious Disease Product (QIDP) designation for ORBACTIV (oritavancin diphosphate) Injection for the treatment of Acute Bacterial Skin and Skin Structure Infections.

This letter is to inform you that your application meets the criteria for the 5-year exclusivity extension under section 505E(a) of the Act. Five years of additional exclusivity will be added to any applicable exclusivity periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 505 of the Act; clauses (iii) and (iv) of subsection (c)(3)(E) and clauses (iii) and (iv) of subsection (j)(5)(F) of section 505 of the Act; or section 527 of the Act that are otherwise associated with the approval of this NDA.

If you have any questions, call Naseya Minor, Regulatory Project Manager, at (301) 796-0756.

Sincerely yours,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Antimicrobial Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
08/07/2014

From:Minor, Naseya
Sent:Monday, June 30, 2014 1:37 PM
To:ketna.patel@themedco.com
Subject:NDA 206334 Information Request PMRs

Hi Ketna,

We have a clinical information request regarding the post marketing requirements:

1.We note the two pediatric studies that will be post marketing requirements:

*An Open-label, Dose-finding, Pharmacokinetics, Safety and Tolerability Study of Oritavancin Single-Dose Infusion in Pediatric Subjects <18 Years of Age with Suspected or Confirmed Bacterial Infections.
*A multicenter evaluator blind, randomized, safety and tolerability study of oritavancin in pediatric subjects <18 Years of Age.

For your proposed pediatric Phase 2 safety study please provide a projected study completion date.

2.We are considering a post marketing requirement to conduct a clinical study to characterize the effect of oritavancin on clinical care and warfarin dosing, when oritavancin is administered to patients who are receiving chronic warfarin therapy and who have an infection justifying therapy with oritavancin. The intention is to determine the magnitude and duration, if any, of alterations to warfarin dosing or of clinically important consequences of adding the oritavancin. Study at least 25 patients on chronic warfarin therapy. Monitor the PT/INR frequently and monitor patients for any clinical consequences for at least 2 weeks' time. Submit a full protocol for our review and concurrence before beginning the study. Submit a full study report and all raw datasets.

Please provide your comments on the proposed study. We would also need to determine feasible timelines for this study.

Please submit a response no later Friday, July 11th.

Thanks

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
07/01/2014

From: Minor, Naseya
Sent: Friday, June 27, 2014 11:20 AM
To: ketna.patel@themedco.com
Subject: NDA 206334 Oritavancin Micro Information Request

Hi Ketna,

We have received your recent submission (NDA 206334, Amendment 19, 25 June 2014)
regarding the use of (b) (4)
of Oritavancin. Plea
submit your proposed edits to Section 12.4 of the PI (the complete section), including the
information you feel is appropriate (b) (4)
(b) (4)
(b) (4) and Oritavancin.

Please submit a response no later than Friday, July 11th.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
06/27/2014

From:Minor, Naseya
Sent:Thursday, June 12, 2014 3:50 PM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Carton and Container Labeling Comments

Hi Ketna,

We have additional carton and container labeling comments

Please update the container carton and immediate carton labels as shown below.

- Prominently display “Rx Only”

- Revise the drug name as follows:

Orbactiv (oritavancin) for injection
400 mg per vial

Each vial contains:
Oritavancin 400 mg
(equivalent to 449 mg oritavancin diphosphate)

- Revise the storage statement as shown below:

Store at 20ºC to 25ºC (68º to 77ºF); excursions permitted to 15ºC to 30ºC [see USP Controlled Room Temperature]

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
06/13/2014

From:Minor, Naseya
Sent:Tuesday, May 20, 2014 9:45 AM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Carton/Container Labeling Recommendations

Hi Ketna,

The Division of Medication Error and Prevention Analysis (DMEPA) has reviewed the proposed carton and container labels for Orbactiv for areas of vulnerability that could lead to medication errors. Based on the review, DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Carton labeling:

1. Replace (b)(4) with the conditionally acceptable name “Orbactiv” and present “Orbactiv” in title case to improve readability.
2. The product strength and the route of administration are located at the top portion of the labeling, separated from the proprietary name and established name. Relocate the product strength (400 m vial) and route of administration to below the established name. The highlighted (b)(4) section appears to take attention away from important information on the panel, such as the proprietary name and established name. Consider changing or remove the color of the highlighted section in order to not detract from important information on the labeling.
3. Revise the route of administration statement ‘For Intravenous (b)(4) to read‘ For Intravenous Infusion Only’ to minimize the risk of administering the drug too fast and prior to further dilution.
4. The net quantity statement (3 Single Use Vials per Dose) should be placed away from the product strength and have less prominence to avoid confusion with the strength of the product.
5. Consider removing the (b)(4) of the company name as this information already appears in black text on the labeling.
6. To ensure consistency with the container label, replace the word (b)(4) to “Exp.”
7. Relocate the NDC number to comply with CFR 207.35 (3) (i) which states that “the NDC number shall appear prominently in the top third of the principal display panel of the label on the immediate container and of any outside container or wrapper.”

B. Container Label
1. See comments A.1, A.2, A.3, and A.5 above.
2. For clarity, consider spelling out “CRT” as it may not be apparent that CRT is the abbreviation for controlled room temperature.

DAIP will provide package insert recommendations on or by May 31st. Please let me know if you have any questions in the meantime.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
05/20/2014

From:Minor, Naseya
Sent:Monday, May 19, 2014 11:36 AM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Oritavancin IR

Hi Ketna,

We have an information request for you:

Study MDCO-ORI-12-03 showed that concomitant administration of oritavancin can increase the exposure to warfarin by approximately 30%, and you have recommended that patients should be closely monitored for signs of bleeding in proposed product labeling. Additionally, you have stated in your application that “In vitro studies indicate that PTT results after an oritavancin dose may remain falsely elevated until oritavancin concentrations fall below 15 ?g/ml.” Pharmacokinetic data from MDCO-ORI-12-03 indicate that the concentration of oritavancin would fall below 15 mcg/mL between 24 and 48 hours post dose. Please clarify the extent and duration degree of the expected PTT elevation and comment on issues which can arise with concomitant use with heparin. Also, please clarify the duration of prolongation of INR that is expected during concomitant oritavancin and warfarin use.

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
05/19/2014

From:Minor, Naseya
Sent:Tuesday, May 06, 2014 8:50 AM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334Information Request

Hi Ketna,

We have a stats information request for you:

Comparing the tables for MSSA for the early clinical response and PTE in Table 26 (Clinical study reports: page 96 for SOLO I and page 95 of SOLO II)) do not match with the patients reported in Table 41 of summary of Clinical Efficacy (section 2.7.3). There a difference of 2 patients (n=266 vs. n= (b)(4) in oritavancin group and 5 patients (n=267 vs. n= (b)(4) in vancomycin group. Please recreate Table 41 (every entry) so that the number matches with the individual study reports.

Please submit a response as soon as possible.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
05/06/2014

From:Minor, Naseya
Sent:Friday, April 04, 2014 8:10 AM
To:ketna.patel@themedco.com
Subject:NDA 206334 Information Request

Importance:High

Hi Ketna,

We appreciate that you provided the BIMO Site Level Data in Module 5.3.5.4 of your submission. However, the data listings for Listing II.h.1 Primary efficacy outcome at ECE by treatment and Listing II.h.2 Investigator-assessed clinical cure at PTE by treatment contain derived endpoints (i.e. fever within 48 - 72 hours, no increase in lesion size and cure/failure, respectively). We request that you submit raw data listings used to generate the derived endpoint (i.e. endpoint outcome – yes/no, cure/failure). We request that you submit these data listings for the following site:
SOLO I: Site # 191008

Please submit this information to the NDA by close of business April 11, 2014.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
04/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206334

MID-CYCLE COMMUNICATION

The Medicines Company
Attention: Ketna Patel, PharmD
Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Patel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orbactiv (Oritavancin diphosphate) sterile, lyophilized powder for injection.

We also refer to the teleconference between representatives of your firm and the FDA on March 18, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Naseya Minor, Regulatory Project Manager at (301) 796-0756.

Sincerely,

{See appended electronic signature page}

John J. Alexander, MD, MPH
Clinical Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 18, 2014, 11:00 AM to 12:00 PM

Application Number: NDA 206334
Product Name: Oritavancin diphosphate
Indication: Acute bacterial skin and skin structure infections
Applicant Name: The Medicines Company

Meeting Chair: John Alexander, MD, MPH
Meeting Recorder: Naseya Minor, MPH

FDA ATTENDEES

Office and Antimicrobial Products (OAP)

John Farley, MD	Deputy Director
David Roeder, MS	Associate Director of Regulatory Affairs

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, MD, MPH	Division Director
Katherine Laessig, MD	Deputy Director
Mayurika Ghosh, MD	Medical Officer
Yuliya Yasinskaya, MD	Medical Officer
Kerry Snow	Microbiology Team Leader
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Dorota Matecka, PhD	CMC Team Leader
Hitesh Shroff, PhD	CMC Reviewer
Frances LeSane	Chief, Project Management Staff
Carmen DeBellas, RPh, PharmD	Regulatory Project Manager
Mona Atkinson, MS/MBA	Regulatory Project Manager
Naseya Minor, MPH	Regulatory Project Manager

Eastern Research Group, Inc.

(b) (4)	Consultant
(b) (4)	Consultant

APPLICANT ATTENDEES

The Medicines Company

Ketna Patel, PharmD	Director, Regulatory
Gopal Krishna, PhD	Vice President, Pharmaceutical Development
Judy Lee PhD	Senior Director, Regulatory/CMC

Hai Jiang, PhD	Senior Director, Biostatistics
Gregory Moeck, PhD	Senior Director, Microbiologist
Brad Zerler, PhD	Vice President Pre-Clinical Safety
S. Eralp Bellibas, MD, PhD	Senior Director, Clinical Pharmacologist
Dimitrios G Kountis, PhD	Senior Vice President, Global Launch Leader
Matthew Wikler, MD	Vice President, Clinical
Nuoyu Huang, MD	Medical
Yanshan Ma, MD	Senior Director, Global Pharmacovigilance
(b) (4)	Regulatory Consultant, (b) (4)
(b) (4)	Regulatory Consultant, (b) (4)

1.0 INTRODUCTION

After introductions, the Clinical Team Leader conveyed the following information:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

The following information requests have been issued and are pending:

Clinical: Dr. Alexander indicated during the meeting that there would be an information request, including a request for some case report forms, sent to the Medicines Company. See section 7.0 below.

Chemistry, Manufacturing, and Controls:
Provide a list and justifications of critical steps in the fermentation process (b) (4) .

In a tabular format, provide process parameters employed in critical steps of the fermentation process (b) (4)

Reference ID: 3481943

Provide a certificate from the manufacturer stating that the (b) (4) bulk drug substance storage (b) (4) materials comply with appropriate 21 CFR sections related to (b) (4) regulations.

Revise the drug product composition table in Sec. 3.2.P.1 to reflect both salt and free base amount per vial as follows: 449 mg oritavancin diphosphate (equivalent to 405 mg oritavancin free base)

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

FDA stated that there were no major safety concerns identified at this time; however at the time of the Mid-Cycle meeting, the Office of New Drugs and the Office of Surveillance and Epidemiology have not conclusively determined whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. A final determination on the need for REMS is expected to be made during the review of your application.

5.0 ADVISORY COMMITTEE MEETING

NDA 206334 is not expected to be taken to the Advisory Committee.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

May 31, 2014: The Division will be conveying preliminary, proposed revisions to the product labeling to you electronically. Be advised that these revisions may be limited to a certain section (or sections) of the label in stepwise fashion, as reviews are ongoing. In addition, we will communicate with you regarding any preliminary assessment(s) as to whether or not there will be post marketing commitments (PMC) and/or requirements (PMR).

June 3, 2014: This will be the date of your Late Cycle Review Meeting. You may elect to have this meeting by teleconference or in person with the review team at the White Oak Campus. We will provide a briefing document for this meeting to you electronically on or about May 30, 2014. Topics of discussion at the meeting include, but are not limited to substantive review issues, additional applicant data (e.g., to be submitted in response to any pending information request or at the applicant's discretion), REMS or other risk management actions, potential PMRs/PMCs and major labeling issues (if applicable).

August 6, 2014: The Agency will take an action on your application.

The Division confirmed that the information conveyed would be documented in the meeting minutes. During the teleconference, The Medicines Company inquired about the proprietary name review. The Division of Medication Errors Prevention and Analysis (DMEPA) has issued a letter stating that the proposed proprietary name, Orbactiv, is conditionally acceptable. There were no further questions/clarifications and the teleconference ended amicably.

7.0 POST-MEETING ADDENDUM

Reference ID: 3481943

On March 24, 2014, the clinical information request below was conveyed to The Medicines Company via e-mail.

Provide CRFs for the following subjects:

TMC-ORI- 10-01-101001-102, 101001-035, 101001-056, 101001-009, 101003-022, 101002-023, 101002-039, 101046-015, 101046-042, 101046-004, 101046-003, 101046-032, 101005-010, 191009-024

TMC-ORI-10-02-291002-022, 291003-008, 291003-008, 291006-025, 291006-038, 201035-006, 201035-040, 201001-159, 201001-173, 201001-189, 201001-106, 201001-050, 202001-007, 207002-005, 207002-027, 207002-040.

Define the parameter "Sustained Clinical Response-FDA" in the clinical response dataset. This is not clear from the reviewer's guide or the define file.

Define the denominator used for tabulation of data in Table 59 of the Integrated Summary of Safety report titled "Potentially clinically significant hematology results (Safety population)".

Reference ID: 3481943

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/s/

JOHN J ALEXANDER
04/02/2014

From:Ketna Patel <ketna.patel@THEMEDCO.com>
Sent:Monday, March 24, 2014 10:48 AM
To:Minor, Naseya
Subject:RE: NDA 206334 Mid-Cycle Telecon March 18
Attachments:emfalert.txt

Thanks Naseya,
We will get started on pulling the information together and let you know if we have any questions.
Best regards
Ketna

From: Minor, Naseya [mailto:Naseya.Minor@fda.hhs.gov]
Sent: Monday, March 24, 2014 9:14 AM
To: Ketna Patel
Subject: RE: NDA 206334 Mid-Cycle Telecon March 18

Hi Ketna,

Thank you. I received the notification. The clinical information request is included in the mid cycle meeting minutes but I am including it here as well. Please let me know if you have any questions.

Provide CRF for the following subjects:

TMC-ORI- 10-01-101001-102, 101001-035, 101001-056, 101001-009, 101003-022, 101002-023, 101002-039, 101046-015, 101046-042, 101046-004, 101046-003, 101046-032, 101005-010, 191009-024

TMC-ORI-10-02-291002-022, 291003-008, 291003-008, 291006-025, 291006-038, 201035-006, 201035-040, 201001-159, 201001-173, 201001-189, 201001-106, 201001-050, 202001-007, 207002-005, 207002-027, 207002-040.

Define the parameter “Sustained Clinical Response-FDA” in the clinical response dataset. This is not clear from the reviewer’s guide or the define file.

Define the denominator used for tabulation of data in Table 59 of the Integrated Summary of Safety report titled “Potentially clinically significant hematology results (Safety population)”.

Naseya

From: Ketna Patel [mailto:ketna.patel@THEMEDCO.com]
Sent: Friday, March 21, 2014 12:35 PM
To: Minor, Naseya
Subject: RE: NDA 206334 Mid-Cycle Telecon March 18

Hi Naseya,
Just wanted to let you know that we submitted the Information request for CMC.
I understood from the mid-cycle meeting that there was another information request that could possibly come our way – should we be expecting this soon?
Thanks
Ketna

From: Minor, Naseya [mailto:Naseya.Minor@fda.hhs.gov]
Sent: Tuesday, March 18, 2014 11:34 AM
To: Ketna Patel
Subject: RE: NDA 206334 Mid-Cycle Telecon March 18

Hi Ketna,

Thanks for the quick teleconference. Can you provide a list of attendees?

Thanks,

Naseya

From: Ketna Patel [mailto:ketna.patel@THEMEDCO.com]
Sent: Tuesday, March 18, 2014 9:39 AM
To: Minor, Naseya
Subject: RE: NDA 206334 Mid-Cycle Telecon March 18

Hi Naseya,
Are we all set for today?
Thanks
Ketna

From: Minor, Naseya [mailto:Naseya.Minor@fda.hhs.gov]
Sent: Thursday, March 06, 2014 3:33 PM
To: Ketna Patel
Cc: DeBellas, Carmen
Subject: NDA 206334 Mid-Cycle Telecon March 18

Hi Ketna,

The Mid-Cycle meeting for NDA 206334 is scheduled for Tuesday, March 18th at 11:00-12 noon.
Please provide a call-in number and passcode.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
04/01/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 051292
NDA 206334

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

ATTENTION: Ketna Patel, PharmD
Director, Regulatory Affairs

Dear Dr. Patel:

Please refer to:

- Your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oritavancin Diphosphate for Injection, 400 mg per vial

- Your New Drug Application (NDA), dated and received December 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oritavancin diphosphate for Injection, 400 mg per vial

We also refer to:

- Your correspondence dated October 17,2013,and received October 21,2013, requesting review of your proposed proprietary name, Orbactiv, for your IND

- Your correspondence, dated and received, December 13, 2013, requesting review of your proposed name, Orbactiv, for your NDA.

We have completed our review of the proposed proprietary name, Orbactiv, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 13, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Naseya Minor, Regulatory Project Manager in the Office of New Drugs at (301) 796-0756.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/06/2014

From:Minor, Naseya
Sent:Wednesday, February 26, 2014 2:43 PM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Clinical Information Request

Hi Ketna,

I have a clinical information request for you.

1.We note that there is a difference in the baseline value and analysis value of lesion size area at screening for a few subjects. Define baseline value and analysis value of lesion size area at screening .
2.Submit photographs in PDF for subjects TMC ORI- 10-01-197002-003, TMC ORI- 10-01-191003-009, TMC ORI- 10-01- 197002-007, TMC ORI- 10-02- 201001-032, TMC ORI- 10-02- 201035-037, TMC ORI- 10-02- 201001-018.

Let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
02/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206334

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

The Medicines Company
Attention: Ketna Patel, PharmD
Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Patel:

Please refer to your New Drug Application (NDA) dated December 6, 2013, and received December 6, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ORBACTIV (oritavancin diphosphate) Sterile, Lyophilized Powder for Injection 400 mg/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is August 6, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post marketing requirement/commitment requests by May 31, 2014. In addition, the planned date for our internal mid-cycle review meeting is March 14, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Naseya Minor, Regulatory Project Manager, at (301) 796-0756.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
02/07/2014

From:Minor, Naseya
Sent:Friday, February 07, 2014 3:02 PM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Information Request #8

Hi Ketna,

Below is the stats information request I mentioned over the phone.

Please provide concordance/discordance for the listed outcomes at 48-72 hours, End-of-Therapy (EOT), and PTE based on the following criteria.

1.Outcome at 48-72 hours (a composite endpoint of cessation of spread or reduction in size of the baseline lesion, with/without fever, and no rescue antibiotic medication), EOT (Clinical response as defined in the protocol), PTE (Clinical response as defined in the protocol).
2.Outcome at 48-72 hours (as stated in #1), PTE (complete resolution of all signs and symptoms). The symptoms include erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth.
3.Outcome at 48-72 hours (as stated in #1), PTE (complete resolution of all signs and symptoms) and any residual lesion size compared to baseline not more than 5%, or 10%.
4.List of patients with their outcomes for the following categories:
*Patients with missing or indeterminate values for clinical response at 48-72 hours, EOT and PTE. (include reasons for missing/indeterminate)
*Patients who were non-responders at 48-72 hours and became clinical cures at EOT.
*Patients who were responders at 48-72 hours and became clinical failures at EOT.
*Patients who were clinical cures at EOT and became clinical failures at PTE.
*Patients who were clinical failures at EOT and became clinical cures at PTE
*List of patients who used additional systemic antibiotics from start of study drug to 48-72 hours, from start of study drug to EOT and from start of study drug to PTE (include the treatment arm, the systemic antibiotic(s) used and the relative study day initiated, reason(s) for systemic antibiotics use, region, infection type, clinical outcome)

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
02/07/2014

From:Minor, Naseya
Sent:Friday, February 07, 2014 10:58 AM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Information Request #7

Hi Ketna,

We have another information request for you.

1. In order to assist in our assessment of the population pharmacokinetic and pharmacokinetic-pharmacodynamic (PK/PD) analysis included in your submission, please submit the following datasets and codes/scripts (or provide the location, submission date/number, etc. if previously submitted):

- The PK and PK/PD dataset(s) described in ICPD-00142-01 and ICPD-00142-02. All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a separate pdf file. Any data points and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- The codes/ scripts and output files for the PK and PK/PD analysis described in ICPD-00142-01 and ICPD-00142-02. Output files should include individual parameter estimates and simulated individual data. Model codes and output listings should be provided for all major model building steps. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_R.txt, myfile_sas.txt).

2. Please submit the method validation reports for the methods used to assess the concentrations of oritavancin, warfarin, midazolam, omeprazole, dextromethorphan, 1U, AFMU, and all relevant metabolites from the study MDCO-ORI-12-03.

It would assist in the review if a response to this information request was received by February 21, 2014. Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
02/07/2014

From:Minor, Naseya
Sent:Tuesday, February 04, 2014 2:56 PM
To:ketna.patel@themedco.com
Cc:DeBellas, Carmen
Subject:NDA 206334 Information Request #6

Importance:High

Hi Ketna,

This email is a follow up to my phone call this afternoon. We have a time sensitive information request for NDA 206334.

Please clarify location of photographs in CRF. There appears to be a problem in viewing the photographs with the links in the CRF. (Please submit this information as soon as possible.)

Additionally please submit amended datasets for the following:
-There appears to be a problem linking relevant rows in MB (microbiology data) and MS (microsusceptibility) properly. The variable called MSGRPID should be utilized as according to the SDTMIG to link these rows accurately.
-The AE domain for all studies needs the EPOCH variable to be populated consistent with the SDTMIG.
-There appear to be duplicate rows in the XR and XD domains in study tmc-ori-10-02. These domains should be constructed as to follow the SDTMIG section 2.6 and any duplicates should be removed.

Baseline assessments appear to be missing for key labs (ALT, ALP, AST) and ECGs in study tmc-ori-10-02 for a significant number of subjects (32 subjects in LB and 25 subjects in EG). If baseline assessments were made, then these data should be included. If baseline assessments were made and included in the data, then baseline flags (--BLFL) need to indicate which measurements are baseline. LB and ECG data should be submitted with baseline flags fully and appropriately populated.

Submit CRF for TMC-ORI-10-01-101002-088

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
02/07/2014

From: Minor, Naseya
Sent: Wednesday, January 08, 2014 11:08 AM
To: ketna.patel@themedco.com
Cc: DeBellas, Carmen
Subject: NDA 206334 Information Request #4

Hi Ketna,

We have identified that the financial disclosure information reported in Module 1.3.4 is incomplete. It does not contain the attachment listing all investigators with no reportable/reportable disclosures. Please provide a complete financial disclosure information as per the Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators, February 2013, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
01/08/2014

From: Minor, Naseya
Sent: Monday, December 30, 2013 10:01 AM
To: ketna.patel@themedco.com
Cc: DeBellas, Carmen
Subject: NDA 2063344 Information Request #3

Hi Ketna,

We have another information request for you. Can you please send your SAS programs for the primary,
sensitivity, and proposed secondary analyses?

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
12/30/2013

From: DeBellas, Carmen
Sent: Friday, December 20, 2013 1:59 PM
To: ketna.patel@themedco.com
Cc: Minor, Naseya
Subject: Oritavancin Information Request #2

Hi Ketna,

We have another information request for you.

"We have identified the following discrepancy regarding the actual treatment arms of two patients in the demographics domain of the datasets. The actual treatment arm in the SDTM is listed as oritavancin while the actual treatment arm in the ADAM dataset is reported as vancomycin. Clarify the actual study drug used for these patients. The patient's unique subject identifier are TMC-ORI-10-01-101014-006 and TMC-ORI-10-01-191002-094".

Happy Holiday,

Carmen
Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
12/20/2013

To:ketna.patel
Cc:DeBellas, Carmen
Subject:NDA 206334 Information Request #1 OSI datasets

Hi Ketna,

It was nice speaking with you today. I look forward to working with you on this NDA. Please see the information request below regarding the datasets.

We appreciate your submission of the clinsite.xpt dataset for use in CDER's Clinical Site Selection Tool; however, the provided dataset contains errors in the TRTEFFE and TRTEFFS variables that prevent utilization in the Tool. Specifically, the values included for each treatment arm, within each study, are identical across all sites. Please consider resubmission of the clinsite.xpt dataset incorporating site specific, by treatment arm values for the TRTEFFE and TRTEFFS variables.

Please let me know if you have any questions.

Thanks,

Naseya Minor, MPH
Regulatory Project Manager
Food and Drug Administration
CDER/OND/OAP/DAIP
10903 New Hampshire Ave.
Building 22, Room 6219
Silver Spring, MD 20993
Phone: 301-796-0756

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/s/

NASEYA N MINOR
12/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 51,292

MEETING MINUTES

The Medicines Company
Attention: Ketna Patel, PharmD
Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oritavancin.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on September 16, 2013. The purpose of the meeting was to discuss the results from the Phase 3 (SOLO I and II) clinical trials to be included in the New Drug Application (NDA) submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, PharmD, RPh, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 16, 2013
Meeting Location: FDA, White Oak, Bldg 22, Room 1415

Application Number: IND 51,292
Product Name: Oritavancin diphosphate
Indication(s): Acute Bacterial Skin and Skin Structure Infections
Sponsor/Applicant Name: The Medicines Company

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Maureen Dillon-Parker

FDA ATTENDEES

Division of Anti-Infective Products (DAIP)

John Alexander, MD, MPH	Clinical Team Leader
Maureen Dillon-Parker	Chief, Project Management Staff
Mayurika Ghosh, MD	Clinical Reviewer
Margaret Gamalo, PhD	Statistical Reviewer
Katherine Laessig, MD	Deputy Director
Sumathi Nambiar, MD, MPH	Acting Director
Kerry Snow, MS	Acting Clinical Microbiology Team Leader
Thamban Valappil, PhD	Statistical Team Leader
Avery Goodwin, PhD	Microbiology Reviewer
Ryan Owen, PhD	Clinical Pharmacology Reviewer
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Wendy Schmidt, PhD	Pharmacology/Toxicology Team Leader

Eastern Research Group

(b) (4)	Independent Assessor

SPONSOR ATTENDEES

The Medicines Company (TMC)

Paul Watkins, MD	Director, Hamner-UNC Institute*
Dimitrious Gkountis	Senior Vice President, Team Leader for Anti-Infectives
Hai Jiang	Senior Director, Biostatistics
Gregory Moeck, PhD	Senior Director, Microbiologist
Matthew Wikler, MD	Vice President, Clinical

Ketna Patel, PharmD	Director, Regulatory Affairs
(b) (4)	Consultant, VP, Institute for Clinical Pharmacodynamics
Nuoyu Huang, MD	Clinical Expert
(b) (4)	Clinical Expert, Consultant
	Clinical Expert, Consultant
	Regulatory Consultant, (b) (4)
	Regulatory Consultant, (b) (4)
	Associate Professor of Cardiology, Consultant*

*phone

BACKGROUND

On May 15, 2013, The Medicines Company (TMC) requested a face-to-face meeting with the Division of Anti-Infective Products (Division) to discuss the results of the SOLO I and II Phase 3 clinical trials to be submitted in the NDA. On August 15, 2013, the briefing package for the scheduled September 16, 2013, meeting was submitted.

On September 11, 2013, the Division provided TMC with preliminary responses to the questions outlined in the briefing package.

The purpose of the meeting was to discuss and clarify the Division's responses.

DISCUSSION

- Following introductions, The Medicines Company (TMC) gave the Division an overview of the history of product development, noting that in November 2008 the product was licensed from Targanta. They also thanked the Division for the ongoing communications throughout the development of oritavancin.
- TMC stated that there are over 400 MRSA patients in the SOLO trials, which was initiated in December 2010. The results appear positive and on par with the efficacy seen for vancomycin. The risk/benefit profile also seems comparable to vancomycin.
- TMC commented that a November NDA submission is planned. Additionally, a meeting with the European Medicines Agency (EMA) is planned and a rapporteur meeting is scheduled for February.

Each of the Division's comments outlined in the preliminary responses was addressed as follows; see **Meeting Comment(s)**:

Question 1: Efficacy / Division Additional Comments/Requests #1-#8:
Comment #1: Provide a frequency distribution of the surface area of the lesion at the time of enrollment. A similar distribution should also be provided by infection type and by outcome in both study arms.

Reference ID: 3389826

Meeting Comments:

- TMC appreciated the Division's responses to the questions outlined in the briefing package. With regard to Comment #1, TMC clarified that they plan to present the data in quartiles of lesion size. The Division stated that they would need to see the distribution and the range of the lesion sizes. TMC agreed to provide a detailed histogram.

Comment #2: Provide analyses that compare consistency/concordance of the outcomes (including missing values) at 48-72 hours, EOT and follow-up visits for both the treatment groups. Explain why 87.3% (n=394) patients in the oritavancin group in SOLO I trial had an outcome of success for ECE (CE population) but 77.9% (n=394) had sustained clinical response at PTE.

Meeting Comment:

- The requested analyses will be provided.

Comment #3: Provide analysis of early clinical response without the fever component both for cessation of spread and 20% reduction in size of the baseline lesion in the modified ITT (mITT) population and in the subgroup of patients with MRSA.

Meeting Comment:

- The Division clarified that analysis of cessation of spread without the fever component is the information being requested.

Comment #4: Provide more details of the reasons for missing assessment of sustained clinical cure at the PTE visit (e.g. death, lost to follow-up, etc.). Also, provide patient status before they were missing after EOT.

Meeting Comment:

- TMC will include the information requested in the NDA submission.

Comment #5: Identify patients who had surgical drainage of abscesses or surgical procedure(s) which may affect the primary or secondary endpoints in the datasets. Also, state the type and timing of surgery performed in these cases. Analyze the differences in primary and secondary efficacy outcomes at the early clinical evaluation visit according to surgical procedure.

Meeting Comment:

- TMC will include the information requested in the NDA submission.

Comment #6: List adjunctive therapy used, if any, for example use of revascularization, wound dressings, hyperbaric oxygen therapy, etc.

Meeting Comment:

- TMC cannot provide as this information as it was not captured on the CRF. The Division acknowledged this information.

Reference ID: 3389826

Comment #7: Provide data on vancomycin trough levels if available. On page 20 of the briefing document you state that oritavancin was compared with "Vancomycin 15 mg/kg or 1 g every 12 hours". Clarify if the datasets will clearly indicate which patients received weight-based dosing of vancomycin and which patients received a fixed dose regimen. Clarify if the datasets will have information on vancomycin trough levels and information about which patients had vancomycin dose adjustments.

Meeting Comments:

- Trough levels were collected on 80% of the subjects. The administered dose was captured but they did not capture information on which dosing method was chosen (weight-based or fixed-dose). TMC will provide information available on the subjects who had dose adjustments.

Comment #8: Submission data should be CDISC compliant. We expect that numeric results are numeric in the SAS datasets, normal reference range variables are numeric, visit number is a numeric value, use of baseline flag to depict baseline values, even if visit name identifies baseline results. Study Day should exist based on 1st day exposed and dataset columns and labels should not contain special characters; including returns and tabs. We expect a date formatted variable for all dates.

Meeting Comment:

- TMC clarified that the new trials will be in the requested format, however, the data from the legacy studies will be in the previous format.

Question 2: Safety, Adverse Events of Interest Comments

There was no further discussion of (b) or (c). Comments on point (a) are as follows:

- TMC stated that they will provide the requested information along with an extensive analysis of all patients. Hepatic safety evaluation(s) will also be included.
- TMC also confirmed that the random sample of CRFs have been received and will be provided as requested.

Concerning **Questions 3** [NDA Filing], **4** [Regulatory Process], and **5** [Post-Approval Requirements/Commitments] and the requests under "**Additional Comments**" TMC stated that the requested information will be provided.

ADDITIONAL MEETING COMMENTS

- The Division requested that TMC submit a timeline for the conduct of the pediatric studies. TMC will provide this information and conveyed that they plan to begin the studies at the end of the year.
- The 4-month safety update would be due prior to commencing the pediatric studies. TMC and the Division agreed to submission of a letter indicating there are no ongoing studies in lieu of the 4-month safety update, if there are no new safety issues.

Reference ID: 3389826

- The eCTD will contain all the new studies as well as the legacy studies, Modules 4 and 5, and a Reviewer's guide. A legacy statement that there have been no changes to the originally submitted data will be included. If any changes are made, these will be clearly marked.
- A November submission is targeted.
- The Division reminded TMC that the NDA will be reviewed as a "Program Application" under PDUFA V.

SUBMISSION REMINDERS - CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion regarding the need for a REMS was not held as it was conveyed in the pre-meeting comments that a REMS would not be likely. However, post-approval required (PMR) studies (pediatrics and a surveillance study) are necessary and the outline of the requirement was provided to TMC.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and, therefore, there are no agreements for late submission of application components.

- In addition, we note that a chemistry pre-submission meeting was held on June 27, 2013. We refer you to the minutes of that meeting dated August 6, 2013, for any additional agreements that may have been reached and where any requests for specific information regarding the contents of the NDA submission will be stated.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Minutes of the meeting	FDA	Within 30-days of the meeting date
Submission of the NDA	Sponsor	November (anticipated)

ATTACHMENT

Division communication dated September 11, 2013, to TMC containing preliminary responses to questions from the meeting package.

Reference ID: 3389826

ATTACHMENT [Sent 09-11-13 to TMC]

Question 1: Efficacy

MDCO plans on using the results of the Phase 3 SOLO I and SOLO II studies as the basis of a NDA submission to support the use of a single 1200 mg IV dose of oritavancin for the treatment of ABSSSI caused by susceptible isolates of Gram-positive microorganisms, including MRSA.

Results from 2 independent studies of identical design, SOLO I and II, support the conclusion that a single 1200 mg dose of oritavancin demonstrates clinical non-inferiority to 7-10 days of twice-daily vancomycin using a prespecified non-inferiority margin of 10% in the mITT population, which was also confirmed in the CE population. The efficacy results in those patients microbiologically confirmed with MRSA infections were also consistent to the overall population in both studies.

Does the Agency agree that both trials have demonstrated efficacy of a single 1200 mg dose of oritavancin treatment for ABSSSI including MRSA as per the results of the primary and secondary endpoints in accordance with the SPA agreement?

FDA response: The review of the NDA will determine whether a single 1200 mg dose of oritavancin is efficacious in the treatment of ABSSSI. However, the summary of efficacy results of the SOLO I and SOLO II trials, as presented in the briefing package, appear adequate to support an NDA submission.

We have the following additional comments/requests for both trials that can be addressed in the NDA dossier:

1. Provide a frequency distribution of the surface area of the lesion at the time of enrollment. A similar distribution should also be provided by infection type and by outcome in both study arms.

2. Provide analyses that compare consistency/concordance of the outcomes (including missing values) at 48-72 hours, EOT and follow-up visits for both the treatment groups. Explain why 87.3% (n=394) patients in the oritavancin group in SOLO I trial had an outcome of success for ECE (CE population) but 77.9% (n=394) had sustained clinical response at PTE.

3. Provide analysis of early clinical response without the fever component both for cessation of spread and 20% reduction in size of the baseline lesion in the modified ITT (mITT) population and in the subgroup of patients with MRSA.

4. Provide more details of the reasons for missing assessment of sustained clinical cure at the PTE visit (e.g. death, lost to follow-up, etc.). Also, provide patient status before they were missing after EOT.

Reference ID: 3389826

5. Identify patients who had surgical drainage of abscesses or surgical procedure(s) which may affect the primary or secondary endpoints in the datasets. Also, state the type and timing of surgery performed in these cases. Analyze the differences in primary and secondary efficacy outcomes at the early clinical evaluation visit according to surgical procedure.

6. List adjunctive therapy used, if any, for example use of revascularization, wound dressings, hyperbaric oxygen therapy, etc.

7. Provide data on vancomycin trough levels if available. On page 20 of the briefing document you state that oritavancin was compared with "Vancomycin 15mg/kg or 1 g every 12 hours". Clarify if the datasets will clearly indicate which patients received weight-based dosing of vancomycin and which patients received a fixed dose regimen. Clarify if the datasets will have information on vancomycin trough levels and information about which patients had vancomycin dose adjustments.

8. Submission data should be CDISC compliant. We expect that numeric results are numeric in the SAS datasets, normal reference range variables are numeric, visit number is a numeric value, use of baseline flag to depict baseline values, even if visit name identifies baseline results. Study Day should exist based on 1st day exposed and dataset columns and labels should not contain special characters; including returns and tabs. We expect a date formatted variable for all dates.

Question 2: Safety, Adverse Events of Interest:

The SOLO I and SOLO II studies demonstrated that a single 1200 mg IV dose of oritavancin is well tolerated and has a similar safety profile to that of 7 to 10 days of IV vancomycin treatment.

The safety evaluation in the Integrated Summary of Safety will be based on the pooled SOLO I and II studies, as well as the totality of clinical experience with oritavancin in 3,042 subjects, consistent with the previous FDA feedback.

Based on the known glycopeptide class effects, antibiotic related effects, and the clinical experience with oritavancin, MDCO intends to evaluate the following adverse events of interest in the NDA: (1) Infusion Related Reactions and Hypersensitivity (2) Infusion Site Reactions/Phlebitis (3) Hepatic Effects (4) Renal Effects and (5) Cardiac Effects.

Additionally, the ISS will evaluate the following safety events in the system organ class of Infections and Infestations based on the events identified as part of the FDA complete response letter. Specifically, the following events will be further evaluated in the NDA: (1) Fungal and Mycobacterial Infections to evaluate the effect of oritavancin accumulation in macrophages (2) Sepsis/Septic Shock and Related Events; and (3) Osteomyelitis.

Reference ID: 3389826

At this time only individual study results from SOLO I and II are available and presented in the briefing package. Based on the data presented in the briefing package:

a) **Does the Agency have any comments on the safety results from the SOLO I and II studies?**

b) **Does the Agency agree with the planned evaluation of adverse events of special interest?**

c) **Does the Agency agree with MDCO's risk management approach, consisting of labeling and routine pharmacovigilance for oritavancin?**

FDA response:

a) We note that 11 patients in the oritavancin group in the SOLO trials had TEAE of alanine aminotransferase elevated while none had alkaline phosphatase increased (Page 7 of appendix 5 of the briefing package). Provide the case report forms (CRF) and include case narratives in the ISS for these 11 patients. At the least, the ISS should include a list of the patient numbers for these individuals, to allow us to easily locate the CRF. We note the summary of the case (patient 29100316) who appeared in the Hy's law quadrant in the eDISH plot. Provide additional details if available for this case in the ISS.

   The results of the thorough QT study will be reviewed upon submission of the NDA.

b) We agree.

c) Your risk management approach appears reasonable at this point. We will provide recommendations regarding product labeling and pharmacovigilance for oritavancin upon completion of the review of your NDA.

Question 3: NDA Filing

Does the Agency agree that the overall safety and efficacy results support an NDA filing of oritavancin for the treatment of ABSSSI caused by susceptible isolates of Gram-positive organisms including MRSA?

FDA response: We agree that the summary of the safety and efficacy results of the SOLO I and SOLO II trials, as presented in the briefing package, appear to be appropriate to support an NDA submission for oritavancin for the treatment of ABSSSI caused by susceptible isolates of Gram-positive organisms including MRSA.

Reference ID: 3389826

Question 4: Regulatory Process

a) What are the Agency's expectations for the NDA review process, interactions with the Sponsor and timing of milestone activities such as: Communication of fileability, Application Orientation Meeting, Midcycle review meeting, GMP inspection, and BIMO inspection?

b) Since there are no clinical or pre-clinical studies currently ongoing with oritavancin and none planned to be initiated prior to the timing of the 4 Month Safety Update, with the possible exception of a pediatric pharmacokinetic study, MDCO proposes to not submit a 4 month safety update. Does the Agency agree?

c) As part of the previous NDA submission and review process, an Anti-Infective Drugs Advisory committee was held on November 19, 2008. Does the Agency foresee the need for an Advisory committee for this NDA?

FDA response:

a) Applications are expected to be complete at the time of original submission of the application. Incomplete applications, including applications with components that are not received within 30 calendar days after receipt of the original submission, will be subject to a Refuse-to-File decision.

Review of unsolicited amendments, including those submitted in response to an FDA communication of deficiencies, will be handled in accordance with the guidance "Good Review Management Principles and Practices (GRMPs) for PDUFA Products."

Day 74 Letter: FDA will follow existing procedures and performance goals regarding identification and communication of filing review issues in the "Day 74 letter." The planned review timeline included in the Day 74 letter for applications in the Program will include the planned date for the internal mid-cycle review meeting.

Mid-Cycle communication: The FDA Regulatory Project Manager (RPM) will call the applicant, generally within 2 weeks following the Agency's internal mid-cycle review meeting, to provide the applicant with an update on the status of the review of their application. The update should include any significant issues identified by the review team to date, any information requests, information regarding major safety concerns and preliminary review team thinking regarding risk management, proposed date(s) for the late-cycle meeting, updates regarding plans for the AC meeting and other projected milestones dates for the remainder of the review cycle.

FDA intends to complete primary and secondary discipline reviews of the application and issue discipline review (DR) letters in advance of the planned late-cycle meeting. In cases where a DR letter is not issued in advance of the planned late-cycle meeting, substantive

Reference ID: 3389826

issues identified to date from that discipline will be communicated in the brief memorandum.

Late-Cycle meeting: For all applications included in the Program, a meeting will be held between the FDA review team and the applicant to discuss the status of the review of the application late in the review cycle.

FDA intends to convene AC meetings no later than 3 months (standard review) or no later than 2 months (priority review) prior to the PDUFA goal date. The Agency briefing package for the late-cycle meeting will consist of the Agency's background package for the AC meeting, which will be sent to the applicant not less than 20 calendar days before the AC meeting, any discipline review letters issued to date, current assessment of the need for REMS or other risk management actions, and a brief memorandum from the review team outlining substantive application issues including potential questions and/or points for discussion for the AC meeting. FDA intends to provide final questions for the AC to the sponsor in advance of the AC meeting. The Agency background package for the late-cycle meeting, which will be sent to the applicant not less than 12 calendar days before the meeting, will consist of any discipline review letters issued to date, current assessment of the need for REMS or other risk management actions, and a brief memorandum from the review team outlining substantive application issues.

Inspections: FDA's goal is to complete all GCP, GLP, and GMP inspections for applications in the Program within 6 months of the date of original receipt for priority applications and within 10 months of the date of original receipt for standard applications.

b) Since there are no clinical or pre-clinical studies currently ongoing with oritavancin and none planned to be initiated prior to the timing of the 4 Month Safety Update, with the possible exception of a pediatric pharmacokinetic study, MDCO proposes to not submit a 4 month safety update. Does the Agency agree?

FDA response: We agree. However, if relevant safety information from other sources, for example the published literature becomes available then it is expected that you will submit these reports. If a pediatric pharmacokinetic study is initiated, then it is expected that you will submit a safety update report [See 21 CFR 314.50 (3)(vi)(b)]. It is also our expectation that your NDA will contain complete safety information from all completed trials. We recommend that you submit a letter stating that there are no ongoing studies at the time of the 4 month safety update.

Reference ID: 3389826

c) As part of the previous NDA submission and review process, an Anti-Infective Drugs Advisory committee was held on November 19, 2008. Does the Agency foresee the need for an Advisory committee for this NDA?

FDA response: Under FDAAA, the safety and efficacy of all NDAs for new molecular entities are expected to be discussed at an Advisory Committee meeting.

Question 5: Post-Approval Requirements/Commitments

Based on the overall development program for oritavancin, MDCO anticipates the following post-approval requirement studies:

- Pediatric Studies: The pediatric development plan submitted to FDA consists of two studies, a Phase 1 pharmacokinetic study followed by a Phase 2 safety and efficacy study of oritavancin in children with ABSSSI
- Surveillance Study: MDCO intends to conduct a prospective study over a five year period after introduction of oritavancin to the market to determine if decreased susceptibility is occurring in the target bacteria included in the final approved label.

With the understanding that final assessment will depend on FDA's final review of all data in the NDA does the Agency foresee other post-approval requirements/commitments for oritavancin at this time?

FDA response: The need for post-marketing requirements/commitments will be decided upon review of the NDA. The postmarketing studies outlined in your meeting package (pediatrics and surveillance study) appear reasonable and further comments will be provided during the NDA review.

Additional comments:

The NDA should contain the following:

1. Clinical study report(s) following the ICH E3 Structure and Content of Clinical Study Reports guidance. We refer you to the following guidance documents:http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129456.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM336889.pdf

2. Preparation of integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50. Assessment of safety as per the Guidance for Industry: Pre-marketing Risk Assessment available at:

Reference ID: 3389826

http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126958.pdf.

3. For patients listed as discontinued due to "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

4. Provide complete CRFs for all patients with serious adverse reactions, in addition to deaths and discontinuations due to adverse reactions. You should be prepared to supply any additional CRFs upon request

5. The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/UCM080121.pdf

6. Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

7. Use a single version of MedDRA for the submission. It does not have to be the most recent version. We recommend that the WHO drug dictionary be used for concomitant medications. Refer to the CDISC terminology for lab test names. Issues regarding ranges for laboratory measurements should be addressed.

8. To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

    - Exposure-Response Relationships - important exposure-response assessments.
    - Less common adverse reactions (between 0.1% and 1%).
    - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
    - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
    - Marked outliers and dropouts for laboratory abnormalities.

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- Analysis of vital signs focused on measures of central tendencies.
- Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- Marked outliers for vital signs and dropouts for vital sign abnormalities.
- A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse reactions involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- Explorations for

  a. Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

  b. Dose dependency for adverse findings.

  c. Provide summary tables of the incidence of adverse reactions based on the cumulative dose and the average dose administered.

  d. Time dependency for adverse finding

  e. Provide data summarizing the length of time subjects experience adverse reactions.

  f. Drug-demographic interactions, drug-disease interactions, drug-drug interactions and dosing considerations for important drug-drug interactions.

Reference ID: 3389826

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/s/

SUMATHI NAMBIAR
10/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 51,292 **MEETING MINUTES**

The Medicines Company
Attention: Ketna Patel, Pharm.D.
Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oritavancin Diphosphate.

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2013. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Controls (CMC) portion of your NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Animicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA/CMC
Meeting Date:	June 27, 2013
Application Number:	IND 51,292
Product Name:	Oritavancin Diphosphate
Indication:	Acute Bacterial Skin and Skin Structure Infections
Sponsor/Applicant Name:	The Medicines Company

FDA ATTENDEES

Dr. Katherine Laessig	Deputy Director
Dr. Sumathi Nambiar	Deputy Director for Safety
Dr. John Alexander	Clinical Team Leader
Dr. Mayurika Ghosh	Clinical Reviewer
Dr. Carmen DeBellas	Project Manager
Dr. Robert Mello	Sterile Product Microbiology Reviewer
Dr. Mark Seggel	Chemistry Reviewer
Dr. Dorota Matecka	CMC Lead
Dr. Stephen Miller	Acting Branch Chief, Office of New Drug Quality Assessment

SPONSOR ATTENDEES

Dr. Gopal Krishna	Vice President, Pharmaceutical Development
Dr. Judy Lee	Senior Director, Regulatory/CMC
Dr. Ketna Petal	Director Regulatory
(b) (4)	Consultant, Regulatory Affairs

BACKGROUND

The Sponsor requested a Pre-NDA Chemistry, Manufacturing and Controls meeting in preparation for their NDA submission. The Sponsor received Agency responses to questions contained in the meeting background package prior to the meeting.

DISCUSSION

CMC and Product Quality Microbiology Q/A

Drug Substance

5.1 Cell Bank Specification

MDCO provided information in the briefing document (section 4.1.3) for the cell bank control and specification. This information is intended for the proposed NDA and encompasses the response to Question 2a of the FDA original review on cell bank specifications (see Appendix 5C). Does FDA have further comments on our approach for cell bank specification?

FDA Response:
The tests and acceptance criteria for Cell Bank (CB) and Working Cell Bank (WCB) provided in Table 4, Control and Specification for CB and WB, p. 13 of the meeting package are not adequately detailed. Details of the test methods as well as detailed descriptions of the acceptance criteria (b) (4) should be submitted in the NDA. Additionally, we recommend CB and WCB specification to include tests (b) (4)

Given the changes in the nomenclature of the producer organism, please provide in the NDA a brief description of the (b) (4) studies with the producer strain and comparator organisms (b) (4)

We understand that no changes have been made to the cell bank since submission of NDA 22-153. However, any new information regarding the characterization of the cell bank and its stability should be submitted to the NDA.

Meeting Discussion:

The Sponsor stated that details of the test methods and acceptance criteria will be provided in the NDA. The Sponsor explained that (b) (4)

The Sponsor added that if new cell bank characterization and stability become available it will be provided in the NDA.

5.2 Specification and Justification

The specification for drug substance assay is based on statistical analysis of the data generated and the specification for the impurities are set based on ICH Q6A and levels qualified through nonclinical toxicity studies (see section 4.1.5 in this briefing document). Only release and stability data from batches produced (b) (4) In addition, MDCO proposes to (b) (4)

Does the FDA have any further comments to this approach?

FDA Response:
Although you may perform statistical analyses on a subset of available batches in order to set acceptance criteria, the overall acceptability of the acceptance criteria for assay and impurities will be based on the totality of available data submitted to the NDA.

The proposed (b) (4) is an NDA review issue. However, given the (b) (4), it is unlikely that the proposed (b) (4) would be acceptable (b) (4)

Meeting Discussion:
The Sponsor confirmed that all information on batches used in clinical studies will be provided in the NDA submission. The specifications for assay and impurities will be based on all batches produced after the process has been completed.
The Agency stated that it is too early in the process to commit to the number of batches that will be needed before a recommendation could be made.

5.3 Retest period for drug substance
A commercial retest period for (b) (4) months at (b) (4) storage condition is proposed for oritavancin drug substance. Until longer retest period is established, it is also proposed (b) (4) (b) (4) Is this proposed approach acceptable?

FDA Response:
This approach (b) (4) is not acceptable. Please refer to (b) (4) (b) (4)

Meeting Discussion:
The Agency advised the Sponsor that there is no definition of "immediately" in the guidance and it is usually defined by the quality group at the site. The Sponsor asked if (b) (4) (b) (4) would be acceptable. The Agency replied that (b) (4) could be proposed in the NDA submission and that it would be a review issue. The Sponsor added that (b) (4) will be provided in the NDA.

Drug Product

5.4 Microbiological stability of the dilutes solution for infusion
MDCO has initiated the microbiological studies with dilutes product in 5% dextrose to support the requested (b) (4) (see section 4.2.3 in this briefing document). The data will be provided in the submission. This information is intended for the proposed NDA and encompasses the response to Question 1 of the FDA original review (Appendix 5A) and the second request from an FDA (email from Targanta to FDA, Appendix 5B on microbiological stability of the diluted solution for infusion? Does FDA have any further comment?

FDA Response:
(b) (4) is a review issue that will be addressed following NDA submission. However, the study outlined in section 4.2.3 is consistent with our current thinking. We would advise you, at this time, to structure the studies with several sampling points within the initial 24 hour period (b) (4)
In this way, you will be better able to assess the start of a growth phase following any potential lag phase. This will provide a better insight into the microbial growth potential of the diluted drug solution for infusion.

5.5 Specification and justification

The impurity limits justification will be set based on the statistical analysis of the data generated from 400 mg primary batches and supportive 100 mg batches according to ICH Q6A and levels qualified through toxicology studies. In addition, MDCO proposes to (b) (4) Does FDA have any additional comments?

FDA Response:
Although you may perform statistical analyses on a subset of available batches in order to set acceptance criteria, the overall acceptability of the acceptance criteria will be based on the totality of available data submitted to the NDA.
The proposed (b) (4) is an NDA review issue. However, given the (b) (4), it is unlikely that the proposed (b) (4) would be acceptable (b) (4)

Meeting Discussion:
The Sponsor informed the Agency that the acceptance criteria for assay and impurities will be based on all data available on the primary and supportive stability batches and information on product used in the clinical trial will be submitted in the NDA.

5.6 Qualification of sterility and endotoxin assay for the proposed 400 mg strength

MDCO intends to re-qualify the sterility assay (bacteriostasis/fungistasis) and bacterial endotoxins assay (interference testing) for the proposed 400 mg strength at (b) (4) the proposed manufacturing site following USP compendial procedures (see section 4.2.5 in this briefing document). This is to address the inquiry from FDA product quality microbiology reviewer (e-mail dated 3/26/13, Appendix 5H). Does FDA have any further comment?

FDA Response:
There are no further comments at this time. We will address the adequacy of the microbiological assays as part of the review of the NDA.

Meeting Discussion:
No meeting discussion

Reference ID: 3352579

5.7 Shelf-life for the proposed 400 mg strength

MDCO will propose a shelf-life of 36 months for the 400 mg/vial presentation based on available data from the 400 mg/vial along with the supportive stability data from the 100 mg/vial presentation. MDCO also will commit to place the three validation batches on long-term and accelerated stability (See section 4.2.6 in this briefing document). Does FDA agree with this approach?

FDA Response:
The proposal to submit stability on two batches of 400 mg / vial product manufactured at (b) (4) and two batches manufactured at the proposed commercial site, (b) (4) along with supportive stability data on the 100 mg /vial product, is acceptable. In addition, submit release data, and at least six months long term and accelerated stability data from a third, pilot scale or larger, 400 mg / vial batch manufactured at (b) (4) The determination of an appropriate expiration dating period will be based on the totality of data submitted in the NDA, although data from the proposed commercial site will be particularly important.

The commitment to place the three validation batches on long-term and accelerated stability is acceptable.

Meeting Discussion:

The Sponsor asked for clarification concerning the requirement of submitting the release and at least 6 months stability data from a third batch for the NDA submission. The Agency explained that an NDA should contain the information from three registration batches from the manufacturing site. The Sponsor explained that the validation data will not be ready for NDA submission. The Agency asked the Sponsor to provide information on what will be provided in the NDA as soon as possible for comment.

General

5.8 This briefing document summarizes the strategy for our CMC module for the proposed NDA. Appendix 5 includes the CMC related questions from FDA review of the previously submitted original NDA and responses from Targanta (the submitter of the original NDA) as well as the CMC question from FDA review of the IND submission (Appendix 5H). Several areas were specifically discussed in questions above. We believe that we have addressed all areas of FDA questions and the information will be provided in the appropriate CMC sections in the NDA submission. Does FDA have any additional comments to the responses provided or have any recommendations that can facilitate the review of the NDA?

FDA Response:

1. In the forthcoming NDA, please submit for review all CMC sections appropriately revised and include a detailed list of all changes made since the submission of NDA 22-153, as amended [through 02-DEC-2008]. The rationale for the changes should be discussed, and supported with data as necessary.

2. Please note that all accelerated stability protocols should include testing at a minimum of 4 time points (e.g., 0, 1, 3 and 6 months).

Reference ID: 3352579

3. Because different analytical methods were used during product development, indicate which analytical methods were used to generate data submitted in the NDA.

4. Include the results of the study to justify the overfill in the 400 mg vial configuration in the NDA.

5. Indicate the proposed scale of commercial drug product manufacture.

6. The comparability of drug substance used in clinical trial lots and commercial, (b) (4) drug substance must be demonstrated. In this regard it will be useful to provide a tabulation of all clinical trial and commercial drug substance lots and drug product lots. The tabulation should identify the manufacturers, processes (b) (4) scale, date of manufacture, etc. Analytical data for all batches should be included in the NDA.

7. Include in the NDA results of product - diluent compatibility studies and stability data to support the proposed holding times for the reconstituted and further diluted solutions.

8. The process flow diagram provided on page 22 indicated that the bulk formulated solution is (b) (4) non-sterile bulk formulations will need to be validated from a microbiological perspective prior to NDA submission.

+

Meeting Discussion:

The Sponsor stated that the CMC section of the NDA will be totally revised as new information has been generated for the drug substance and drug product. The Sponsor stated that future accelerated stability protocols will have four time points. The Sponsor added that the same analytical test methods were used during the new product development and that earlier methods used will also be submitted.

The Agency commented that a study to justify the overfill in the 400 mg vial product should be conducted. The Sponsor stated that one had been completed and the results will be provided in the NDA. The Sponsor stated that the current proposal for commercial production is (b) (4) vials.

The Sponsor stated that the table requested in Agency response #6 will be provided in the NDA.

The Sponsor stated that information to support diluent compatibility, and the hold time for reconstituted and further diluted solution will be provided in the NDA submission. The Agency questioned if more compatibility testing had been done since the last NDA filing. The Sponsor stated that saline was found to be incompatible from previous studies and no new studies have been completed. The only compatible diluent was 5% dextrose in water.

In response to item #8, the Sponsor stated that a revised manufacturing flow diagram will be provided to show (b) (4) The Sponsor commented

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that the (b) (4) (b) (4) **The specification was met and the data will be provided in the NDA submission. The Sponsor stated that a bulk hold study will be performed during process validation. The Agency advised the Sponsor to validate the** (b) (4)

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) no later than 60 days after an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

> if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
>
> if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htmCHOOSE A OR B

Reference ID: 3352579

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Reference ID: 3352579

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/s/

SUMATHI NAMBIAR
08/06/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206334

LATE-CYCLE MEETING MINUTES

The Medicines Company
Attention: Ketna Patel, Pharm.D
Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Dr. Patel:

Please refer to your New Drug Application (NDA) dated December 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ORBACTIV (oritavancin diphosphate) sterile, lyophilized powder for injection 400 mg/vial.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 3, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Naseya Minor, Regulatory Project Manager at (301) 796-0756.

Sincerely,

{See appended electronic signature page}

Yuliya Yasinskaya, MD
Cross-Discipline Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 3, 2014 1:00- 2:00 PM
Meeting Location: White Oak Building 22, conference room 1309

Application Number: NDA 206334
Product Name: ORBACTIV
Applicant Name: The Medicines Company

Meeting Chair: Yuliya Yasinskaya, MD
Meeting Recorder: Naseya Minor, MPH

FDA ATTENDEES

Office and Antimicrobial Products (OAP)

Edward Cox, MD, MPH	Director
John Farley, MD, MPH	Deputy Director

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, MD, MPH	Director
Katherine Laessig, MD	Deputy Director
Dmitri Iarikov, MD PhD	Acting Deputy Director of Safety
Mayurika Ghosh, MD	Medical Officer
Yuliya Yasinskaya, MD	Medical Officer
Kerry Snow, MS	Microbiology Team Leader
Avery Goodwin, PhD	Microbiology Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Kimberly Bergman, Pharm.D	Clinical Pharmacology Team Leader
Ryan Owen, PhD	Clinical Pharmacology Reviewer
Mushfiqur Rashid, PhD	Statistical Reviewer
Thamban Valappil, PhD	Statistical Team Leader
Hitesh Shroff, PhD	CMC Reviewer
Carmen DeBellas, RPh, Pharm.D	Regulatory Project Manager
Naseya Minor, MPH	Regulatory Project Manager
Frances LeSane	Chief, Project Management Staff

Division of Hematology Products (DHP)

Qin Ryan, MD	Medical Officer

Division of Medication Error Prevention and Analysis (DMEPA)

Justine Harris, RPh	Labeling Reviewer

EASTERN RESEARCH GROUP ATTENDEES

(b) (4)	Consultant
	Consultant

APPLICANT ATTENDEES

The Medicines Company

Ketna Patel, Pharm.D	Director, Regulatory
Hai Jiang, PhD	Senior Director, Biostatistics
Gregory Moeck, PhD	Senior Director, Microbiologist
Brad Zerler, PhD	Vice President, Pre-Clinical Safety
S. Eralp Bellibas, MD, PhD	Vice President, Clinical Pharmacologist
Matthew Wikler, MD	Vice President, Clinical, Infectious Disease
Nuoyu Huang, MD	Clinical, Infectious Disease
Yanshan Ma, MD	Senior Director, Global Pharmacovigilance
Cynthia Dinella, Pharm.D	Acting Head of Regulatory
Mike McGuire	Vice President, Infectious Disease
Michael N. Dudley, Pharm.D	Chief Scientific Officer, Infectious Disease
(b) (4)	Regulatory Consultant, (b) (4)
	Consultant, (b) (4)

BACKGROUND

NDA 206334 was submitted on December 6, 2013 for ORBACTIV (oritavancin diphosphate).

Proposed indication(s): Acute bacterial skin and skin structure infections

PDUFA goal date: August 6, 2014

FDA issued a Background Package in preparation for this meeting on May 30, 2014.

DISCUSSION

1. Discussion of Substantive Review Issues

   Warning regarding coagulation test interference and drug interaction with warfarin and other anticoagulants

   a. Clinical/Clinical Pharmacology: Study MDCO-ORI-12-03 showed that concomitant administration of oritavancin can increase the exposure to warfarin by approximately 30%, and you have recommended that patients should be closely monitored for signs of bleeding in the proposed product labeling. Additionally, in the NDA, you state that "In vitro studies indicate that aPTT results after an oritavancin dose may remain falsely elevated until oritavancin concentrations fall below 15 µg/ml." Pharmacokinetic data from MDCO-ORI-12-03 indicate that the concentration of oritavancin would fall below 15mcg/mL between 24 and 48 hours post dose.

i. Please clarify the extent and duration of the expected aPTT elevation and comment on issues which can arise with concomitant use of heparin.
ii. Please clarify the duration and the extent of INR prolongation expected during concomitant oritavancin and warfarin use. For patients who have been on warfarin and receive a dose of oritavancin, what recommendations do you have for monitoring or adjusting the warfarin dose until the INR test becomes reliable?
iii. For patients who have been on intravenous heparin and receive a dose of oritavancin, what recommendation do you have for monitoring or adjusting the heparin dose until the aPTT test becomes reliable?

Discussion: In the proposed labeling, the Warnings and Precautions section did not make any reference to concomitant use of heparin. The Division asked if the Applicant had any recommendations for monitoring or adjusting warfarin dose. The Applicant explained most physicians would use individualized dosing for warfarin. The Applicant stated that in individuals on warfarin requiring dose adjustment usually no effect is seen on the INR for 48 hours which corresponds to the time when the PTT/INR testing is inaccurate. The DHP Safety consultant asked the Applicant if they would add language to the proposed labeling to strengthen the monitoring recommendations.

The Division advised the Applicant to conduct analysis and review of medical records/CRFs for patients who received intravenous heparin or warfarin in oritavancin clinical trials. The Applicant agreed to review case report forms to determine how patients were managed. The Applicant mentioned that a PT/INR study is in progress and they will submit the preliminary results as a submission to the application in July 2014.

2. Discussion of Minor Review Issues

   a. Potential hepatic effects
   Post baseline elevation of hepatic transaminases and total bilirubin are being evaluated. There were increased number of subjects with post baseline ALT $\geq$10xULN and total bilirubin $\geq$1.5xULN in the oritavancin arm compared to vancomycin arm.

Discussion: The Division explained that the review is ongoing and potential triggers for these elevations will be evaluated.

3. Additional Applicant Data

The Applicant understood that reviews are ongoing and labeling negotiations are forth coming.

The Applicant stated that development of (b) (4) has been delayed (b) (4) and that the (b) (4) may not be available for clearance by the Agency until 2015. Due to this problem, the Applicant would like to explore the possibility of using (b) (4) of Oritavancin, and asked if the Agency would consider such (b) (4) The

Agency responded that it would consider such a proposal, and suggested that the Applicant submit the proposal and supportive information to the NDA.

4. Postmarketing Requirements/Postmarketing Commitments

   a. Pediatric: A meeting has been scheduled with the Pediatric Review Committee to discuss the Pediatric plan and Phase 1 protocol for oritavancin in patients 0 to < 18 years of age. The required oritavancin pediatric development program will likely include the following trials:

      i. Phase 1 open-label, dose-finding, pharmacokinetics, safety and tolerability study of oritavancin single-dose infusion in pediatric subjects 0 to <18 years of age with suspected or confirmed bacterial infections.

      ii. Phase 2 multicenter, evaluator-blinded, randomized safety, tolerability, and efficacy trial in pediatric patients 0 to less than 18 years of age with ABSSSI.

   b. Clinical Microbiology:
      A surveillance study to monitor for the development of resistance to oritavancin

Discussion: The Division will provide comments to the Applicant after the Pediatric Review Committee has reviewed the proposed Pediatric plan.

5. Review Plans, Wrap-up, and Action Items

At the conclusion of the meeting the Division stated that discipline reviews are ongoing. The Division will provide labeling comments to the Applicant electronically as they become available. Any Post Marketing Requirements and/or Commitments will be communicated once the Pediatric Review Committee has reviewed the Pediatric plan and discipline reviews are completed.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

POST MEETING NOTE

During the June 11, 2014 meeting with the Division, the Pediatric Review Committee agreed to the Applicant's proposed pediatric plan and recommended not to delay enrollment in the Phase 2 study until after completion of Phase 1 study. Applicant is encouraged to start Phase 2 study enrollment upon completion and analysis of data for each of the prespecified age cohorts in a stepwise fashion.

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/s/

YULIYA I YASINSKAYA
06/12/2014