

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206334Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 206334  
Product Name: ORBACTIV

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PMR Description: 2165-1: An open-label, dose-finding, pharmacokinetics, safety and tolerability study of Orbactiv (oritavancin diphosphate) single dose infusion in pediatric subjects less than 18 years of age with suspected or confirmed bacterial infections.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>12/16/2013</u>
	Study/Trial Completion:	<u>03/30/2017</u>
	Final Report Submission:	<u>09/30/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The applicant requested a deferral of the Phase 1 pediatric PK study under PREA as ORBACTIV is ready for approval in adults. This deferred pediatric study required under section 505B (a) of the Federal Food, Drug and Cosmetic Act (FDCA) is therefore appropriate as a post marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is 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. The following age cohorts will be recruited in a step-down fashion: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, and birth to <3 months (includes 0-28 day neonates). The applicant will also collect CSF to determine oritavancin levels in the CSF. The objective of the study is to evaluate the pharmacokinetics (PK), safety, and tolerability of an intravenous (IV) infusion of oritavancin in children with suspected or confirmed Gram positive bacterial infection.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply) N/A**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as: N/A**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is 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. The following age cohorts will be recruited in a step-down fashion: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, birth to <3 months (includes 0-28 day neonates).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials  
*Continuation of Question 4*

Additional data or analysis required for a previously submitted or expected study/clinical trial  
(provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

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Other  
an open-label, dose-finding, pharmacokinetics, safety and tolerability study

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug  
 There is not enough existing information to assess these risks  
 Information cannot be gained through a different kind of investigation  
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and  
 The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

## PMR/PMC Development Template

NDA/BLA # 206334  
Product Name: ORBACTIV

PMR Description: 2165-2: A multicenter evaluator blind, randomized study to evaluate safety and tolerability of single dose IV Orbactiv (oritavancin diphosphate) versus vancomycin for the treatment of pediatric subjects less than 18 Years of age with acute bacterial skin and skin structure infections.

PMR Schedule Milestones:	Final Protocol Submission:	<u>09/30/2017</u>
	Study/Trial Completion:	<u>07/31/2020</u>
	Final Report Submission:	<u>12/30/2020</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The applicant requested deferral of the Phase 2 pediatric PK study under PREA as ORBACTIV is ready for approval in adults. This deferred pediatric study required under section 505B (a) of the Federal Food, Drug and Cosmetic Act (FDCA) is therefore appropriate as a post marketing requirement. The study could initiate enrollment only after the completion of enrollment/data collection and analysis for the individual age cohorts in an on-going dose finding PK, safety and tolerability study in pediatric patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A multicenter evaluator-blinded, randomized, safety and tolerability study of oritavancin in pediatric subjects <18 Years of Age. The trial will commence upon completion of the pediatric PK trial and the dose and infusion volume to be used in this trial have been determined. Approximately 336 subjects will be stratified by the following age category: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, birth to <3 months. The primary objective will be to assess the safety of oritavancin relative to comparator (intravenous vancomycin) according to vital signs, laboratory abnormalities, all-cause mortality, and the incidence and the time to resolution of AEs and SAEs. The secondary objective will be to assess 1) the clinical response (clinical cure) of treatment with single dose intravenous oritavancin compared with vancomycin at day 14 and the post therapy evaluation visit in the modified intent to treat population, 2) early clinical response ( $\geq 20\%$  lesion size reduction from baseline) of treatment with single dose intravenous oritavancin compared with vancomycin at early clinical evaluation visit in the modified intent to treat population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply) N/A**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as: N/A**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A multicenter evaluator blind, randomized, safety and tolerability study of oritavancin in pediatric subjects <18 Years of Age. The phase 2 trial will commence upon completion of the Phase 1 trial and the dose and volume to be used in the Phase 2 trial have been determined. Approximately 336 subjects will be stratified by the following age category: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, birth to <3 months.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials  
*Continuation of Question 4*

Additional data or analysis required for a previously submitted or expected study/clinical trial  
(provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

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Other  
as described in item 2 of this template

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug  
 There is not enough existing information to assess these risks  
 Information cannot be gained through a different kind of investigation  
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and  
 The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

## PMR/PMC Development Template

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NDA/BLA #                      NDA 206334  
Product Name:                      ORBACTIV

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PMR Description:                      2165-3: A US surveillance study over a five-year period from the date of marketing Orbactiv (oritavancin diphosphate) to determine if resistance to oritavancin has developed in those organisms specific to the indication in the label for ABSSSI.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/09/2014</u>
	Study/Trial Completion:	<u>12/2019</u>
	Final Report Submission:	<u>04/2020</u>
	Other: Interim reports	04/2015
		04/2016
		04/2017
		04/2018
		<u>04/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study is required to determine if resistance to ORBACTIV is occurring in the target population of bacteria specific to the indication in the label for ABSSSI.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

**Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective study over a five year period on the susceptibility of target bacteria to ORBACTIV

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety

- Other (provide explanation)

A study of mechanisms of resistance to ORBACTIV if such isolates are identified during the 5 year US surveillance study

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

## PMR/PMC Development Template

NDA/BLA # NDA 206334  
Product Name: ORBACTIV (oritavancin)

PMR Description: 2165-4 An open label trial evaluating the safety of a single 1200 mg IV dose of Orbactiv (oritavancin diphosphate) in patients on concomitant chronic warfarin therapy who are being treated for ABSSSI.

PMR Schedule Milestones:	Final Protocol Submission:	<u>12/2014</u>
	Study/Trial Completion:	<u>05/2016</u>
	Final Report Submission:	<u>08/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Orbactiv increases warfarin exposure by 30%, potentially increasing the risk of bleeding. In addition, Orbactiv interferes with phospholipid-dependent laboratory coagulation tests *in vitro*. Orbactiv has been shown to artificially prolong prothrombin time (PT) by binding to the phospholipid reagents commonly found in laboratory coagulation tests. Effects on INR are expected, potentially affecting monitoring of warfarin anticoagulation. However, the clinical significance of the increase in warfarin concentration of 30% is unknown.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Orbactiv increases warfarin exposure by 30%, potentially increasing the risk of bleeding. This risk might be compounded by the infectious process Orbactiv being prescribed for. The magnitude of clinical effect of Orbactiv on coagulation system in patients with ABSSSI on warfarin therapy needs characterization.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To characterize the effect of oritavancin on clinical care and warfarin dosing in patients on chronic warfarin therapy, to determine the magnitude and duration, if any, of alterations to warfarin dosing, and to determine the safety of, and clinically important consequences which may result from the concomitant use of warfarin and oritavancin

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials  
*Continuation of Question 4*

Additional data or analysis required for a previously submitted or expected study/clinical trial  
(provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug  
 There is not enough existing information to assess these risks  
 Information cannot be gained through a different kind of investigation  
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and  
 The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

## PMR/PMC Development Template

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NDA/BLA #                    NDA 206334  
Product Name:                ORBACTIV (oritavancin)

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PMR Description:            2165-5: An open-label trial to assess the clinical significance of the drug-drug interaction between a single 1200 mg IV dose of oritavancin and warfarin in healthy volunteers.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>11/2014</u>
	Study/Trial Completion:	<u>04/2015</u>
	Final Report Submission:	<u>06/2015</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Orbactiv increases warfarin exposure by 30%, potentially increasing the risk of bleeding. In addition, Orbactiv interferes with phospholipid-dependent laboratory coagulation tests *in vitro*, such as the aPTT and PT. Orbactiv has been shown to artificially prolong prothrombin time (PT) by binding to the phospholipid reagents commonly found in laboratory coagulation tests. Effects on INR are expected, potentially affecting monitoring of warfarin anticoagulation. However, the clinical significance of the increase in warfarin concentration of 30% is unknown.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Orbactiv increases warfarin exposure by 30%, potentially increasing the risk of bleeding. The clinical significance of Orbactiv increase in warfarin plasma levels in healthy individuals needs characterization.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To evaluate the effects of a single 1200 mg infusion of oritavancin on the safety (AE and PT/INR monitoring) and pharmacokinetics of warfarin and to determine the magnitude and duration of this interaction to gain insights into the possible need for alterations in warfarin dosing.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials  
*Continuation of Question 4*

Additional data or analysis required for a previously submitted or expected study/clinical trial  
(provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug  
 There is not enough existing information to assess these risks  
 Information cannot be gained through a different kind of investigation  
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and  
 The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

## PMR/PMC Development Template

---

NDA/BLA # NDA 206334  
Product Name: ORBACTIV (oritavancin)

---

PMR Description: 2165-6: A single-center, open-label trial to evaluate the effects of a single 1200 mg IV dose of Orbactiv (oritavancin diphosphate) on the results of multiple coagulation tests in healthy volunteers

---

PMR Schedule Milestones:	Final Protocol Submission:	<u>10/2014</u>
	Study/Trial Completion:	<u>03/2015</u>
	Final Report Submission:	<u>05/2015</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Orbactiv interferes with phospholipid-dependent laboratory coagulation tests *in vitro*. Orbactiv has been shown to artificially prolong activated partial thromboplastin time and prothrombin time (PT) by binding to the phospholipid reagents commonly found in laboratory coagulation tests. Effects on INR are expected, potentially affecting monitoring of warfarin anticoagulation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Orbactiv increases warfarin exposure by 30%, potentially increasing the risk of bleeding. Monitoring of IV heparin anticoagulation effect is impaired. The magnitude and duration of Orbactiv PT/INR and other coagulation tests interference in humans needs characterization.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To evaluate the magnitude and duration of any false prolongation of multiple coagulation tests in healthy volunteers following a single 1200 mg oritavancin infusion.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Study the effect of oritavancin on coagulation tests in healthy volunteers

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

---

Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

## PMR/PMC Development Template

NDA/BLA # NDA 206334  
Product Name: ORBACTIV (oritavancin)

PMC Description: 2165-7: A study to evaluate the effects of oritavancin on phospholipid and non-phospholipid based coagulation tests *in vitro*.

PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2014</u>
	Study/Trial Completion:	<u>04/2015</u>
	Final Report Submission:	<u>04/2015</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Orbactiv interferes with phospholipid-dependent laboratory coagulation tests *in vitro*. Orbactiv has been shown to artificially prolong activated partial thromboplastin time (aPTT) and prothrombin time (PT) by binding to the phospholipid reagents commonly found in laboratory coagulation tests. Effects on ACT and INR are expected, potentially affecting monitoring of anticoagulation/hemostasis.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Inability to monitor anticoagulation effect of medications, e.g. warfarin and heparin, may put patients receiving anticoagulants at risk of bleeding or hypercoaguable state. Characterization of Orbactiv effect on an array of coagulation monitoring tests is needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

**Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

**Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in vitro study to characterize the effect of Orbactiv on phospholipid and non-phospholipid based coagulation tests.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety

- Other (provide explanation)

In vitro evaluation of Orbactiv effect on a battery of coagulation tests

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YULIYA I YASINSKAYA  
08/06/2014

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** [NDA 206334](#)

**Application Type:** [New NDA](#)

**Name of Drug/Dosage Form:** Orbactiv (Oritavancin diphosphate) Sterile, lyophilized powder for injection

**Applicant:** The Medicines Company

**Receipt Date:** December 6, 2013

**Goal Date:** August 6, 2014

## 1. Regulatory History and Applicant's Main Proposals

Oribactiv was previously submitted under NDA 22153 and received a Complete Response because of lack of substantial evidence of efficacy based on the non-inferiority margin. The NDA was withdrawn on March 22, 2013. Following the Complete Response letter, The Medicines Company acquired Orbactiv and initiated a new clinical development program. This application is under Priority review since QIDP designation was granted on October 31, 2013. On December 6, 2013 The Medicines Company submitted an Original NDA for the treatment of adult patients with acute bacterial skin and skin structure infections.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

The Applicant submitted the Physicians Labeling Rule Label (PLR) following the CDER style guide for formatting and instructions for PLR labeling. No waiver has been requested for the size of the highlight section. This reviewer references the discipline review teams for information in the prescribing information sections.

## 3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

The submitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required

## Selected Requirements of Prescribing Information

• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- N/A** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

### Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- N/A** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- NO** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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NASEYA N MINOR  
07/01/2014

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** June 4, 2014

**To:** Naseya Minor  
Regulatory Project Manager  
Division of Anti-Infective Products (DAIP)

**From:** Carrie Newcomer, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject: NDA: 206334**  
**ORBACTIV** (oritavancin) for injection, for intravenous use

---

### Background

On February 19, 2014, DAIP consulted OPDP to review the proposed package insert (PI) for ORBACTIV (oritavancin) for injection, for intravenous use (ORBACTIV).

Please note that OPDP has reviewed the proposed PI and our comments are based on the substantially complete version of the draft label received via e-mail from DAIP on May 21, 2014. Our comments are provided in the attachment.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov).

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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CARRIE A NEWCOMER  
06/04/2014

MEMORANDUM

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

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CLINICAL INSPECTION SUMMARY

DATE: May 13, 2014

TO: Naseya Minor, M.P.H., Regulatory Project Manager  
Mayurika Ghosh, M.D., Medical Officer  
John Alexander, M.D., M.P.H., Cross-Discipline Team Leader  
Division of Anti-Infective Products

FROM: Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206334

APPLICANT: The Medicines Company

DRUG: Oritavancin  
NME: Yes  
THERAPEUTIC CLASSIFICATION: Priority review

INDICATIONS: Treatment of acute bacterial skin and skin structure infections

CONSULTATION REQUEST DATE: January 8, 2014  
INSPECTION SUMMARY GOAL DATE: June 1, 2014  
DIVISION ACTION GOAL DATE: August 6, 2014  
PDUFA DATE: August 6, 2014

## I. BACKGROUND:

The Medicines Company has submitted NDA 206334 for oritavancin for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of Gram positive bacteria. Oritavancin is a lipoglycopeptide that has antibacterial activity against Gram positive bacteria, including methicillin- and vancomycin-resistant staphylococci and penicillin-resistant streptococci. Two identical studies, TMC-ORI-10-01 (SOLO 1) and TMC-ORI-10-02 (SOLO 2), entitled “A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin versus IV Vancomycin for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infection,” were submitted in support of this application.

### TMC-ORI-10-01 (SOLO 1) and TMC-ORI-10-02 (SOLO 2)

SOLO1 and SOLO2 were identically-designed.

The studies were Phase 3, randomized, double-blind, active-comparator, noninferiority studies designed to evaluate the efficacy and safety of a single dose of IV oritavancin compared to IV vancomycin for 7-10 days for the treatment of patients with ABSSSI suspected or proven to be caused by Gram positive bacteria. Patients were randomized in a 1:1 fashion to receive IV oritavancin or IV vancomycin in a double-blinded fashion.

The primary efficacy endpoint was based on the size of the infected site relative to baseline and whether a patient had a fever at 48-72 hours after initiation of therapy. A success was defined as cessation of spread or reduction in the size of the baseline lesion (based on length, width, and calculated surface area), absence of fever (temperature  $<37.7^{\circ}\text{C}$  at the last 3 consecutive readings by same route (oral only) taken every 6 hours between 48 and 72 hours), and no rescue antibiotic administered. Resolution of the signs and symptoms related to skin infection (erythema, induration, edema, purulent drainage, fluctuance, pain, tenderness, heat or localized warmth) after initiation of study drug at early clinical evaluation (ECE), end of therapy (EOT), Day 10, and post-therapy evaluation (PTE) were assessed as secondary endpoints.

## II. RESULTS (by Site):

<b>Site # Name of CI, Location</b>	<b>Protocol # and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification</b>
Site #101046 Jeffrey S. Overcash, M.D. 5565 Grossmont Center Drive, Building 3, Ste. 525 La Mesa, CA 92942	SOLO I 69 subjects	March 25 – April 14, 2014	NAI
Site #101002 Heidi A. Kabler, M.D. 3196 South Maryland Parkway, #207 Las Vegas, NV 89109	SOLO I 153 subjects	March 25 – April 2, 2014	VAI
Site #191008 Ashwin Porwal, M.D. Survey no 15, Near KPCT Mall Fatima Nagar Pune 411040 India	SOLO I 63 subjects	April 28 – May 8, 2014	Pending Preliminary VAI
Site #201005 Richard C. Keech, M.D. 3055 West Orange Ave., Ste 204 Anaheim, CA 92804	SOLO II 106 subjects	March 3 – 20, 2014	VAI
Site #201002 Paul J. Manos, M.D. eStudy Site, Oceanside 3998 Vista Way, Ste., 102 Oceanside, CA 92056	SOLO II 112 subjects	March 17 – 31, 2014	Pending Preliminary VAI
The Medicines Company 8 Sylvan Way Parsippany, NJ 07054	MC-ORI-10-01 (SOLO I) MC-ORI-10-02 (SOLO II)	March 14 – 21, 2014	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

## 1. Jeffrey S. Overcash, M.D.

5565 Grossmont Center Drive, Building 3, Ste. 525  
La Mesa, CA 92942

## a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from March 25 to April 14, 2014. At this site, 74 subjects were screened, 69 subjects were randomized, and 43 subjects completed the study. Twenty six (26) subjects were lost to follow-up.

An audit of 37 subjects' records was conducted. Records reviewed included informed consents, case history source documents, monitoring reports, IRB correspondence, and drug accountability records.

## b. General observations/commentary:

The informed consent forms for the 37 subjects audited were signed prior to study procedures.

The primary endpoint was verifiable. There was no under-reporting of adverse events. No significant regulatory violations were noted and no Form FDA 483, Inspectional Observations was issued.

The inspector did take note of the relatively high number of subjects (26) lost to follow-up. The CI noted that the patient population and study design contributed to the challenges to maintain the study population. There was evidence that the site exercised due diligence (including repeated phone calls and sending certified letters) in attempting to maintain the study population.

## c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

## 2. Heidi A. Kabler, M.D.

3196 South Maryland Parkway, #207  
Las Vegas, NV 89109

## a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from March 25 to April 2, 2014. At this site, 160 subjects were screened, 153 subjects were randomized, and 125 subjects completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Dr. Kabler assumed the responsibility of principal investigator while the study was ongoing.

All 153 randomized subjects signed informed consent forms prior to study procedure. An audit of 51 subjects' records was conducted for eligibility and primary efficacy endpoint. A complete audit of 25 subjects' records was performed. Data listings submitted to the NDA were compared and verified against source documents and case report forms.

Inspection revealed that the site was generally in compliance with good clinical practices. However, a Form FDA 483, Inspectional Observations, was issued to the clinical investigator for failure to conduct the investigation in accordance with the investigational plan. Specifically:

- Study personnel did not adequately insure proper storage of reconstituted test article/investigational pharmaceutical product as required by the pharmacy manual. Multiple temperature excursions outside the range of 2-8°C were observed in a review of pharmacy logs for refrigerated storage.

*OSI reviewer comment: Temperature excursions occurred at both ends of the spectrum (i.e. below and above recommended storage temperatures). In Dr. Kabler's response, she notes that other than the initial infusion of oritavancin which was reconstituted at the time of randomization and infused shortly thereafter, infusions were either vancomycin or placebo. Both vancomycin and placebo are stable at room temperature, therefore the temperature excursions were unlikely to affect stability.*

*However, there were several minimum temperatures recorded that may have been below the freezing point (i.e. the temperatures were recorded as negative numbers in °C), although the maximum temperatures recorded for the day were within the specified range. It is unclear whether storage temperatures below 0°C for vancomycin for a period of time would have adversely impacted safety or activity of the drug.*

- Study personnel did not report all adverse events. Nausea and dysuria were listed as AEs for Subject #101002/128 however were not entered into the Electronic Data Capture reporting to the sponsor.

*OSI reviewer comment: Dr. Kabler's response notes that this was a transcription omission.*

- Subject #101002/144 was designated as a clinical success at the ECE and EOT assessments, however the subject experienced a fever of 99.9° within the 48-72 hour period. According to the protocol, a fever above 99.86° does not qualify the subject to be listed as a clinical success.

*OSI reviewer comment: When the assessment of error of clinical success was noted for the ECE visit it was corrected in the EDC system and counted in the data system as a*

*failure. However, the study staff did not correct the source document worksheet to reflect the subject was deemed a clinical failure at this visit.*

Dr. Kabler responded adequately to these observations in a letter dated April 16, 2014.

c. Assessment of data integrity:

The regulatory violations noted above appear to be minor, although the effect of potential periods (duration unknown) of sub-zero temperatures on reconstituted vancomycin is not clear (i.e. whether this could have altered the safety profile or activity of the drug). The review division may wish to consult with chemistry about this issue. Otherwise the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Ashwin Porwal, M.D.  
Survey no 15, Near KPCT Mall  
Fatima Nagar  
Pune 411040 India

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from April 28 to May 8, 2014. At this site, 67 subjects were screened, 63 subjects were randomized, and 63 subjects completed the study. Subject records for 21 subjects were reviewed.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

The source documents were very detailed and all visit requirements spelled out in the subject files. All subjects had definite need for treatment. All subjects reviewed appeared to meet eligibility requirements. From review of the records audited and photos, and lack of fever etc. it appeared that the treatment was effective for all the subjects. Once the subjects left the hospital they had a hard time getting them to return for a visit. They would talk to them at the 60 day visit and even before but they would not always show up as promised.

The primary efficacy endpoint data were verifiable for all but two subjects who withdrew from the study. No one audited had fevers and no one had their infection return or escalate. All of the wounds healed to the point they considered them successfully cured. Pictures showed this to be true. There was no evidence of under-reporting of adverse events.

A one item Form FDA 483, Inspectional Observations, was issued for failure to prepare and maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, 30 study site identified protocol deviations were not entered

into the electronic case report forms on the Deviation Case Report Form for each of the subjects.

*OSI Reviewer Comment: The ORA investigator described these protocol deviations as being minor (e.g. hematology samples not having platelets measured, ECGs not done). Dr. Porwal's written response dated April 14, 2014 was adequate. He noted that the study coordinator performed a final reconciliation of subject data prior to the close out visit and identified these deviations. Per Dr. Porwal, the study database had been locked and therefore the identified deviations were not included in the sponsor data listing. Going forward, he states care will be taken to avoid protocol deviations and if they do occur, they will be immediately identified and recorded per the sponsor requirement.*

c. Assessment of data integrity:

Notwithstanding the above violation, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Richard C. Keech, M.D.  
3055 West Orange Ave., Ste 204  
Anaheim, CA 92804

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from March 3 to 20, 2014. At this site, 121 subjects were screened, 106 subjects were randomized, and 95 subjects completed the study. An audit of 39 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

In general, the clinical site was compliant with good clinical practices. A Form FDA 483, Inspectional Observations was issued for not conducting the investigation in accordance with the protocol. Specifically,

- Subject #201005073 was enrolled with a screening alanine aminotransferase (ALT) of 143 U/L, which is more than 3X the female upper limit of normal (33-40 U/L). The subject should have been excluded based on Exclusion Criterion #19.
- The baseline screening blood glucose for Subject #201005060 was 380 mg/dL. Protocol Amendment 3, Section 6.3.1, requires a blood sample test for HbA1c at treatment visits for subjects whose glucose level is >170 mg/dL at baseline.
- A mild, nonserious adverse event of erythema and redness at an IV site was recorded in the source documents but was not included on the eCRF.
- Worsened or abnormal laboratory findings were not recorded as adverse events on the

eCRF or reported to sponsor. For example,

- Subject #201005030 had a baseline ALT of 60 U/L and the post-therapy evaluation (PTE) ALT was 126 U/L, which is an increase more than 3X the male upper limit of normal of 40-41 U/L
- Subject #201005035 had a baseline ALT of 113 U/L (local lab), ALT increased to 165 U/L at early clinical evaluation, 172 U/L at end of therapy, and 198 U/L at post therapy evaluation, which is an increase to more than 3X the male upper limit of 40-41 U/L
- Subject #201005098 had aspartate aminotransferase (AST) of 46 U/L which increased to 113 U/L at post-therapy evaluation which is more than 3X female upper limit of normal of 36 U/L.

*OSI reviewer comment: The protocol seems somewhat ambiguous on reporting of abnormal laboratory values as adverse events. "An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding)..." This does not mean that all abnormal laboratories need to be reported as adverse events. Although rising laboratory values (like ALT) are concerning, particularly when persisting to the post-therapy evaluation, these laboratory parameters will be evaluated separately as part of the safety review of the application.*

*Dr. Keech responded adequately to these observations in a letter dated March 31, 2014*

c. Assessment of data integrity:

Notwithstanding the above violations, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Paul J. Manos, M.D.  
eStudy Site, Oceanside  
3998 Vista Way, Ste., 102  
Oceanside, CA 92056

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from March 17 to 31, 2014. At this site, 130 subjects were screened, 112 subjects were randomized, and 91 subjects completed the study. Thirty (30) subjects' records were reviewed.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

All subjects signed informed consent forms prior to participating in the study.

Primary efficacy endpoint data was verifiable. There was no under-reporting of adverse events.

In general, the site was in compliance with good clinical practices. A one item Form FDA 483 was issued for failing to conduct an investigation in accordance with the investigational plan. Specifically, required lab tests were not consistently performed. The protocol states that blood is to be drawn for clinical laboratory assessment for End of Therapy (EOT), Day 10, and Post Therapy (PTE) visits. Relevant examples include:

- i) The Day 10 worksheet for Subject 201002025, dated 5/17/12 noted that labs were not clinically indicated for this visit.
- ii) The Post Therapy Visit for Subject 201002025, dated 5/22/12 noted that labs were not clinically indicated for this visit.
- iii) The Day 10 worksheet for Subject 201002027, dated 5/24/12 noted that labs were not clinically indicated for this visit.
- iv) The Post Therapy Visit for Subject 201002027, dated 5/31/12 noted that labs were not clinically indicated for this visit.
- v) The Day 10 worksheet for Subject 201002029, dated 6/2/12 noted that labs were not clinically indicated for this visit.

Dr. Manos responded adequately in a letter dated April 14, 2014. He noted that while a source document worksheet was being revised, the clinical research coordinator erroneously changed the worksheets for the Day 10 and Post Therapy Visits to indicate that labs were to be done only if clinically indicated. The error was discovered and the source worksheets were revised to correct the error.

c. Assessment of data integrity:

Notwithstanding the protocol violation noted above, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

6. The Medicines Company  
8 Sylvan Way  
Parsippany, NJ 07054

a. What was inspected:

The inspection was conducted from March 14-21, 2014. The inspection reviewed the following: personnel, investigator training, financial disclosures, IRB oversight, contracts with contract research organizations and vendors, monitoring activities and correspondence, test article integrity and accountability, data collection, SAE reporting, and quality assurance.

b. General observations/commentary:

The sponsor maintained satisfactory oversight of the studies. A Form FDA 483, Inspectional Observations, was not issued at the end of inspection.

The ORA investigator found that one site (Site #240002, Dr. Condrea, Bucharest, Romania) that participated in SOLO 2 was closed due to repeated GCP deficiencies. The site closure was reported to the FDA in an IND submission dated September 26, 2012. This site had enrolled eight subjects. Two subjects were ineligible (one subject (#240002002) had an inconclusive urine pregnancy test, later confirmed to have a positive serum pregnancy test and the other subject (#240002008) had elevated LFTs). Three subjects (#s 240002001, 240002002, and 240002003) did not have Gram stains sent to the central laboratory and tests were only done locally.

c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For the studies supporting this NDA, inspections of five clinical investigator sites and the sponsor were performed. The final classification for the inspections of Dr. Jeffrey Overcash and the sponsor, The Medicines Company, is No Action Indicated (NAI). The final classification for the inspections of Drs. Heidi Kabler and Dr. Richard Keech is Voluntary Action Indicated (VAI). The preliminary classification for the inspections of Drs. Porwal and Manos is VAI.

In general, the regulatory violations observed at Drs. Kabler, Keech, Manos, and Porwal sites are minor and have minimal impact on data integrity or human subject safety. Data from these sites and as submitted by the sponsor are acceptable for use in support of the respective indication.

Observations noted above for Dr. Porwal and Dr. Manos are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

#### CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief

Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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JANICE K POHLMAN  
06/03/2014

KASSA AYALEW  
06/03/2014

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## LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	May 19, 2014
<b>Requesting Office or Division:</b>	Division of Anti-Infective Products (DAIP)
<b>Application Type and Number:</b>	NDA 206334
<b>Product Name and Strength:</b>	Orbactiv (Oritavancin Diphosphate) for Injection, 400 mg per vial
<b>Product Type:</b>	Single Ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	The Medicines Co
<b>Submission Date:</b>	December 6, 2013
<b>OSE RCM #:</b>	2014-87
<b>DMEPA Primary Reviewer:</b>	Justine Harris, RPh
<b>DMEPA Acting Team Leader:</b>	Tingting Gao, PharmD
<b>DMEPA Acting Team Leader:</b>	Julie Neshiewat, PharmD, BCPS

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## 1 REASON FOR REVIEW

DAIP requested that we evaluate the proposed container labels, carton labeling, and prescribing information labeling for Orbactiv (Oritavancin Diphosphate) Injection, NDA 206334, submitted on December 6, 2013, for areas of vulnerability that could lead to medication errors. This is a New Molecular Entity (NME) application under the PDUFA V Program.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B - N/A
Previous DMEPA Reviews	C
Human Factors Study	D - N/A
ISMP Newsletters	E - N/A
Other	F - N/A
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified the following areas of vulnerability to medication errors in the container labels, carton labeling, and prescribing information labeling:

- Product is to be administered by intravenous infusion only and label and labeling revisions are recommended to minimize the risk of wrong route of administration
- The use of abbreviations and symbols in the labels and labeling may be misinterpreted and lead to medication errors
- The layout and placement of important information can be improved for readability and clarity.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the container label and carton labeling, and clarify important information in the prescribing information labeling, to promote the safe use of the product.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

#### A. Dosage and Administration, Highlights of Prescribing Information

1. Revise the “IV” abbreviation to “intravenous” to avoid misinterpretation per FDA Guidance for Industry titled: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which states that “The route of administration should be described without abbreviation”.

#### B. Dosage and Administration, Full Prescribing Information

1. In Section 2.2, we recommend revising “for intravenous (b) (4)” to “for intravenous infusion”. We recommend this to minimize the risk of administering the drug too fast based on our post marketing experiences.
2. Revise all “IV” abbreviations to “intravenous” to avoid misinterpretation per FDA Guidance for Industry titled: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which states that “The route of administration should be described without abbreviation”.
3. In Section 2.1, revise the statement “patient  $\geq$  18 years of age” to “patients 18 and older” to avoid misinterpretation of the symbol ‘ $\geq$ ’.

### 4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

Based on this 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 mg per vial) and route of administration to below the established name. The highlighted (green) 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) Only' 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) vertical text 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 'expiry' 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.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Orbactiv (Oritavancin diphosphate) that The Medicines Co. submitted on December 6, 2013.

Table 2. Relevant Product Information for Orbactiv	
Active Ingredient	oritavancin diphosphate
Indication	the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of the following Gram-positive microorganisms: <i>Staphylococcus aureus</i> (including MSSA and MRSA), <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <i>Streptococcus dysgalactiae</i> , <i>Streptococcus anginosus</i> group, and <i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)
Route of Administration	intravenous
Dosage Form	powder for injection
Strength	400 mg
Dose and Frequency	1200 mg administered as a single dose by intravenous infusion over 3 hours
How Supplied	sterile powder in a 50 mL capacity glass vial
Storage	store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Container Closure	3 single use vials packed in a carton

### APPENDIX C. PREVIOUS DMEPA REVIEWS

#### C.1 Methods

We searched the L:Drive on April 1, 2014 using the terms, 'Oritavancin', to identify reviews previously performed by DMEPA.

#### C.2 Results

A proprietary name review was conducted in OSE Review # 2013-2477 for IND 051292 and NDA 206334 on March 3, 2014 and the name Orbactiv was tentatively approved.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the followingoritavancin diphosphate labels and labeling submitted by The Medicines Co on December 6, 2013.

- Carton labeling (Appendix G.2.1)
- Container label (Appendix G.2.2)
- Full Prescribing Information (No Image)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JUSTINE HARRIS  
05/19/2014

TINGTING N GAO  
05/19/2014

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 206334 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: ORBACTIV Established/Proper Name: Oritavancin diphosphate Dosage Form: Sterile, lyophilized powder for injection Strengths: 400 mg/vial		
Applicant: The Medicines Company Agent for Applicant (if applicable):		
Date of Application: December 6, 2013 Date of Receipt: December 6, 2013 Date clock started after UN:		
PDUFA Goal Date: August 6, 2014		Action Goal Date (if different):
Filing Date: January 6, 2014		Date of Filing Meeting: January 30, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1P		
Proposed indication(s)/Proposed change(s): Treatment of acute bacterial skin and skin structure infections (ABSSSI)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</b></i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		
Type of Original BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i><b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</b></i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

<input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 51292				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears																			
<p><b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes, # years requested:</b> 10 years  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ( <i>Original 351(a)BLAs/BLA supplements only</i> )  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Information

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				requested January 8, 2014 and received January 10, 2014
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Field Office should have access to the EDR.
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A Risk Management Plan has been submitted.
<b><u>Prescription Labeling</u></b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels			
	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent			
	<input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT IRT Consult sent January 16, 2014.  Methods Validation Consult sent January 22, 2014
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> June 27, 2013 September 16, 2013  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-NDA CMC
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> June 8, 2010  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 30, 2014

**BLA/NDA/Supp #:** NDA 206334

**PROPRIETARY NAME:** ORBACTIV

**ESTABLISHED/PROPER NAME:** Oritavancin diphosphate

**DOSAGE FORM/STRENGTH:** 400 mg/vial

**APPLICANT:** The Medicines Company

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Actue bacterial skin and skin structure infections (ABSSSIs)

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Naseya Minor	Y
	CPMS/TL:	Frances Le Sane	N
Cross-Discipline Team Leader (CDTL)	John Alexander		Y
Clinical	Reviewer:	Mayurika Ghosh	Y
	TL:	Yuliya Yasinkaya	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Avery Goodwin	Y
	TL:	Kerry Snow	Y

Clinical Pharmacology	Reviewer:	Ryan Owen	Y
	TL:	Kim Bergman	Y
Biostatistics	Reviewer:	Mushfiqur Rashid	Y
	TL:	Thamban Valappil	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Nostrandt	Y
	TL:	Wendy Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Dorota Matecka	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Vinayak Pawar	Y
	TL:	Bryan Riley	Y
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Karen Townsend	Y
	TL:	Christine Corser	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Olga Salis		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments  <b>List comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?  <b>If no, explain:</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: the application did not raise significant safety or efficacy issues
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> <li>    <b>If no</b>, was a complete EA submitted?   <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> <li>    <b>If EA submitted</b>, consulted to EA officer (OPS)?   <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <p><b>Comments:</b></p>	
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?   <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?   <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p>

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Edward Cox, OAP Director</p>	

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): March 4, 2014

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

### REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review

### ACTIONS ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"><li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li><li>• notify OMPQ (so facility inspections can be scheduled earlier)</li></ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)

<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NASEYA N MINOR  
04/04/2014