CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209776Orig1s000

OTHER REVIEW(S)
PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (OPQ) or biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

<table>
<thead>
<tr>
<th>NDA #</th>
<th>209776</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Conduct extractable/leachable studies on the drug product commercial container-closure system. The results of the extraction studies should be used to monitor the drug product stability samples for potential leachables. The drug product representative stability batches should be tested for leachables through expiry by appropriate analytical techniques as established in a study protocol. The data from these studies along with the final report should be submitted as a prior-approval (PAS) supplement.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PMC Schedule Milestones:</th>
<th>Final Protocol Submission:</th>
<th>1-Dec-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interim Report:</td>
<td>1-Sep-2018</td>
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<tr>
<td></td>
<td>Study/Trial Completion:</td>
<td>1-Feb-2019</td>
</tr>
<tr>
<td></td>
<td>Final Report Submission:</td>
<td>1-April-2019</td>
</tr>
</tbody>
</table>

- ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.
- INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.
- DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE

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

- [ ] Need for drug (unmet need/life-threatening condition)
- [ ] Long-term data needed (e.g., stability data)
- [ ] Only feasible to conduct post-approval
- [ ] Improvements to methods
- [ ] Theoretical concern
- [ ] Manufacturing process analysis
- [ ] Other

The drug product container closure system should be tested for extractables and leachables. However, this product (stopper undergoes minimal contact with the reconstituted solution so the risk of potential leachables is relatively low. Therefore, the drug product representative stability batches will be tested for leachables through expiry by appropriate analytical techniques as established in a study protocol and based on the results of extractable studies. This information will be obtained post-approval.
2. Describe the particular review issue and the goal of the study.

Conduct extractable/leachable studies on the drug product commercial container-closure system. The results of the extraction studies should be used to monitor the drug product stability samples for potential leachables. The drug product representative stability batches should be tested for leachables through expiry by appropriate analytical techniques as established in a study protocol. The objective of the study is to ensure that the product does not become contaminated with excessive amounts of compounds that leach from the container-closure system.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

☐ Dissolution testing
☐ Assay
☐ Sterility
☐ Potency
☐ Product delivery
☐ Drug substance characterization
☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☒ Other

Describe the agreed-upon study:

Conduct extractable/leachable studies on the drug product commercial container-closure system.

5. To be completed by OPQ/OBP Manager:

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

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.

(signature line for BLAs only)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE A DEAN
08/29/2017
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.

SECTION A: Administrative Information

NDA/BLA # 209776
Product Name: Vabomere
Applicant Name: Rempex Pharmaceuticals Inc.
ODE/Division: OND/OAP/DAIP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

PMR 3248-I: Conduct a Phase-1, open-label, sequential study to assess the PK, safety, and tolerability of VABOMERE and the PK of meropenem and vaborbactam in children from birth to < 18 years of age with selected serious bacterial infections.

2. PMR/PMC Schedule Milestones

   Final Protocol Submission: Submitted
   Study/Trial Completion: 09/2019
   Final Report Submission: 03/2020

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study/clinical trial in the text box below.

Under PREA, Vabomere for the treatment of cUTI is to be evaluated in pediatric patients. This study will evaluate the pediatric dose for a subsequent safety pediatric trial and inform the labeling.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

   - [ ] Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
   - [ ] Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
   - [X] PREA PMR: Meets PREA postmarketing pediatric study requirements [Skip to Q.5]
   - [ ] FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [Go to Q.3]
☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [Go to Q.3]

3. For FDAAA PMRs and 506B PMCs only: N/A

4. For FDAAA PMR Complete this entire section: N/A

5. For all PMRs and PMCs: What type of clinical trial is needed to achieve the goal described in Q1 above?

<table>
<thead>
<tr>
<th>TYPE OF CLINICAL TRIAL</th>
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<tbody>
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<td>☐ Combined PK/PD, safety and/or efficacy trial (PREA* PMRs only)</td>
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<td>☐ Thorough Q-T clinical trial</td>
</tr>
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<td>☐ Other (describe) ______</td>
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SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).
   ☐ Yes
   ☑ No

Reference ID: 4144540
2. This study or clinical trial focuses on the following special population(s) or circumstance(s): [Select all that apply]

☐ For non-PREA pediatric studies/trials only: Pediatric population
☐ Geriatric population
☐ Lactating/nursing mothers
☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
☐ Orphan or rare disease population
☐ Pregnant women
☐ Racial/ethnic population
X Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

N/A

SECTION E: PMR/PMC Development Coordinator Statements

1. The PMR/PMC is clear, feasible, and appropriate because: [Select all that apply]
   ☒ The study/clinical trial meets criteria for a PMR or a PMC.
   ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
   ☒ The applicant has adequately justified the choice of milestone dates.
   ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:
   - There is a significant question about the public health risks of the drug.
   - There is not enough existing information to assess the public health risks of the drug.
   - Information about the public health risks cannot be gained through a different kind of investigation.
   - The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
   - The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ 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
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

SECTION A: Administrative Information
NDA/BLA # 209776
Product Name: Vabomere
Applicant Name: Rempex Pharmaceuticals Inc.
ODE/Division: OND/OAP/DAIP

SECTION B: PMR/PMC Information
3. PMR/PMC Description

PMR 3248-2: Conduct a phase 2, randomized, single-blind, active comparator study to evaluate the safety, tolerability, and PK of VABOMERE versus piperacillin/tazobactam for the treatment of pediatric subjects from 3 months to <18 years of age with Complicated Urinary Tract Infections (cUTIs) including acute pyelonephritis and.

4. PMR/PMC Schedule Milestones
   - Draft Protocol Submission: 05/2018
   - Final Protocol Submission: 09/2018
   - Study/Trial Completion: 09/2021
   - Final Report Submission: 03/2022

SECTION C: PMR/PMC Rationale
1. Describe the particular review issue and the goal of the study/clinical trial in the text box below.

Under PREA, Vabomere for the treatment of cUTI to be evaluated in pediatric patients. This study will evaluate the pediatric dose that can be described in labeling.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)
   - [ ] Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
   - [ ] Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
   [X] PREA PMR: Meets PREA postmarketing pediatric study requirements [Skip to Q.5]
   - [ ] FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [Go to Q.3]

Reference ID: 4144540
☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [Go to Q.3]

3. For FDAAA PMRs and 506B PMCs only: N/A

4. For FDAAA PMR Complete this entire section : N/A

5. For all PMRs and PMCs: What type of clinical trial is needed to achieve the goal described in Q1 above?

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SECTION D: PMR/PMC Additional Information
1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).
   ☐ Yes
   ☑ No
2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]
- For non-PREA pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

X Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

N/A

SECTION E: PMR/PMC Development Coordinator Statements

1. The PMR/PMC is clear, feasible, and appropriate because: [Select all that apply]
   - The study/clinical trial meets criteria for a PMR or a PMC.
   - The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
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   - The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:
   - There is a significant question about the public health risks of the drug.
   - There is not enough existing information to assess the public health risks of the drug.
   - Information about the public health risks cannot be gained through a different kind of investigation.
   - The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
   - The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. 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

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

SECTION A: Administrative Information

NDA/BLA # 209776
Product Name: Vabomere
Applicant Name: Rempex Pharmaceuticals Inc.
ODE/Division: OND/OAP/DAIP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

PMR 3248-3: Conduct a Phase 2 open-label, active comparator study to evaluate the PK, safety, and tolerability of multiple doses of VABOMERE vs comparator in neonates (≤ 90 days of age) with late onset sepsis.

2. PMR/PMC Schedule Milestones

Draft Protocol Submission: 11/2019
Final Protocol Submission: 03/2020
Study/Trial Completion: 12/2024
Final Report Submission: 06/2025

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study/clinical trial in the text box below.

Under PREA, VABOMERE for the treatment of cUTI is to be evaluated in pediatric patients. This study will evaluate the PK and safety of VABOMERE the labeling.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]

☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]

X PREA PMR: Meets PREA postmarketing pediatric study requirements [Skip to Q.5]

☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [Go to Q.3]
PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [Go to Q.3]

3. For FDAAA PMRs and 506B PMCs only : N/A

4. For FDAAA PMR Complete this entire section : N/A

5. For all PMRs and PMCs: What type of clinical trial is needed to achieve the goal described in Q1 above?

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SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

□ Yes

X No
2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For non-PREA pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population

X Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

N/A

SECTION E: PMR/PMC Development Coordinator Statements

1. The PMR/PMC is clear, feasible, and appropriate because: [Select all that apply]

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

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

3. 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
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

SECTION A: Administrative Information

NDA/BLA #: 209776
Product Name: Vabomere
Applicant Name: Rempex Pharmaceuticals Inc.
ODE/Division: OND/OAP/DAIP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

**PMR 3248-4:** Conduct a US surveillance study for five years from the date of marketing to determine if resistance to VABOMERE has developed in those organisms specific to the indications in the label.

2. PMR/PMC Schedule Milestones

Final Protocol Submission: 09/2017
Interim Study Report: 09/2018
Interim Study Report: 09/2019
Interim Study Report: 09/2020
Interim Study Report: 09/2021
Study/Trial Completion: 09/2022
Final Report Submission: 06/2023

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study/clinical trial in the text box below.

Long term microbiologic surveillance data are needed to study development of resistance to bacterial pathogens specific to the cUTI indication.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- [ ] Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
- [ ] Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
- [ ] PREA PMR: Meets PREA postmarketing pediatric study requirements [Skip to Q.5]
FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [Go to Q.3]

 PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [Go to Q.3]

3. For FDAAA PMRs and 506B PMCs only
The study or trial can be conducted post-approval because: [Select all that apply]

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected “other reason,” expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed prior to approval.]

4. For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section
   a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]

- Assess a known serious risk related to the use of the drug
- Assess a signal 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

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 above?
[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

<table>
<thead>
<tr>
<th>TYPE OF STUDY</th>
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<tbody>
<tr>
<td>Drug interaction or bioavailability studies (nonclinical only)</td>
</tr>
<tr>
<td>Epidemiologic (observational) study related to safe drug use</td>
</tr>
<tr>
<td>Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)</td>
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<td>Immunogenicity study (nonclinical)</td>
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<td>Meta-analysis or pooled analysis of previous observational studies</td>
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<td>Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)</td>
</tr>
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<td>Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)</td>
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TYPE OF STUDY

☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☒ Other (describe) Microbiological evaluation of patient-level culture data to track resistance patterns in the United States

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).
   ☐ Yes
   ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
   [Select all that apply]
   ☐ For non-PREA pediatric studies/trials only: Pediatric population
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   ☐ Orphan or rare disease population
   ☐ Pregnant women
   ☒ Racial/ethnic population
   ☒ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

   N/A

SECTION E: PMR/PMC Development Coordinator Statements

Error! Reference source not found.

1. The PMR/PMC is clear, feasible, and appropriate because: [Select all that apply]
   ☒ The study/clinical trial meets criteria for a PMR or a PMC.
   ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
   ☒ The applicant has adequately justified the choice of milestone dates.
   ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.
2. **X (If the PMR/PMC is a randomized controlled clinical trial)** The following ethical considerations were made with regard to:
   - There is a significant question about the public health risks of the drug.
   - There is not enough existing information to assess the public health risks of the drug.
   - Information about the public health risks cannot be gained through a different kind of investigation.
   - The trial will be appropriately designed to answer questions about a drug’s efficacy or safety.
   - The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **X** 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
For 506B Reportable PMRs and PMCs only

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

SECTION A: Administrative Information
NDA/BLA #: 209776
Product Name: Vabomere
Applicant Name: Rempex Pharmaceuticals Inc.
ODE/Division: OND/OAP/DAIP

SECTION B: PMR/PMC Information
1. PMR/PMC Description
PMR 3248-5: Conduct a “Thorough QT/QTc Study” to evaluate whether VABOMERE has a threshold pharmacologic effect on cardiac repolarization.

2. PMR/PMC Schedule Milestones
Draft Protocol Submission: 11/2017
Final protocol submission: 01/2018
Study completion: 08/2018
Final report submission: 01/2019.

SECTION C: PMR/PMC Rationale
1. Describe the particular review issue and the goal of the study/ or clinical trial in the text box below.
The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed the cardiac safety report submitted with the NDA. Overall ECG acquisition and interpretation of the study appeared acceptable with no clinically relevant effects on PR and QRS intervals. However, the studies described in the NDA submission cannot be used to exclude small effects (10 msec) as per the ICH E14 and ICH E14 Q&A (R3) guidelines. Therefore, the Applicant should conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold).

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)
   - Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
   - Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [Skip to Q.5]
   - PREA PMR: Meets PREA postmarketing pediatric study requirements [Skip to Q.5]
X  FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial. [Go to Q.3]

☐  PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [Go to Q.3]

3. For FDAAA PMRs and 506B PMCs only
   The study or trial can be conducted post-approval because: [Select all that apply]
   - Longer-term data needed to further characterize the safety/efficacy of the drug
   - Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
   - Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
   - Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
   ■ Study/trial is to further explore a theoretical concern that does not impact the approval determination
   X  Other reason (describe in text box below)

The Applicant has submitted a cardiac safety report summarizing findings related to cardiac safety from the non-clinical and clinical studies in the vabomere development program. The objective of this report was evaluation of QT prolongation potential with administration of vabomere. The QT studies submitted with the NDA were reviewed by the FDA Interdisciplinary Review Team (IRT). The Overall ECG acquisition and interpretation of the study appeared acceptable with no clinically relevant effects on PR and QRS intervals. However, the studies described in the NDA submission cannot be used to exclude small effects (10 msec) as per the ICH E14 and ICH E14 Q&A (R3) guidelines. Therefore, the Applicant should conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold).

4. For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section
   a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]
      - Assess a known serious risk related to the use of the drug
      - Assess a signal of serious risk related to the use of the drug
      X  Identify an unexpected serious risk when available data indicate the potential for a serious risk
b. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: [Select all that apply then go to Q.4.e]

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

As a part of this NDA submission, data from 6 studies were submitted (Phase 1 Studies 402, 501, 503, 504 and Phase 3 Studies 505, 506). FDA IRT team deemed 4 of these studies to be not appropriate for our further evaluation. Thus, evaluation focused on only Studies 402 and 501. These two studies failed to exclude 10 ms with the by-time analysis and the C-QTc analysis, but they did not definitively show concentration-dependent prolongation (no significant slope but large intercept) for vaborbactam or meropenem-vaborbactam (vabonere) combination. There are several limitations of these studies which make them uninterpretable for excluding small QTc effects (10 ms):

- Dose cohorts in the studies were too small for meaningful conclusions and they were not designed to exclude 10 ms mean effects.

- There was no supratherapeutic dose/exposure studied. The QTc effects at the high clinical exposure scenario have not been characterized. The primary route of elimination for the drug is renal route. Thus renal impairment likely constitutes the worst case high exposure scenario for the same therapeutic dose. There was no PK information available for quantifying this high exposure scenario and there was no supratherapeutic dose studied to cover such exposures.

- ECG assay sensitivity was not established in the study. The study did not have any higher dose to evaluate effects at multiple-fold (at least 2-fold) of clinically relevant highest exposure to waive the requirement of a positive control as per ICH E14 Q&A (R3) guidance for early phase studies.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

<table>
<thead>
<tr>
<th>TYPE OF CLINICAL TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Combined PK/PD, safety and/or efficacy trial <em>(PREA</em> PMRs only)*</td>
</tr>
<tr>
<td>□ Dose-response clinical trial</td>
</tr>
<tr>
<td>□ Dosing trial (e.g., alternative dosing schedule)</td>
</tr>
<tr>
<td>□ Drug interaction or bioavailability clinical trial (clinical only)</td>
</tr>
</tbody>
</table>
### TYPE OF CLINICAL TRIAL

- [ ] Immunogenicity trial (clinical)
- [ ] Meta-analysis or pooled analysis of previous clinical trials
- [ ] Pharmacogenetic or pharmacogenomic clinical trial
- [ ] Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- [ ] Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- [ ] Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – excludes SOT
- [ ] Safety outcomes trial (SOT)**
- [x] Thorough Q-T clinical trial
- [ ] Other (describe) __________

### SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).
   - [ ] Yes
   - [x] No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
   [Select all that apply]
   - [ ] For non-PREA pediatric studies/trials only: Pediatric population
   - [ ] Geriatric population
   - [ ] Lactating/nursing mothers
   - [ ] Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
   - [ ] Orphan or rare disease population
   - [ ] Pregnant women
   - [ ] Racial/ethnic population
   - [x] Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

   N/A
SECTION E: PMR/PMC Development Coordinator Statements

1. The PMR/PMC is clear, feasible, and appropriate because: [Select all that apply]
   - X The study/clinical trial meets criteria for a PMR or a PMC.
   - X The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
   - X The applicant has adequately justified the choice of milestone dates.
   - X The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. X (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:
   - There is a significant question about the public health risks of the drug.
   - There is not enough existing information to assess the public health risks of the drug.
   - Information about the public health risks cannot be gained through a different kind of investigation.
   - The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
   - The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. X 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.

Insert electronic signature (usually the Deputy Director for Safety)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE A DEAN
08/25/2017

JOSEPH G TOERNER
08/25/2017
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: August 24, 2017
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 209776
Product Name and Strength: Vabomere (meropenem and vaborbactam) for Injection, 2 g per vial
Applicant/Sponsor Name: Rempex Pharmaceuticals, Inc. (a wholly-owned subsidiary of The Medicines Company)
Submission Date: August 23, 2017
OSE RCM #: 2017-8-2
DMEPA Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMO
The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Vabomere (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews. a,b

2 CONCLUSION
The revised container label and carton labeling for Vabomere is acceptable from a medication error perspective. We have no further recommendations at this time.

a Myers, D. Label and Labeling Review Memo for Vabomere (NDA 209776). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 18. RCM No.: 2017-8-1.
b Myers, D. Label and Labeling Review for Vabomere (NDA 209776). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 03. RCM No.: 2017-8.
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/s/

DEBORAH E MYERS
08/24/2017

OTTO L TOWNSEND
08/24/2017
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: August 18, 2017
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 209776
Product Name and Strength: Vabomere (meropenem and vaborbactam) for Injection, 2 g per vial
Applicant/Sponsor Name: Rempex Pharmaceuticals, Inc. (a wholly-owned subsidiary of The Medicines Company)
Submission Date: August 17, 2017
OSE RCM #: 2017-8-1
DMEPA Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMO
The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Vabomere (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review\(^a\) and the Agency’s August 14, 2017 email communication to the Applicant (see Appendix B).

2 CONCLUSION
The revised container label is unacceptable from a medication error perspective. We note that the barcode is placed at the bottom of the principal display panel of the container label. Barcodes in a horizontal position may not scan due to the curvature of the container. Therefore, we recommend that the barcode be relocated and reoriented to a vertical position to improve the scannability.

\(^a\) Myers, D. Label and Labeling Review for Vabomere (NDA 209776). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 03. RCM No.: 2017-8.
3 RECOMMENDATIONS FOR REMPEX PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 209776:

1. We note that the barcode has been placed at the bottom of the principal display panel of the container label. Barcodes placed in a horizontal position may not scan due to the curvature of the container. Consider reorienting the barcode on the container label to a vertical position to improve the scannability.

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

DEBORAH E MYERS
08/18/2017

OTTO L TOWNSEND
08/18/2017

Reference ID: 4141552
Clinical Inspection Summary

Date: August 2, 2017

From: John Lee, M.D., Medical Officer
       Janice Pohlman, M.D., M.P.H., Team Leader
       Kassa Ayalew, M.D., M.P.H., Branch Chief
       Good Clinical Practice Assessment Branch (GCPAB)
       Division of Clinical Compliance Evaluation (DCCE)
       Office of Scientific Investigations (OSI)

To: Jane Dean, R.N., M.S.N., Regulatory Project Manager
    Rama Kapoor, M.D., Medical Officer
    Dmitri Iarikov, M.D., Ph.D., Clinical Team Leader
    Division of Anti-Infective Products (DAIP)

Applications: NDA 209776

Applicant: Rempex Pharmaceuticals, Inc.

Drug: Meropenem and Vaborbactam (Carbavance®)

Original NME NDA: Yes

Review Priority: Priority

Proposed Indication: Treatment of complicated urinary tract infection in adults

Consultation Date: January 26, 2017

CIS Goal Date: August 4, 2017 (extended); June 29, 2017 (original)

Action Goal Date: August 29, 2017

PDUFA Due Date: August 29, 2017

I. OVERALL ASSESSMENT OF FINDINGS

Study REMPEX-505 was audited at good clinical practice (GCP) inspections of a contract research organization (CRO) for study oversight and management, and four clinical investigator (CI) sites: (1) Site 300-001, Evaggelos Giamarellos-Bourboulis (Athens, Greece); (2) Site 804-005, Oleksiy Sagan (Zaporizhzhia, Ukraine); (3) Site 804-002, Viktor Stus (Dnipropetrovsk, Ukraine); and (4) Site 804-009, Ievgenii Sonnyk (Poltava, Ukraine).

For all inspections, no significant GCP deficiencies were observed and a Form FDA 483 was issued. Study conduct appeared adequately GCP-compliant, including sponsor/CRO oversight of study conduct. All audited data were acceptably verifiable against source records and case report forms (CRFs). The data from the four inspected CI sites appear reliable as reported by the sponsor/CRO in the NDA.

Reference ID: 4133876
II. BACKGROUND

This 505 (b)(2) NDA from Rempex Pharmaceuticals, Inc. (RP) supports meropenem-vaborbactam (Carbavance®) for the treatment of complicated urinary tract infections (cUTI) including acute pyelonephritis (AP) in adults (age ≥ 18 years). The NDA relies on known safety/efficacy of meropenem (reference product) and on new RP-sponsored Carbavance® studies. Based on potential efficacy against carbapenem-resistant Enterobacteriaceae (CRE), Carbavance® was designated Qualified Infectious Disease Product (2013) and granted Fast Track Status (2016) during product development.

Meropenem is an injectable carbapenem antibiotic approved for the treatment of complicated skin and skin structure infections (cSSSI, adults/pediatric), complicated intra-abdominal infections (cIAI, adults/pediatric), and bacterial meningitis (BM, pediatric). Vaborbactam is the prototype cyclic boronate beta-lactamase inhibitor which inhibits Class A serine carbapenemases. Clinical experience to date indicates that the meropenem-vaborbactam is safe and effective in treating cUTI, including AP and infections caused by CRE, when given by intravenous (IV) infusion.

Based primarily on the results of Study REMPEX-505 (545 subjects, 272 test / 273 reference), RP claims that the efficacy of Carbavance® in treating cUTI (including infection known/suspected to be caused by CRE) is statistically superior to that of the comparator (piperacillin-tazobactam, PT) with similar safety profiles. Study-505 was originally intended and designed as a non-inferiority study.

REMPEX-505: A Phase III, multi-center, randomized, double-blind, double-dummy study to evaluate the efficacy, safety, and tolerability of Carbavance (meropenem/RPX7009) compared to piperacillin/tazobactam in the treatment of complicated urinary tract infections (cUTI) including acute pyelonephritis (AP) in adults

This randomized controlled trial (RCT) was conducted over 17 months (2014 - 2016) at 60 clinical investigator (CI) sites in 17 countries: Brazil, Belarus, Bulgaria, Czech Republic, Greece, Hungary, Italy, Peru, Poland, Romania, Slovakia, Slovenia, South Korea, Spain, Taiwan, Ukraine, and United States. The primary study objective was to evaluate the safety, efficacy, and pharmacokinetics (PK) of IV meropenem-vaborbactam in adult subjects with cUTI including AP.

- Primary endpoint/analysis: Overall Treatment Success (OTS) as a composite endpoint of clinical (Cure or Improvement) and microbiologic (Eradication at End of IV Treatment, EOIVT) outcomes using Microbiological Modified Intent-to-Treat (m-MITT) analysis

- Study groups, treatment regimen, and study medications: randomization in equal ratio to Carbavance® or PT, IV infusion over 3.5 hours every 8 hours for at least 5 days:
  - Carbavance®: 2 grams each of meropenem and vaborbactam in 250 mL normal saline (NS), infusion over 3 hours followed by 100 mL of NS over 30 minutes
  - PT: 4 grams of piperacillin and 0.5 grams of tazobactam in 100 mL NS, infusion over 30 minutes followed by 250 mL NS over 3 hours
  - Levofoxacin: 500 mg oral tablets given every 24 hours in lieu of Carbavance® or PT if all step-down criteria were met (including receipt of ≥ 15 doses of study medication)
## III. INSPECTION OUTCOMES: Study REMPEX-505

<table>
<thead>
<tr>
<th>Clinical Investigator (1)</th>
<th>Site / Enrollment (2)</th>
<th>Inspection Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaggelos Giamarellos-Bourboulis&lt;br&gt;ATTIKON General University Hospital&lt;br&gt;1 Rimini Street&lt;br&gt;Athens, Greece</td>
<td>Site 300-001&lt;br&gt;32 subjects</td>
<td>May 22 – 26, 2017&lt;br&gt;NAI</td>
</tr>
<tr>
<td>Ievgenii Sonnyk&lt;br&gt;Ukrainian Medical Dentistry Academy&lt;br&gt;23 Shevchenko Street&lt;br&gt;Poltava, Ukraine</td>
<td>Site 804-009&lt;br&gt;34 subjects</td>
<td>May 29 – June 2, 2017&lt;br&gt;NAI (3)</td>
</tr>
<tr>
<td>Oleksiy Sagan&lt;br&gt;Communal Institution Zaporizhzhia&lt;br&gt;10 Gorikhivske Lane&lt;br&gt;Zaporizhzhia, Ukraine</td>
<td>Site 804-005&lt;br&gt;46 subjects</td>
<td>June 5 – 9, 2017&lt;br&gt;NAI</td>
</tr>
<tr>
<td>Viktor Stus&lt;br&gt;Municipal Institution Dnipropetrovsk&lt;br&gt;14 Zhovtneva Square&lt;br&gt;Dnipropetrovsk, Ukraine</td>
<td>Site 804-002&lt;br&gt;36 subjects</td>
<td>June 12 – 15, 2017&lt;br&gt;NAI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contract Research Organization (4)</th>
<th>Inspection Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAI (b) (4)</td>
</tr>
</tbody>
</table>

**Compliance Classification of Inspection Outcome**

NAI = No Action Indicated, no significant deviations from regulations  
VAI = Voluntary Action Indicated, minor deviations from regulations  
OAI = Official Action Indicated, major deviations from regulations

(1) CI site selection: (1) largest region (Eastern Europe), (2) large subject enrollment with high site-specific efficacy results, (3) many subject discontinuations (Site 300-001), and (4) few reported AEs (Sites 804-002, 804-005, and 804-009)
The following table shows the OTS rates (at EOIVT) reported in the NDA for the four CI sites selected for GCP inspection, site-specific efficacy results that raised review concerns as “too good to be true” (yet consistent with overall study outcome). A major common goal of the inspections was to rule out GCP non-compliance that may have been unblinding and/or related to biased efficacy assessment, including biased laboratory assessment (microbiologic culture) favoring Carbavance® over PT.

<table>
<thead>
<tr>
<th>CI Site</th>
<th>Carbavance®</th>
<th>piperacillin-tazobactam</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>300-001 (Giamarellos-B)</td>
<td>11/11 (100%)</td>
<td>9/11 (82%)</td>
<td>18</td>
</tr>
<tr>
<td>804-009 (Sonnyk)</td>
<td>9/9 (100%)</td>
<td>9/9 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>804-005 (Sagan)</td>
<td>20/20 (100%)</td>
<td>17/17 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>804-002 (Stus)</td>
<td>12/12 (100%)</td>
<td>9/9 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

(2) CI site inspections: The audit of subject case records included detailed review for 11 - 12 subjects (selected at random and/or guided by audit findings). The major study data (NDA data, Listings 1 - 11) were verified against on-site source records and CRFs: subject screening and selection, randomization, discontinuation, AEs, protocol deviations, primary and secondary efficacy endpoints, and concomitant medication use.

(3) Preliminary outcome assessment: For Site 804-009 (Sonnyk), the establishment inspection report (EIR) has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. An addendum to this clinical inspection summary (CIS) may be forwarded to the review division if new significant findings are discovered at EIR receipt and review; otherwise, OSI’s written correspondence to CI Sonnyk (to be copied to review division) indicates completion of EIR review with confirmation of the findings reported in this CIS.

(4) CRO inspection: Study records were audited with emphasis on CI site monitoring, data management, and recordkeeping for the 3 inspected CI sites. NDA data listings were not (could not be) verified against source records.

1. Evaggelos Giamarellos-Bourboulis

Study REMPEX-505, Site 300-001: 32 subjects were screened, 32 were enrolled, 9 were discontinued (5 lost to follow up, 3 withdrawal of consent, 1 adverse event) and 23 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 11 subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following deficiency observations were verbally discussed: (1) subjects often did not return for the late follow up visit, and documentation of the reasons (or attempt to contact subject) was typically inadequate; and (2) electrocardiograms (ECGs) were often not performed (or performed outside protocol-specified timeframe).

These deficiency observations appeared minor and unlikely to be significant. Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.
2. Ievgenii Sonnyk

Study REMPEX-505, Site 804-009: 34 subjects were screened, 34 were enrolled, and 33 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 12 subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following deficiency observations were verbally discussed:

- Subject 503: (1) was randomized without laboratory results for liver function (eligibility criteria), acceptable test results confirmed after; and (2) received doxycycline within 48 hours before randomization (exclusion criterion).
- Subject 516: One (abnormal) of two results for the same liver function test (aspartate aminotransferase) was not resolved before subject enrollment and randomization.
- Subject 527: One-time use of paracetamol (documented on source records) was apparently not reported and not shown on the concomitant medication data listing.
- Subject 501: The original copy of Day 3 laboratory report was missing (disposition unknown), and an unofficial copy showed laboratory values that require CI evaluation.

These deficiency observations appeared minor and unlikely to be significant. Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

3. Oleksiy Sagan

Study REMPEX-505, Site 804-005: 46 subjects were screened, 46 were enrolled, and 45 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 11 subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

4. Viktor Stus

Study REMPEX-505, Site 804-002: 38 subjects were screened, 36 were enrolled, 36 completed study treatment, and 35 completed the study (all evaluations). Case records were reviewed for all enrolled subjects, including detailed review for 11 subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

5. Study REMPEX-505, CRO: Study records on-site were audited against written center operating procedures for all major areas of study management and oversight (as contracted with the sponsor), including CI site monitoring, data management (collection, compilation, and analyses), and preparation of the clinical study report. CI site monitoring records were reviewed in detail for the four CI sites inspected for this NDA.
No significant deficiencies were observed and a Form FDA 483 was not issued. The CRO’s study oversight and management appeared GCP-compliant overall. The data from the four inspected CI sites appear reliable as reported in the NDA.

{See appended electronic signature page}
John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}
Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
DAIP / Division Director / Sumathi Nambiar
DAIP / Clinical Team Leader / Dmitri Iarikov
DAIP / Medical Officer / Rama Kapoor
DAIP / Regulatory Project Manager / Jane Dean
OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

Reference ID: 4133876
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/s/

JONG HOON LEE
08/02/2017

JANICE K POHLMAN
08/02/2017

KASSA AYALEW
08/02/2017
Memorandum

Date: June 15, 2017

To: Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products (DAIP)

From: Puja Shah, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 209776
TRADENAME® (meropenem and vaborbactam) for injection, for intravenous use

As requested in DAIP's consult dated January 10, 2017, OPDP has reviewed the draft Package Insert (PI) and Carton and Container Labeling (CCL) for TRADENAME® (meropenem and vaborbactam) for injection, for intravenous use. OPDP’s comments are based on the substantially complete version of the labeling titled “NDA 209776 Package Insert draft labeling 3-9-2017.docx” which was accessed via http://sharepoint.fda.gov/ orgs/CDER-OAP-DAIP/Active%20Documents/ NDA%20209776%20Package%20Insert%20draft%20labeling%203-9-17.docx on June 5, 2017.

Package Insert
Our comments on the draft PI are included directly on the attached copy of the labeling.

Carton and Container Labeling
OPDP reviewed the following proposed CCL accessed on June 15, 2017, and does not have any comments at this time:

- Draft US Package Labeling (vial and carton) accessed via cdseub1\evsprod\nda209776\0001\m1\us\114-labeling\draft\carton-and-container\us-package-labeling-vial-and-carton.pdf

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov.
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/s/

----------------------------------------------------
PUJA J SHAH
06/15/2017
**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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<thead>
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<th>May 3, 2017</th>
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<tr>
<td>Application Type and Number:</td>
<td>NDA 209776</td>
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<tr>
<td>Product Name and Strength:</td>
<td>Vabomere (meropenem and vaborbactam) for Injection, 2 g per vial</td>
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<td>Product Type:</td>
<td>Multi-Ingredient Product</td>
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<td>Applicant/Sponsor Name:</td>
<td>Rempex Pharmaceuticals, Inc. (a wholly-owned subsidiary of The Medicines Company)</td>
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<td>Submission Dates:</td>
<td>December 29, 2016, March 9, 2017, and April 4, 2017</td>
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<td>OSE RCM #:</td>
<td>2017-8</td>
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<td>DMEPA Primary Reviewer:</td>
<td>Deborah Myers, RPh, MBA</td>
</tr>
<tr>
<td>DMEPA Team Leader (acting):</td>
<td>Otto L. Townsend, PharmD</td>
</tr>
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1  REASON FOR REVIEW

This review is written in response to a request from the Division of Anti-Infective Products (DAIP) to review the proposed container label, carton labeling, and Prescribing Information submitted by Rempex Pharmaceuticals, Inc. for Vabomere for Injection [NDA 209776] for areas of vulnerability that may lead to medication errors.

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.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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<tr>
<td>Product Information/Prescribing Information</td>
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<td>Previous DMEPA Reviews</td>
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<td>Human Factors Study</td>
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<td>FDA Adverse Event Reporting System (FAERS)*</td>
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<tr>
<td>Labels and Labeling</td>
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N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3  OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling identified areas that can be improved to increase clarity and readability, and include important information to minimize the risk of medication errors and promote the safe use of Vabomere for Injection.

We note that the National Drug Code (NDC) numbers, on both the container label and carton labeling, as well as in Section 16, How Supplied/Storage and Handling of the Full Prescribing Information, are currently denoted by placeholders. We will request that the Applicant submit the revised container label and carton labeling with the updated NDC numbers for this product for our review with the next carton and container revision.

Prescribing Information

We note the use of the abbreviation “g” to indicate the units of measurement, gram or grams, in the renal impairment dosage adjustment tables included in the Highlights of Prescribing Information, Dosage and Administration and Full Prescribing Information, Section 2.2. To
minimize the potential for misinterpretation and provide clarity within these tables, we recommend replacing the abbreviation “g” with the word “gram” or “grams” as appropriate.

We note in the Highlights of Prescribing Information, Dosage Forms and Strengths that the strength and established name are not included. Therefore, to provide clarity we recommend adding this information.

We also note the use of the abbreviation “g” in the Full Prescribing Information, Section 2.1, Recommended Dosage. To minimize the potential for misinterpretation and provide clarity we recommend defining the abbreviation, “g”, by replacing the first abbreviation “g” with the word “grams.”

We note in the Full Prescribing Information, Section 2.2, Dosage Adjustments in Patients with Renal Impairment the use of the abbreviation “(b) [4]” To minimize the potential for misinterpretation and to provide clarity we recommend replacing the abbreviation “(b) [4]” with “or defining the abbreviation “(b) [4]”).

We note Table 2 in the Full Prescribing Information, Section 2.3, Preparation of TRADENAME for Intravenous Infusion does not include the volume (in mL) to withdraw from the reconstituted vial to achieve the dose. We recommend this information be added to provide clarity and decrease the potential of wrong preparation (wrong strength or concentration) medication errors, which could ultimately result in improper dose medication errors. We also note the concentration range of the final infusion solution is expressed as 2 to 8 mg/mL. The unit of measurement should be added after each number so that the lower end of the concentration range is not overlooked.

We note in the Full Prescribing Information, the units of measurement following the first numbers in the temperature range (e.g., degree and Centigrade symbols (°C) following the number 2 and degree and Fahrenheit symbols (°F) following the number 36) are missing and we recommend that they be added for clarity. Additionally, we note lack of a temperature range following diution “(b) [4]” We recommend that the temperature range for room temperature be added to decrease the potential of wrong storage and deteriorated drug medication errors.

We note in the Full Prescribing Information, Section 3, Dosage Forms and Strengths that the strength and established name are not included. Also, the word “sterile” is not included prior to the word “powder.” To provide clarity we recommend adding this information. Additionally in Section 3, to aid in readability and maintain consistency throughout the labeling we recommend changing “1 g of meropenem and 1 g of vaborbactam” to instead read “meropenem 1 gram (equivalent to 1.14 grams meropenem trihydrate) and vaborbactam 1 gram.”

We note in Section 16, How Supplied/Storage and Handling, that:

- The NDC is denoted by a placeholder (65293-XXX-XX). Since the NDC numbers on the submitted container labels and carton labeling are also denoted by a placeholder
(65293-XXX-XX), we have requested that the Applicant submit the final assigned NDC numbers for this product for our review with the next container label and carton labeling revision.

- “The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100)” is not included. According to 21 CFR 201.57(c)(17)(ii), Section 16, How Supplied/Storage and Handling, must include, as appropriate, “the units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100).” We recommend that the Applicant add the appropriate units in which the dosage form will be available.

- There is no information included to facilitate the identification of the dosage form. Therefore we recommend adding a description of identifying characteristics, white to light yellow powder, of the dosage form in accordance with 21 CFR 201.57(c)(17)(iii).

- Within the storage statement the abbreviation for Centigrade, “C”, following 15° and Fahrenheit, “F”, following 59° are missing and we recommend that these be added for clarity.

- There currently is no post-constitution storage and expiration information included in this section. To decrease the potential of wrong storage and deteriorated drug medication errors we recommend adding the post-constitution storage and expiration information to this section.

We note the use of the package type term, “single-dose” in Section 3, Dosage Forms and Strengths as well as in the corresponding Highlights for Prescribing Information, Dosage Forms and Strengths, and in Section 16. We defer to the Office of Pharmaceutical Quality (OPQ) on the appropriate package type term, “single-dose” versus “single-dose” to be used in labeling.

Container Label and Carton Labeling

We note that currently the NDC number is denoted by a placeholder (65293-XXX-XX). We have requested that the Applicant add the intended numbers to the container label and carton labeling and submit for our review.

We note the use of the abbreviation “g” within the asterisk statement (*Meropenem 1g (equivalent to 1.14 g meropenem trihydrate) and vaborbactam 1 g). To minimize the potential for misinterpretation we recommend providing definition and clarification by replacing the first abbreviation “g” with the word “gram” in this statement.

We defer to the Office of Pharmaceutical Quality (OPQ) regarding the appropriate package type term, “single-dose” versus “Single-Dose” for the container label and carton labeling.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling that can be revised to increase clarity, improve readability, and add important information to mitigate medication errors and promote the safe use of Vabomere for Injection. We provide recommendations in Sections 4.1 and 4.2 below and advise they are implemented prior to the approval of this NDA.
4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information, Dosage and Administration
   1. To minimize the potential for misinterpretation, within the Table, consider replacing the abbreviation “g” with the word “gram” or “grams” as appropriate.

B. Highlights of Prescribing Information, Dosage Forms and Strengths
   1. Consider adding the strength (2 grams) and established names (meropenem and vaborbactam) following the proposed proprietary name, Vabomere, so that it reads “Vabomere 2 grams (meropenem and vaborbactam) for injection...”

C. Full Prescribing Information, Section 2.1, Recommended Dosage
   1. To minimize the potential for misinterpretation, consider defining the abbreviation, “g”, by replacing the first abbreviation “g” with the word “grams” so that it reads “...Vabomere is 4 grams (meropenem 2 g and....”

D. Full Prescribing Information, Section 2.2, Dosage Adjustments in Patients with Renal Impairment
   1. To minimize the potential for misinterpretation, consider replacing the abbreviation with “ or define the abbreviation (i.e.,..."
   
   2. To minimize the potential for misinterpretation within Table 1, consider replacing the abbreviation “g” with the word “gram” or “grams” as appropriate.

E. Full Prescribing Information, Section 2.3, Preparation of TRADENAME for Intravenous Infusion
   1. Consider adding, in Table 2, the volume (in mL) to withdraw from the reconstituted vial to achieve each dose.
   
   2. The concentration range of the final infusion solution is expressed as 2 to 8 mg/mL. The unit of measurement should be added after each number so that the lower end of the concentration range is not overlooked.
   
   3. To minimize the potential for misinterpretation of the concentration 0.05 g/mL within the second paragraph, consider replacing the abbreviation “g” with the word “grams” so that the concentration reads, 0.05 grams/mL.

F. Full Prescribing Information, Section...
2. Consider adding the temperature range for “room temperature.”

G. Full Prescribing Information, Section 3, Dosage Forms and Strengths

1. To provide clarity, consider adding the strength, established name, and dosage form, following the proprietary name Carbavance, so that it reads, “Carbavance 2 grams (meropenem and vaborbactam) for injection…”

2. Consider adding the word “sterile” prior to the word “powder” and “for constitution” following the word “powder,” so that it reads “…sterile powder for constitution…”

3. Consider changing “…” to instead read “meropenem 1 gram (equivalent to 1.14 grams meropenem trihydrate) and vaborbactam 1 gram.”

H. Full Prescribing Information, Section 16, How Supplied/Storage and Handling

1. As currently presented, the NDC is denoted by a placeholder (65293-XXX-XX). The Applicant should replace the placeholder with the final assigned NDC numbers for this product for review. Since the NDC numbers on the submitted container labels and carton labeling are also denoted by a placeholder (65293-XXX-XX), we will request that the Applicant submit the final assigned NDC numbers for this product for our review with the next container label and carton labeling revision.

2. According to 21 CFR 201.57(c)(17)(ii), Section 16, How Supplied/Storage and Handling, must include, as appropriate, “the units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100).” We note that this information is not included and recommend that the Applicant add the appropriate units in which the dosage form will be available, prior to the NDC number.

3. Add the appropriate information to facilitate identification of the dosage form such as a description of identifying characteristics (e.g., white to light yellow powder) of the dosage form in accordance with 21 CFR 201.57(c)(17)(iii).


5. Consider adding an infusion solution storage statement. For example, “Complete the infusion of TRADENAME solution within 4 hours of preparation when stored at room temperature (INSERT TEMPERATURE RANGE), or within 22 hours when refrigerated at 2°C to 8°C (36°F to 46°F). (cross reference to section 2)”
4.2 RECOMMENDATIONS FOR REMPEX PHARMACEUTICALS, INC. (A WHOLLEY-OWNED SUBSIDIARY OF THE MEDICINES COMPANY)

Based on your April 4, 2017 container label and carton labeling submission, we recommend the following be implemented prior to approval of this NDA:

Container Label and Carton Labeling

1. As currently presented, the National Drug Code (NDC) number is denoted by a placeholder (65293-XXX-XX). Add the intended numbers to the container label, carton labeling and Full Prescribing Information, Section 16, How Supplied/Storage and Handling and submit for our review.

2. Define the abbreviation, g, and minimize the potential for misinterpretation, replace the first abbreviation “g” in the equivalency statement with the word “gram” so that the text reads, “*Meropenem 1 gram (equivalent to 1.14 g meropenem trihydrate) and vaborbactam 1 g”.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4092972
APPENDICIES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vabomere that Rempex Pharmaceuticals, Inc. submitted on March 9, 2017.

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<th>Table 2. Relevant Product Information for Vabomere</th>
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<td><strong>How Supplied</strong></td>
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<td><strong>Storage</strong></td>
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APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 26, 2017, we searched the L:drive and AIMS using the terms, Carbavance and vaborbactam to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews\(^a\),\(^b\), and we confirmed that out previous recommendations were implemented or considered.

\(^a\) Myers, D. Proprietary Name Review for (meropenem and vaborbactam) . Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 15. RCM No.: 2016-8229634.

\(^b\) Myers, D. Proprietary Name Review for Carbavance (meropenem and vaborbactam) NDA 209776. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 17. RCM No.: 2016-12221824.
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/s/

DEBORAH E MYERS
05/03/2017

OTTO L TOWNSEND
05/03/2017
### Application Information

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Proprietary Name:
Established/Proper Name: meropenem – vaborbactam
Dosage Form: powder
Strengths: 1000 mg/1000 mg per vial
Route(s) of Administration: intravenous

Applicant: Rempex Pharmaceuticals, a wholly owned subsidiary of the Medicines Company
Agent for Applicant (if applicable):

Date of Application: December 29, 2016
Date of Receipt: December 29, 2016
Date clock started after Unacceptable for Filing (UN): N/A

PDUFA/BsUFA Goal Date: August 29, 2017
Action Goal Date (if different):

Filing Date: February 27, 2017
Date of Filing Meeting: January 24, 2017

Chemical Classification (original NDAs only):
- [ ] Type 1 - New Molecular Entity (NME); NME and New Combination
- [x] Type 2 - New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
- [ ] Type 3 - New Dosage Form; New Dosage Form and New Combination
- [ ] Type 4 - New Combination
- [ ] Type 5 - New Formulation or New Manufacturer
- [ ] Type 7 - Drug Already Marketed without Approved NDA
- [ ] Type 8 - Partial Rx to OTC Switch
- [ ] Type 9 - New Indication or Claim (will not be marketed as a separate NDA after approval)
- [ ] Type 10 - New Indication or Claim (will be marketed as a separate NDA after approval)

Proposed indication(s)/Proposed change(s): Treatment of complicated urinary tract infections (cUTI) including pyelonephritis in patients 18 years or older caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae species complex*.

Type of Original NDA: [x] 505(b)(1)
Type of NDA Supplement:
- [ ] 505(b)(2)
- [ ] 505(b)(1)
- [ ] 505(b)(2)

*If 505(b)(2)NDA/NDAs Supplement: Draft the “505(b)(2) Assessment” review found at: [http://inside.fda.gov/~/~/file/CDER/OfficeofNewDrugs/ImmediateOffice/UCM097499](http://inside.fda.gov/~/~/file/CDER/OfficeofNewDrugs/ImmediateOffice/UCM097499).*

Type of BLA:
- [ ] 351(a)
- [x] 351(k)

*If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team*

Reference ID: 4059845
Review Classification:

The application will be a priority review if:

- A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)
- The product is a Qualified Infectious Disease Product (QIDP)
- A Tropical Disease Priority Review Voucher was submitted
- A Pediatric Rare Disease Priority Review Voucher was submitted

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<tr>
<td>Tropical Disease Priority Review Voucher</td>
<td>Pediatric Rare Disease Priority Review Voucher</td>
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Resubmission after withdrawal? [ ] Resubmission after refuse to file? [ ]

Part 3 Combination Product? [ ]

If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

Fast Track Designation [ ] Breakthrough Therapy Designation [ ]

(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)

- Rolling Review
- Orphan Designation

- Rx-to-OTC switch, Full
- Rx-to-OTC switch, Partial
- Direct-to-OTC

Other:

Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): IND 120040

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If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.

Are the established/proper and applicant names correct in electronic archive?

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 electronic archive.

Reference ID: 4059845
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: [http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm](http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm)

If no, ask the document room staff to make the appropriate entries.

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<td>☐ Not required</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>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. Contact the User Fee Staff. If appropriate, send UN letter.</th>
<th>Payment of other user fees:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Not in arrears</td>
<td>☒ Yes</td>
</tr>
<tr>
<td>☐ In arrears</td>
<td>☐ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>User Fee Bundling Policy</th>
<th>Has the user fee bundling policy been appropriately applied? If no, or you are not sure, consult the User Fee Staff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒ Yes</td>
<td>☐ No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>505(b)(2) (NDAs/NDA Efficacy Supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application a 505(b)(2) NDA? [Check the 356h form, cover letter, and annotated labeling]. If yes, answer the bulleted questions below:</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- 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)]. □ ☒

- 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)]? □ ☒

If you answered yes to any of the above bulleted 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 for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? □ ☒

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<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>
</tbody>
</table>

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? □ ☒

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency.
and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

<table>
<thead>
<tr>
<th>Exclusivity</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</td>
<td>☒</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, # years requested: 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, 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)?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> 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 (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Format and Content

**Do not check mixed submission if the only electronic component is the content of labeling (COL).**

<table>
<thead>
<tr>
<th></th>
<th>All paper (except for COL)</th>
<th>All electronic</th>
<th>Mixed (paper/electronic)</th>
<th>CTD</th>
<th>Non-CTD</th>
<th>Mixed (CTD/non-CTD)</th>
</tr>
</thead>
</table>

**If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?**

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

**If electronic submission, does it follow the eCTD guidance?**

If **not**, explain (e.g., waiver granted).

<table>
<thead>
<tr>
<th>Index: Does the submission contain an accurate comprehensive index?</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

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:

- legible
- English (or translated into English)
- pagination
- navigable hyperlinks (electronic submissions only)

If **no**, explain.

<table>
<thead>
<tr>
<th>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
</tr>
</tbody>
</table>

**Forms and Certifications**

*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 (3397/3792), 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.

<table>
<thead>
<tr>
<th>Application Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?

**If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].**

Are all establishments and their registration numbers listed on the form/attached to the form?

---


Reference ID: 4059845

Version: 12/05/2016
### Patent Information (NDAs/NDA efficacy supplements only)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td>✗</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

### Financial Disclosure

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
<td>✗</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*

**Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.

### Clinical Trials Database

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td>✗</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”*

*If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant*

### Debarment Certification

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td>✗</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Certification is not required for supplements if submitted in the original application. If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*

**Note:** Debarment Certification should use wording in FD&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...”

### Field Copy Certification (NDAs/NDA efficacy supplements only)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td>☐</td>
<td>☐</td>
<td>✗</td>
<td></td>
</tr>
</tbody>
</table>

*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)*

*If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*
<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For NMEs:</strong> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, date consult sent to the Controlled Substance Staff:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>For non-NMEs:</strong> Date of consult sent to Controlled Substance Staff:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the application trigger PREA?</td>
<td>☑</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</strong></td>
<td>☑</td>
<td>☐</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td><strong>If no, may be an RTF issue - contact DPMH for advice.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</strong></td>
<td>☑</td>
<td>☐</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td><strong>If no, may be an RTF issue - contact DPMH for advice.</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| BPCA: | | | | |
|-------| | | | |
| Is this submission a complete response to a pediatric Written Request? | ☐ | ☐ | | |
| **If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)** | | | | |

---

2 [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm)

3 [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm)

Reference ID: 4059845
<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a proposed proprietary name submitted?</td>
<td>✗</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

_If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”_

<table>
<thead>
<tr>
<th>REMS</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a REMS submitted?</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

_If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox_

<table>
<thead>
<tr>
<th>Prescription Labeling</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check all types of labeling submitted.</td>
<td>Package Insert (Prescribing Information)(PI)</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient Package Insert (PPI)</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Instructions for Use (IFU)</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication Guide (MedGuide)</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carton labeling</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate container labels</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diluent labeling</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (specify)</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Electronic Content of Labeling (COL) submitted in SPL format?</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

_If no, request applicant to submit SPL before the filing date._

| Is the PI submitted in Physician Labeling Rule (PLR) format? | ☑ | ☐ |         |

_If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?_

_If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date._

| For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? | ☑ | ☐ | ☐ |         |
| Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included? | ☐ | ☐ | ☑ |         |

| For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? | ☐ | ☐ | ☑ |         |

_If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date._


Reference ID: 4059845
### Has all labeling ([PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling]) been consulted to OPDP?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? *(send WORD version if available)*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### OTC Labeling

- [ ] Outer carton label
- [ ] Immediate container label
- [ ] Blister card
- [ ] Blister backing label
- [ ] Consumer Information Leaflet (CIL)
- [ ] Physician sample
- [ ] Consumer sample
- [ ] Other (specify)

### Is electronic content of labeling (COL) submitted?

**If no, request in 74-day letter.**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### Are annotated specifications submitted for all stock keeping units (SKUs)?

**If no, request in 74-day letter.**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### If representative labeling is submitted, are all represented SKUs defined?

**If no, request in 74-day letter.**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### All labeling/packaging sent to OSE/DMEPA?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

### Other Consults

- [ ] Are additional consuls needed? *(e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)*

**If yes, specify consult(s) and date(s) sent:**

### Meeting Minutes/SPAs

- [ ] End-of Phase 2 meeting(s)?
  **Date(s):**

- [ ] Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?
  **Date(s):** November 3, 2016

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
</tr>
</thead>
</table>

---

**ATTACHMENT**

Version: 12/05/2016

Reference ID: 4059845
MEMO OF FILING MEETING

DATE: January 24, 2017

BACKGROUND: The Applicant submitted a new drug application (NDA) for the treatment of complicated urinary tract infections, including pyelonephritis, in adult patients. The product is a fixed combination product of the antibiotic meropenem and the beta lactamase inhibitor vaborbactam. It is designed to address emerging resistance in gram-negative bacteria, particularly that due to KPC-producing carbapenem-resistant Enterobacteriaceae (CRE).

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Dean</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: DeBellas</td>
<td>Y</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Dmitri Iarikov, MD, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Division Director/Deputy</td>
<td>Sumathi Nambiar, MD, MPH</td>
<td>Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>Edward Cox, MD, MPH John Farley, MD, MPH</td>
<td>N</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Rama Kapoor, MD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Dmitri Iarikov, MD, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Social Scientist Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
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</tr>
<tr>
<td>OTC Labeling Review (for OTC products)</td>
<td>Reviewer:</td>
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<td></td>
<td>TL:</td>
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<tr>
<td>Clinical Microbiology (for antimicrobial products)</td>
<td>Reviewer: Kerian Grande Roche, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Tamara Feldblyum, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Zhixia (Grace) Yan, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Seong Jang, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Genomics</td>
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<td>Pharmacometrics</td>
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<tr>
<td>Biostatistics</td>
<td>Daniel Rubin, PhD</td>
<td>Y</td>
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<td></td>
<td>Karen Higgins, ScD</td>
<td>Y</td>
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<tr>
<td>Nonclinical Pharmacology/Toxicology</td>
<td>James Wild, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Terry Miller, PhD</td>
<td>Y</td>
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<tr>
<td>Statistics (carcinogenicity)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Product Quality (CMC) Review Team</td>
<td>ATL: Dorota Matecka, PhD</td>
<td>Y</td>
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<tr>
<td></td>
<td>RBPM: LCDR Luz Rivera, PsyD</td>
<td>N</td>
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<tr>
<td>Drug Substance</td>
<td>Gene Holbert, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Drug Product</td>
<td>George Lunn, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Process</td>
<td>Christine Falabella, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Denise Miller, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Facility</td>
<td>Daniel DeCiero, PhD</td>
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<tr>
<td>Biopharmaceutics</td>
<td>Qi Zhang, PhD</td>
<td>Y</td>
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<tr>
<td>Immunogenicity</td>
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<td>Labeling (BLAs only)</td>
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<tr>
<td>Other (e.g., Branch Chiefs, EA Reviewer)</td>
<td>OPQ Labeling Review will be done by George Lunn</td>
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<tr>
<td>OMP/OMPI/DMPP (MedGuide, PPI, IFU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)</td>
<td>Puja Shah</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Olga Salis</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name, carton/container labeling)</td>
<td>Deborah Myers</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Vicky Borders-Hempshill</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td>Till Olickal</td>
<td>Y</td>
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<tr>
<td></td>
<td>Naomi Redd</td>
<td>N</td>
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<td>OC/OSI/DSC/PMSB (REMS)</td>
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<td>Department/Division</td>
<td>Reviewer</td>
<td>TL</td>
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<td>------------------------------------------</td>
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</tr>
<tr>
<td>Bioresearch Monitoring (OSI)</td>
<td>John Lee, MD</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Janice Pohlman, MD</td>
<td>Y</td>
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<tr>
<td>Controlled Substance Staff (CSS)</td>
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<tr>
<td>Other reviewers/disciplines</td>
<td></td>
<td></td>
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<tr>
<td>DEPI</td>
<td>Adebola Ajao</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Natasha Pratt</td>
<td>N</td>
</tr>
<tr>
<td>DPV</td>
<td>Ron Wassel</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Kelly Cao</td>
<td>N</td>
</tr>
<tr>
<td>Associate Director of Labeling</td>
<td>Abimbola Adebowale, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Deputy Director for Safety</td>
<td>Joseph Toerner, MD, MPH</td>
<td>Y</td>
</tr>
<tr>
<td>Pharmacology/Toxicology Reviewer (DAIP)</td>
<td>Madissa Macon, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Division Director, Biometrics IV</td>
<td>Dionne Price, PhD</td>
<td>Y</td>
</tr>
<tr>
<td>Regulatory Health Project Manager (DAIP)</td>
<td>Deepak Aggarwal, MS, MSPH</td>
<td>Y</td>
</tr>
</tbody>
</table>

**FILING MEETING DISCUSSION:**

**GENERAL**
- 505(b)(2) filing issues:
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?

  Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):

  - The Applicant provided the bridging information including the PK studies, the formulation development and physiochemical characteristics of the proposed product and the listed product in 2.7.1 and 3.2.P.2.2.

- Per reviewers, are all parts in English or English translation?
  - If no, explain:

  | □ Not Applicable | YES ☒ NO |
  | YES ☒ NO        | NO       |

Version: 12/05/2016

Reference ID: 4059845
<table>
<thead>
<tr>
<th>Comments:</th>
<th>Yes/No Options</th>
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<tbody>
<tr>
<td>Electronic Submission comments</td>
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<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td>☑ REVIEW ISSUES FOR 74-DAY LETTER</td>
</tr>
<tr>
<td>Clinical study site(s) inspections(s) needed?</td>
<td>☑ YES &lt;br&gt;□ NO</td>
</tr>
<tr>
<td>If no, explain:</td>
<td></td>
</tr>
<tr>
<td>□ YES &lt;br&gt;Date if known: &lt;br&gt;☑ NO &lt;br&gt;☑ To be determined</td>
<td>☑ REASON: The clinical study design is acceptable.</td>
</tr>
<tr>
<td>□ 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?</td>
<td>☑ Not Applicable &lt;br&gt;☑ YES &lt;br&gt;□ NO</td>
</tr>
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<td><strong>CONTROLLED SUBSTANCE STAFF</strong></td>
<td></td>
</tr>
<tr>
<td>Abuse Liability/Potential</td>
<td>☑ Not Applicable &lt;br&gt;☑ FILE &lt;br&gt;☑ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
<td></td>
</tr>
<tr>
<td><strong>CLINICAL MICROBIOLOGY</strong></td>
<td>☑ Not Applicable &lt;br&gt;☑ FILE &lt;br&gt;☑ REFUSE TO FILE</td>
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<tr>
<td>□ Review issues for 74-day letter</td>
<td></td>
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<tr>
<td><strong>CLINICAL PHARMACOLOGY</strong></td>
<td>☑ Not Applicable &lt;br&gt;☑ FILE &lt;br&gt;☑ REFUSE TO FILE</td>
</tr>
<tr>
<td>Comments:</td>
<td>☐ Review issues for 74-day letter</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| • Clinical pharmacology study site(s) inspections(s) needed? | ☑ YES  
☑ NO |

| BIOSTATISTICS | ☐ Not Applicable  
☑ FILE  
☐ REFUSE TO FILE |
| Comments: | ☐ Review issues for 74-day letter |

| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) | ☐ Not Applicable  
☑ FILE  
☐ REFUSE TO FILE |
| Comments: | ☐ Review issues for 74-day letter |

| PRODUCT QUALITY (CMC) | ☐ Not Applicable  
☑ FILE  
☐ REFUSE TO FILE |
| Comments: | ☐ Review issues for 74-day letter |

| New Molecular Entity (NDAs only) | ☑ YES  
☑ NO |
| Comments: | ☐ Review issues for 74-day letter |

| Environmental Assessment | ☑ YES  
☑ NO |
| Comments: | ☐ Review issues for 74-day letter |

| Facility Inspection | ☐ Not Applicable  
☑ YES  
☑ NO |
| Comments: The [b][4] micronem site [b][4] described in the QOS but is not mentioned in the 356h form. There is not a statement either saying that this plant is ready for inspection. It is also believed that other facilities that are not mentioned in the 356h form are used to manufacture [b][4]. These concerns have been communicated to the applicant. | ☐ Review issues for 74-day letter |
| **Facility/Microbiology Review (BLAs only)** | ☒ Not Applicable  
☐ FILE  
☐ REFUSE TO FILE  
☐ Review issues for 74-day letter |
| Comments: | |
| **CMC Labeling Review (BLAs only)** | ☐ Review issues for 74-day letter |
| Comments: | |
| **APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)** | ☐ N/A |
| - 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? | ☐ YES  
☒ NO; however, it was agreed that stability data could be submitted four months after NDA receipt |
| - If so, were the late submission components all submitted within 30 days? | ☐ YES  
☐ NO |
| - What late submission components, if any, arrived after 30 days? | |
| - Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | ☒ YES  
☐ NO |
| - Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | ☒ YES  
☐ NO |
| - Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | ☒ NO  
☒ The meropenem site is described in the QOS but is not mentioned in the 356h form. There is not a statement either saying that this plant is ready for inspection. It is also believed that |
REGULATORY PROJECT MANAGEMENT

Signatory Authority: Edward Cox, MD, MPH, Director, Office of Antimicrobial Products

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):
March 31, 2017

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☒ No review issues have been identified for the 74-day letter.
☐ Review issues have been identified for the 74-day letter.

Review Classification:

☐ Standard Review
☒ Priority Review

ACTION ITEMS

☒ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).

☐ If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐ 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.

☒ If priority review, notify applicant in writing by day 60 (see CST for choices)

☒ Send review issues/no review issues by day 74

☒ Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☒ Update the PDUFA V DARRTS page (for applications in the Program)
Other

Annual review of template by OND ADRAs completed: April 2016
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE A DEAN
02/22/2017

Reference ID: 4059845
1. Regulatory History and Applicant’s Main Proposals

The Applicant submitted a new drug application (NDA) for the treatment of complicated urinary tract infections, including pyelonephritis, in adult patients. The product is a fixed combination product of the antibiotic meropenem and the beta lactamase inhibitor vaborbactam. It is designed to address emerging resistance and gram-negative bacteria particularly that due to KPC-producing carbapenem-resistant Enterobacteriaceae (CRE).

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 of Prescribing Information (SRPI)” checklist (see Section 4 of this review).

3. Conclusions/Recommendations

One SRPI format deficiency was identified in the review of this PI. See Item 2 in Section 4 of this review.

The SRPI format deficiency of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct the deficiency and resubmit the PI in Word format by March 31, 2017. The resubmitted PI will be used for further labeling review.
4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

#### 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:**

**NO** 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:** Highlights section is slightly longer than one half page.

**YES** 3. A horizontal line must separate:
   - HL from the Table of Contents (TOC), **and**
   - TOC from the Full Prescribing Information (FPI).

**Comment:**

**YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**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 for HL format.

**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. Headings in HL must be presented in the following order:

<table>
<thead>
<tr>
<th>Heading</th>
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</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
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</table>
### Selected Requirements of Prescribing Information

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

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**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

**YES** 11. Initial U.S. Approval 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 title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. Even if there is more than one warning, the term “WARNING” and not “WARNINGS” should be used. For example: “WARNING: SERIOUS
Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement must be placed immediately beneath the BW title, and should be centered 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 title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015.”

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:
Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

*Comment:*

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** 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

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 8/2015”).

*Comment:*
Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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 26. The same title 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 27. In the TOC, all section headings must be bolded and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: The subsection heading 5.5 has an extra space before the Development of Drug-Resistant Bacteria

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “FULL PRESCRIBING INFORMATION: CONTENTS*” must be followed by an asterisk and the following statement must appear at the end of the 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 31. 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.

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “Labor and Delivery”)</td>
</tr>
<tr>
<td>8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “Nursing Mothers”)</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSAGE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

Comment:

YES 32. 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)*].”

Comment:

N/A
Selected Requirements of Prescribing Information

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

  Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading “FULL PRESCRIBING INFORMATION” must be bolded, must appear at the beginning of the FPI, and should be in UPPER CASE.

  Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be bolded.

  Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “WARNING” and not “WARNINGS” should be used.) For example: “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

  Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state “None.”

  Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

  “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 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), 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

40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use
PROPRIETARY NAME safely and effectively. See full prescribing
information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route
of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.
- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE
PROPRIETARY NAME is a (insert FDA established pharmacologic
class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSEAGE AND ADMINISTRATION
- Text (2.x)
- Text (2.x)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSEAGE AND ADMINISTRATION
  2.1 Subsection Title
  2.2 Subsection Title
3 DOSEAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Subsection Title
  5.2 Subsection Title
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Immunogenicity
  6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
  7.1 Subsection Title
  7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation (If not required to be in PLLR format use Labor and
  Delivery)
  8.3 Females and Males of Reproductive Potential (If not required
  to be in PLLR format use Nursing Mothers)
  8.4 Pediatric Use
  8.5 Geriatric Use
  8.6 Subpopulation X

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 Subsection Title
  14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing
information are not listed.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE A DEAN
01/17/2017

Reference ID: 4042704
Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 209776

Name of Drug: meropenem-vaborbactam

Applicant: Rempex Pharmaceuticals Inc.

Labeling Reviewed

Submission Date: December 29, 2016

Receipt Date: December 29, 2016

Background and Summary Description:

The Applicant submitted a new drug application (NDA) for the treatment of complicated urinary tract infections, including pyelonephritis, in adult patients. The product is a fixed combination product of the antibiotic meropenem and the beta lactamase inhibitor vaborbactam. It is designed to address emerging resistance and gram-negative bacteria particularly that due to KPC-producing carbapenem-resistant Enterobacteriaceae (CRE).

Review

This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI is in Physician’s Labeling Rule (PLR) format and it highlights the proposed changes.

Recommendations

The SRPI format deficiency of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct the deficiency and resubmit the PI in Word format by March 31, 2017. The resubmitted PI will be used for further labeling review.

Jane A. Dean, RN, MSN  January 17, 2017
Regulatory Project Manager  Date

Carmen DeBellas, RPh  January 17, 2017
Chief, Project Management Staff  Date
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE A DEAN
01/17/2017