DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209776

NDA APPROVAL

Rempex Pharmaceuticals, Inc.
a wholly owned subsidiary of The Medicines Company
Attention: Starr Shangle
Senior Director, Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for VABOMERE (meropenem and vaborbactam) powder for injection, 1g/1g per vial.

This new drug application provides for the use of VABOMERE powder for injection, for treatment of patients 18 years of age and older with complicated Urinary Tract Infections (cUTI), including pyelonephritis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your August 23, 2017, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for VABOMERE was not referred to an FDA advisory committee because outside expertise was not necessary and there were no issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are deferring submission of your pediatric studies until March 2020, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. The required studies are listed below.

> 3248-1: Conduct an open-label, sequential study to assess the pharmacokinetics (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.

The timetable you submitted on August 22, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Submitted November 2, 2015
Study/Trial Completion:	09/2019
Final Report Submission:	03/2020

> 3248-2: Conduct a 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 (cUTI) including acute pyelonephritis.

The timetable you submitted on August 22, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2018
Final Protocol Submission:	09/2018
Study/Trial Completion:	09/2021
Final Report Submission:	03/2022

3248-3: Conduct an 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.

The timetable you submitted on August 22, 2017, states that you will conduct this study according to the following schedule:

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

Submit the protocol(s) to your IND 120040, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as supplements to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submissions "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the serious risk of development of resistance to VABOMERE in organisms specific to the cUTI indication in the label and to evaluate whether VABOMERE has a threshold pharmacologic effect on cardiac repolarization. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

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.

The timetable you submitted on August 22, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2017
Interim Study Report:	06/2018
Interim Study Report:	06/2019
Interim Study Report:	06/2020
Interim Study Report:	06/2021
Interim Study Report:	06/2022
Study/Trial Completion:	03/2023
Final Report Submission:	06/2023

3248-5: Conduct a "Thorough QT/QTc Study" to evaluate whether VABOMERE has a threshold pharmacologic effect on cardiac repolarization.

The timetable you submitted on August 22, 2017, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/2017
Final protocol submission:	01/2018
Study completion:	08/2018
Final report submission:	01/2019

Submit clinical protocols to your IND 120040 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submissions, as appropriate: "**Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to

investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENT NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

> 3248-6: 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.

The timetable you submitted on August 4, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 1, 2017
Interim Report:	September 9, 2018
Study Completion:	February 1, 2019
Final Report Submission:	April 1, 2019

Submit clinical protocols to your IND 120040 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

EDWARD M COX
08/29/2017