



NDA 212819

**NDA APPROVAL**

Merck Sharp & Dohme Corp.  
a subsidiary of Merck & Co, Inc.  
Attention: Donna Zacholski  
Director, Global Regulatory Affairs  
351 North Sumneytown Pike  
P.O. Box 1000, UG2D-68  
North Wales, PA 19454-2505

Dear Ms. Zacholski:

Please refer to your new drug application (NDA) dated November 16, 2018, received November 16, 2018, and your amendments submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RECARBRIO (imipenem, cilastatin, and relebactam) for injection, for intravenous use.

This new drug application provides for the use of RECARBRIO, for injection in patients 18 years of age and older who have limited or no alternative treatment options for the treatment of the following infections caused by certain susceptible gram-negative bacteria:

- Complicated Urinary Tract Infections (cUTI), including pyelonephritis
- Complicated Intra-abdominal Infections (cIAI)

### **APPROVAL & LABELING**

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.

### **WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

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

FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. 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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 212819**”. Approval of this submission by FDA is not required before the labeling is used.

### **MARKET PACKAGE**

Please submit one market package of the drug product when it is available to the following address:

Christopher Smith  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 6230  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
*Use zip code **20903** if shipping via United States Postal Service (USPS).*  
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

### **ADVISORY COMMITTEE**

Your application for RECARBIO was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial 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 (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies in children for ages birth to less than 18 years of age for this application 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 Federal Food, Drug, and Cosmetic Act (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)(4)(C) of the FDCA. These required studies are listed below.

- 3641-1 Conduct an open label, single-dose study to evaluate the pharmacokinetics, safety and tolerability of imipenem, cilastatin and relebactam in children from birth to less than 18 years of age with proven or suspected Gram-negative infections.

The timetable you submitted on July 12, 2019 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Submitted
Study/Trial Completion:	05/2021
Final Report Submission:	04/2022

- 3641-2 Conduct a randomized, open-label, active controlled trial to evaluate the safety and tolerability of imipenem, cilastatin and relebactam in children from birth to less than 18 years of age with complicated urinary tract infections and complicated intra-abdominal infections.

The timetable you submitted on July 12, 2019 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	Submitted
Final Protocol Submission:	09/2019
Study/Trial Completion:	02/2024
Final Report Submission:	08/2024

Submit the protocol(s) to your IND 108754, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement 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 submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o) of the FDCA authorizes FDA to require holders of approved drugs 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 analysis of spontaneous postmarketing adverse event reports under subsection 505(k)(1) of the FDCA will not be sufficient to identify the serious risk of the development of resistance to RECARBRIO (imipenem, cilastatin and relebactam) in microorganisms specific to the cUTI and cIAI indications in the label.

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 this serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

- 3641-3 Conduct a United States surveillance study for 5 years from the date of marketing to determine if resistance to imipenem, cilastatin and relebactam had developed in those organisms specific to the indication in the label.

The timetable you submitted on July 12, 2019 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2019
First Interim Report Submission:	08/2020
Second Interim Report Submission:	08/2021
Third Interim Report Submission:	08/2022
Fourth Interim Report Submission:	08/2023
Fifth Interim Report Submission:	08/2024

Study Completion:	12/2024
Final Report Submission:	12/2024

Submit the protocol to your IND 108754, with a cross-reference letter to this NDA. Submit the final report to your NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of each submission, 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.

### **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 Prescribing Information, Medication Guide, and Patient Package Insert (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 *Providing Regulatory Submissions in Electronic and*

*Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*<sup>3</sup>

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup> For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.<sup>6</sup>

### **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 FDA.gov.<sup>7</sup>

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biological products 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.

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<sup>3</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>6</sup> <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

<sup>7</sup> <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

If you have any questions, call Christopher L. Smith, PharmD, MPH, Regulatory Project Manager at (301) 796-4851.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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EDWARD M COX  
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