NDA 216974

CORRECTED NDA APPROVAL

Entasis Therapeutics, Inc.
Attention: Shruta Rege, PhD
Vice President, Head of Global Regulatory Affairs
35 Gatehouse Drive
Waltham, MA 02451

Dear Dr. Rege,

Please refer to your new drug application (NDA) dated September 29, 2022, received, September 29, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xacduro (sulbactam for injection; durlobactam for injection), co-packaged for intravenous use.

We also refer to the approval letter dated May 23, 2023, which contained the following error: the temperature excursions permitted text listed in the **DATING PERIOD** section below required revisions.

This corrected action letter incorporates the correction of the error. The effective action date will remain May 23, 2023, the date of the original letter.

This NDA provides for the use of Xacduro in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus* complex.

APPROVAL & LABELING

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

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use) as well as annual reportable changes

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission **"Final Printed Carton and Container Labeling for approved NDA 216974"**. Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Xacduro (sulbactam for injection; durlobactam for injection), co-packaged for intravenous use, shall be 24 months from the date of manufacture when stored refrigerated at 2°C to 8°C (36°F to 46°F); brief exposure to 8°C to 15°C (46°F to 59°F) permitted [see USP Controlled Cold Temperature]".

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 study until November 2028, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a required postmarketing study. The status of this postmarketing study(ies) must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA.
This required study is listed below:

[2] 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.

4452-1: Conduct a multi-dose study to assess the pharmacokinetics, safety and tolerability of sulbactam-durlobactam in children from birth to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed infection.

Final protocol submission:	12/2023
Study completion:	05/2028
Final report submission:	11/2028

FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

Submit the protocol(s) to your IND 131330, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study 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 this study. 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)(3) of the Federal Food, Drug, and Cosmetic Act (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 assess the serious risk of hypersensitivity reactions (including anaphylaxis), the mutagenic potential of impurity (b) (4), and the levels of unspecified impurities in drug substance and drug product for durlobactam. We have also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of changes in susceptibility of *Acinetobacter baumannii-calcoaceticus* to sulbactam-durlobactam. Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risk(s).

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

4452-2: Conduct a single-arm, open-label, prospective, observational study to assess the safety of sulbactam-durlobactam, including the risk of hypersensitivity reactions (including anaphylaxis) in patients with *Acinetobacter baumannii-calcoaceticus* complex infection.

The timetable you submitted on May 18, 2023, states that you will conduct this trial according to the following schedule:

Final protocol submission:	02/2024
Study completion:	02/2029
Final report submission:	08/2029

4452-3: Conduct a mouse lymphoma TK assay (MLA) or hypoxanthine phosphorylbosyl transferase (HPRT) forward mutation assay to assess the mutagenic potential of impurity (b) (4).

The timetable you submitted on May 10, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2023
Study Completion:	02/2024
Final Report Submission:	05/2024

4452-4: Conduct a US surveillance study for a five-year period after the introduction of sulbactam-durlobactam to the market to monitor changes in susceptibility of *Acinetobacter baumannii-calcoaceticus* complex organisms to sulbactam-durlobactam.

The timetable you submitted on May 10, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2023
Interim Report:	11/2024
Interim Report:	11/2025
Interim Report:	11/2026
Interim Report:	11/2027
Interim Report:	11/2028
Study Completion:	11/2028
Final Report Submission:	02/2029

4452-5: Conduct studies for durlobactam drug substance and drug product, as identified in the final protocol, to further characterize the safety of their impurity profiles and establish drug substance and drug product impurity controls to ensure that each impurity limit is in accordance with ICH Q3A, Q3B, and M7, as applicable.

The timetable you submitted on May 10, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2023
Final Protocol Submission:	03/2024

Interim Report Submission # 1: 06/2024
(*Long term and accelerated stability through 6 months, and in-use stability data using the methods in the NDA*)

Interim Report Submission # 2: 07/2024
(Completion of impurity isolation and characterization studies)

Interim Report Submission # 3: 11/2024
(*HPLC impurities method optimization/re-validation study data*)

Interim Report Submission # 4: 12/2024
(*Long term stability through 12 months and in-use stability data using the methods in the NDA*)

Interim Report Submission # 5: 03/2025
(*Identification and qualification study data, if needed*)

Interim Report Submission # 6: 06/2025
(*Comparability long term and additional in-use stability data based on a revised regulatory HPLC method and a revised IV-bag method [if needed])*

Study completion: 09/2025
Final Report Submission: 12/2025

In the draft and final protocol, these studies should include release and stability testing of three consecutively manufactured drug substance and drug product process validation batches using optimized fully validated methods and identification and qualification studies for impurities found and controlled above applicable ICH identification and qualification thresholds. The final study reports and data generated through the PMR study should be submitted to your NDA in a prior approval supplement.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 131330 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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(a)(1) 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(a)(1) 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 COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4452-6: Complete the repeat dose toxicity study in neonatal 10-day old rats to support the planned clinical trial in children from birth to less than 1 year of age.

The timetable you submitted on May 18, 2023, states that you will conduct this study according to the following schedule:

Study Completion:	09/2023
Final Report Submission:	12/2023

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

We remind you of your postmarketing commitment:

4452-7: Conduct studies to update the manufacturing process for each of the drug product components (i.e., durlobactam for injection and sulbactam for injection) to demonstrate that the labeled vial content can be withdrawn at the lower end of the fill weight variation range following reconstitution, and as appropriate to establish suitable in-process and finished drug product controls/specifications.

The timetable you submitted on May 18, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2023
Final Protocol Submission:	03/2024
Interim Report Submission:	12/2024
Final Report Submission:	04/2025

The interim report submission should include results of studies to update manufacturing processes, available release/stability data, any interim in-process controls and finished product specification, etc. The final report submission should include data generated under this PMC (including 3-month long-term drug product stability data) and should be submitted to your NDA as a prior approval supplement. The final report submission should be identified as "Final Report Submission for PMC 4452-7" in addition to being identified as a "Prior Approval Supplement."

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 131330 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/subjects 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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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 J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

- Prescribing Information
- Healthcare Provider Instructions for Use
- Carton and Container Labeling

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.

/s/

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