NDA 218275

NDA APPROVAL

Basilea Pharmaceutica International, Ltd., Allschwil
c/o Kleinfeld, Kaplan and Becker
Attention: Daniel Dwyer, US Agent
1850 M Street, N.W.
Washington, DC 20036

Dear Daniel Dwyer:

Please refer to your new drug application (NDA) dated and received August 3, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zevtera (ceftobiprole medocaril sodium for injection), 667 mg/vial.

This NDA provides for the use of Zevtera for treatment of the following:

- Adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia) (SAB) including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates

- Adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, and *Klebsiella pneumoniae*

- Adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible isolates), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae, Escherichia coli*, and *Klebsiella pneumoniae*

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of the 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.[1] 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.*[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 submitted on March 27, 2024, 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 218275**." 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 Zevtera (ceftobiprole medocaril sodium for injection) shall be 48 months from the date of manufacture when stored refrigerated at 2°C to 8°C (36°F to 46°F) protected from light.

ADVISORY COMMITTEE

Your application for Zevtera 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.

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

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 waiving the pediatric study requirement for ages birth to less than 3 months for the CABP indication because necessary studies are impossible or highly impractical. This is because CABP is infrequent in this age group.

We are deferring submission of your pediatric studies for ABSSSI and SAB, 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)(4)(C) of the FDCA. These required studies are listed below:

4612-1 Conduct a randomized, controlled study to evaluate the safety, tolerability, and efficacy of ceftobiprole medocaril sodium for injection in pediatric patients from birth to less than 18 years of age with acute bacterial skin and skin structure infections (ABSSSI) requiring intravenous antibacterial drugs.

Draft Protocol Submission: 10/2024
Final Protocol Submission: 02/2025
Study Completion: 10/2027
Final Report Submission: 04/2028

4612-2 Conduct a randomized, controlled study to evaluate the safety, tolerability, and efficacy of ceftobiprole medocaril sodium for injection in pediatric patients from birth to less than 18 years of age with *Staphylococcus aureus* bacteremia (SAB).

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Study Completion: 10/2028
Final Report Submission: 04/2029

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 protocols to your IND 64407 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)(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 assess a signal of serious risk of adverse events associated with the coadministration of ceftobiprole medocaril sodium for injection and OATP1B1 and OATP1B3 transporter substrates. 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 serious risk of developing resistance to ceftobiprole in bacterial pathogens specific to the indications in labeling.

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 risks.

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

4612-3 Conduct an in vivo drug interaction study evaluating ceftobiprole medocaril sodium for injection as an inhibitor of OATP1B1 and OATB1B3 transporters in healthy subjects.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2024
Final Protocol Submission:	09/2024
Study Completion:	06/2025
Final Report Submission:	12/2025

4612-4 Conduct a US surveillance study for a five-year period after the introduction of ceftobiprole medocaril sodium for injection to the market to determine if bacterial resistance to ceftobiprole has developed in those organisms specific to the indications in the labeling.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2024
Final Protocol Submission:	01/2025
Interim Report:	06/2026
Interim Report:	06/2027
Interim Report:	06/2028
Interim Report:	06/2029
Interim Report:	06/2030
Final Report Submission:	03/2031

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 64407 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).**

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.

[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.

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

We remind you of your postmarketing commitments:

4612-5 Conduct studies to establish additional controls in the finished drug product specification and adequate in-process controls in the manufacturing process to demonstrate that the labeled vial content can be withdrawn at the lower end of the fill weight variation range following reconstitution.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2024
Final Report Submission: 08/2025

4612-6: Conduct stability studies on three drug product batches manufactured by basing the weight of the drug substance (b) (4) (b) (4) and propose appropriately revised acceptance criteria for assay and impurities.

The timetable you submitted on March 28, 2024, states that you will conduct this study according to the following schedule:

Interim Report Submission:01/2026
Final Report Submission: 07/2026

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 64407 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]

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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website.[7]

[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
[7] https://www.uspnf.com/

If you have any questions, contact J. Christopher Davi, MS, Senior Regulatory Project Manager, at christopher.davi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- 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/

JOHN J FARLEY
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