NDA 213400

ACCELERATED APPROVAL

Epizyme, Inc.
Attention: Huiping Jiang, PhD
Vice President, Regulatory Affairs
400 Technology Square
4th Floor
Cambridge, MA 02139

Dear Dr. Jiang:

Please refer to your new drug application (NDA) dated December 18, 2019, received December 18, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAZVERIK (tazemetostat) tablet.

This new drug application provides for the use of TAZVERIK (tazemetostat) tablet for

- the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- the treatment of adult patients with R/R FL who have no satisfactory alternative treatment options.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of*

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

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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213400**." Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 16, 2020. This requirement, along with required completion dates, is listed below.

3872-1 Submit the final report and datasets from a randomized, phase 3 clinical trial that verifies and describes the clinical benefit of tazemetostat in patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for the interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without tazemetostat. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate.

Final Protocol Submission: 02/2020 (completed)
Trial Completion: 12/2024
Final Report Submission: 07/2025

[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.

3872-2 Submit the final report and datasets from a randomized, phase 3 clinical trial that verifies and describes the clinical benefit of tazemetostat in patients with relapsed or refractory follicular lymphoma whose tumors do not have an EZH2 mutation as detected by an FDA-approved test. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for the interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without tazemetostat. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate.

Final Protocol Submission: 02/2020 (completed)
Trial Completion: 12/2024
Final Report Submission: 07/2025

Submit clinical protocols to your IND 124025 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement 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.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 known serious risk of acute myeloid leukemia, myelodysplastic syndrome, T-lymphoblastic lymphoma, and other secondary malignancies in patients receiving tazemetostat.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

3872-3 Submit annual safety updates for 10 years from a cumulative, integrated safety analyses of patients with lymphoid malignancies enrolled in clinical trials and from post-marketing reports to characterize the risk of acute myeloid leukemia, myelodysplastic syndrome, T-lymphoblastic lymphoma, and other secondary malignancies in patients receiving TAZVERIK. Include incidence rates, time to onset, predisposing factors, and outcomes in the interim and final reports. These safety evaluations may inform labeling of patient populations at highest risk and to provide evidence-based monitoring recommendations.

The timetable you submitted on June 16, 2020 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2019 (completed)
Study Completion:	03/2029
Interim Report Submission:	04/2021
Interim Report Submission:	04/2022
Interim Report Submission:	04/2023
Interim Report Submission:	04/2024
Interim Report Submission:	04/2025
Interim Report Submission:	04/2026
Interim Report Submission:	04/2027
Interim Report Submission:	04/2028
Interim Report Submission:	04/2029
Interim Report Submission:	04/2030
Final Report Submission:	04/2030

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 protocols to your IND 124025 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 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 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3872-4 Submit the final results and datasets for overall response rate and duration of response from clinical trial E7438-G000-101 in patients with relapsed or refractory follicular lymphoma to further characterize the clinical benefit of tazemetostat.

The timetable you submitted on June 16, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2018 (completed)
Trial Completion: 12/2020
Final Report Submission: 06/2021

3872-5 Submit the final results and datasets for overall response rate and duration of response from a clinical trial in patients with relapsed or refractory follicular lymphoma whose tumors do not have an EZH2 mutation and have received prior therapies including bendamustine, obinutuzumab, rituximab plus lenalidomide, and other therapies consistent with those used in a U.S. population to further characterize the clinical benefit of tazemetostat monotherapy that may inform product labeling.

The timetable you submitted on June 16, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2020

Trial Completion: 08/2023
Final Report Submission: 12/2023

3872-6 Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access program, real-world evidence, and other sources to further characterize the safety and efficacy of tazemetostat monotherapy and tazemetostat in combination with other immunotherapy among U.S. racial and ethnic minority patients with follicular lymphoma.

The timetable you submitted on June 16, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2026

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). We have now administratively closed this NDA. Therefore, all 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, promotional materials and other submissions should be addressed to the original **NDA 211723** for this drug product, not to this NDA. In the future, do not make submissions to this NDA, except for the final printed labeling requested above.

If you have any questions, call Thomas Iype, PharmD, RPh, Senior Regulatory Health Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director (Acting)
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide
- Carton and Container Labeling

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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/

NICOLE J GORMLEY
06/18/2020 12:00:10 PM