NDA 213217/S-004

SUPPLEMENT APPROVAL

BeiGene, Ltd.
Attention: Tania Bekerman
Associate Director, Regulatory Affairs
2955 Campus Drive, Suite 200
San Mateo, CA 94403

Dear Ms. Bekerman:

Please refer to your supplemental new drug application (sNDA) dated December 18, 2020, received December 18, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BRUKINSA (zanubrutinib) capsules.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

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.

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 Food and Drug Administration (FDA) automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling Prescribing Information, Patient Package Insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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]

[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.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

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.

Since Brukinsa (zanubrutinib) was approved on November 14, 2019, we have become aware through clinical trials of an increased risk of second primary malignancies in patients with Waldenström's macroglobulinemia receiving zanubrutinib. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 known serious risk of second primary malignancies.

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 this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of second primary malignancies.

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

4130-1 Conduct an integrated safety analysis of patients with lymphoid malignancies and Waldenström's Macroglobulinemia enrolled in clinical trials and from post-marketing reports to further characterize the risk of second primary malignancies with extended follow-up in patients receiving zanubrutinib. Submit interim reports after 2 years and 3 years containing cumulative safety updates. Include incidence rates, time to onset, predisposing factors including coexisting mutations and outcomes in the interim and final reports.

The timetable you submitted on August 27, 2021 states that you will conduct this study according to the following schedule:

Draft Analysis Protocol Submission:	03/2022
Final Analysis Protocol Submission:	09/2022
Interim Report #1 Submission:	12/2024
Interim Report #2 Submission:	12/2025
Trial Completion:	12/2026
Final Report Submission:	06/2027

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 the protocol(s) to your IND 125326, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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 of the FDCA, as well as

[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.

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:

4130-2 Conduct a study to further characterize the clinical benefit and safety of zanubrutinib for the treatment of patients with newly diagnosed Waldenström's Macroglobulinemia with MYD88 mutation. This should include an assessment of the CXCR4 mutation status. In addition, the study should include a sufficient number of patients enrolled in the United States and sufficient numbers of racial and ethnic minority patients to allow for the interpretation of the results in these patient populations.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2025
Final Report Submission: 03/2026

4130-3 Conduct a study to further characterize the clinical benefit and safety of zanubrutinib in patients with newly diagnosed and relapsed/refractory Waldenström's Macroglobulinemia with MYD88^{wt}. This study should include a sufficient number of patients enrolled in the United States and sufficient numbers of racial and ethnic minority patients to allow for the interpretation of the results in these patient populations.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022

Study Completion: 08/2025
Final Report Submission: 03/2026

4130-4 Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of zanubrutinib in racial and ethnic minorities with Waldenström's Macroglobulinemia.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2023
Study Completion: 01/2028
Final Report Submission: 06/2028

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 125326 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. 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]

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

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

REPORTING REQUIREMENTS

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

If you have any questions, call Bernetta Lane, Regulatory Health Project Manager, at (301) 796-0937.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

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

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

APPEARS THIS WAY ON ORIGINAL

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
08/31/2021 08:42:19 PM