NDA 213217

**ACCELERATED APPROVAL**

BeiGene USA, Inc.
Attention: Julie Boisvert, BSc
Senior Director, Regulatory Affairs
2955 Campus Drive, Suite 200
San Mateo, CA 94403

Dear Ms. Boisvert:

Please refer to your new drug application (NDA) dated June 27, 2019, received June 27, 2019 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brukinsa (zanubrutinib) capsules.

This new drug application provides for the use of Brukinsa (zanubrutinib) capsules for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

## 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, text for the Patient Package Insert). 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 via publicly available labeling repositories.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on October 8, 2019, 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 213217**." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for Brukinsa was not referred to an FDA advisory committee because evaluation of the data when used in the treatment of patients with relapsed or refractory mantle cell lymphoma did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

## 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 November 5, 2019. This requirement, along with required completion dates, is listed below.

| | |
|---|---|
| PMR 3735-1 | Complete and submit the final results of Trial BGB-3111-306 - the ongoing randomized, Phase 3 clinical trial of BRUKINSA in combination with rituximab versus bendamustine and rituximab in patients with previously untreated mantle cell lymphoma. The primary endpoint is progression free survival (PFS) as assessed by Independent Review Committee (IRC). Overall survival (OS) is a key secondary endpoint. PFS and OS would be analyzed based on superiority testing. Enrollment of approximately 500 patients is expected. |

The timetable you submitted on November 5, 2019 states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 10/2026 |
| Final Report Submission: | 02/2027 |

Submit clinical protocols to your IND 125326 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)**."

## 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.

## POST MARKETING REQUIREMENTS UNDER FDAAA SECTION 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 a known serious risk of bleeding, to include fatal and severe bleeding, in patients receiving Bruton's tyrosine kinase (BTK) inhibitors.

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 studies:

PMR 3735-2 Determine the effect of a broad range of concentrations of BRUKINSA on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects of zanubrutinib on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

LABORATORY STUDIES: Assess the effect of zanubrutinib on platelet function. Assessment methods should evaluate for effects of zanubrutinib on platelet aggregation, including GPIb mediated aggregation. Evaluation should include patients with concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction).

The timetable you submitted on November 5, 2019 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 02/2020
Final Protocol Submission: 05/2020
Study Completion: 06/2021
Final Report Submission: 12/2021

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of zanubrutinib exposure above those observed at the recommended dose, when administered with concomitant CYP3A4 inhibitors (including ciprofloxacin, diltiazem, erythromycin, fluconazole, posaconazole, voriconazole, and clarithromycin).

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

PMR 3735-3 Conduct an analysis evaluating the pharmacokinetics and safety of zanubrutinib when administered with concomitant CYP3A4 inhibitors (including ciprofloxacin, diltiazem, erythromycin, fluconazole, posaconazole, voriconazole, and clarithromycin) utilizing data from ongoing studies (including but not limited to Studies BGB-3111-AU-003, BGB-3111-214, BGB-3111-215, BGB-3111-302, and BGB-3111-306). Evaluate the effect of each inhibitor on both the $C_{max}$ and AUC of zanubrutinib and assess the safety (including adverse events, dose modifications, dose interruptions,

and dose discontinuations) of the recommended dose modifications before, during, and after the concomitant dosing period. Submit a final report including PK and safety data and analyses from Studies BGB-3111-AU-003, BGB-3111-214, BGB-3111-215, BGB-3111-302, and BGB-3111-306.

The timetable you submitted on November 5, 2019 states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 02 / 2020 |
| Final Protocol Submission: | 06 / 2020 |
| Trial Completion: | 12 / 2021 |
| Final Report Submission: | 02 / 2022 |

Submit clinical protocol(s) to your IND 125326 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 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:

PMC 3735-4 Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of zanubrutinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

The timetable you submitted on November 5, 2019 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 04/2020
Final Protocol Submission: 07/2020
Study/Trial Completion: 01/2021
Final Report Submission: 04/2021

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

Under 21 CFR 314.550, 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 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 314.550, 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 (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products 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.*[3]

## REPORTING REQUIREMENTS

We remind you that you must comply with the 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.[4]

## POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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

[3] 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.

[4] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

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 Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

*{See appended electronic signature page}*

Marc R. Theoret, MD
Deputy Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

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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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