



NDA 218785/Original 2

ACCELERATED APPROVAL

BeOne Medicines USA, Inc.
Attention: Sarah Ansell
Senior Director, Regulatory Affairs
311 Pennington-Rocky Hill Road
Building 51-Suite 1358
Pennington, NJ 08534

Dear Sarah Ansell:

Please refer to your new drug application (NDA) dated and received August 30, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brukinsa (zanubrutinib) tablets.

This NDA provides for the use of Brukinsa (zanubrutinib) tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 218785/Original 1 – Treatment of adult patients with Waldenström’s macroglobulinemia (WM); treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- NDA 218785/Original 2 – Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy; treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen; treatment of adult patients with relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy.

The subject of this action letter is NDA 218785/Original 2. A separate action letter will be issued for NDA 218785/Original 1.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, 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 accelerated approval statutory provisions and regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of 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, 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

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 31, 2025, 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 218785.**” 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 Brukinsa (zanubrutinib) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below,

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>.

we may withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated May 22, 2025. These requirements are listed below.

- 4855-1 Complete and submit the final results of Trial BGB-3111-306, the ongoing randomized clinical trial of zanubrutinib in combination with rituximab versus bendamustine and rituximab, intended to verify and describe the clinical benefit of zanubrutinib 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 May 22, 2025, states that you will conduct this trial according to the following schedule:

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

- 4855-2 Complete a randomized clinical trial intended to verify and describe the clinical benefit of zanubrutinib in patients with relapsed or refractory marginal zone lymphoma. The trial should include sufficient representation of racial and ethnic populations to better reflect the U.S. patient population and allow for interpretation of the results in these patient populations. The primary endpoint should be progression-free survival, with secondary endpoints that include objective response rate and overall survival.

The timetable you submitted on May 22, 2025, states that you will conduct this trial according to the following schedule:

Trial Completion:	05/2028
Final Report Submission:	10/2028

- 4855-3 Complete a randomized clinical trial of zanubrutinib plus obinutuzumab versus lenalidomide plus rituximab, intended to verify and describe the clinical benefit of zanubrutinib in patients with relapsed or refractory follicular lymphoma. The primary endpoint should be progression-free survival, with secondary endpoints that include objective response rate and overall survival. The trial should enroll a sufficiently representative study population that reflects the racial and ethnic populations of the U.S. population of patients with follicular lymphoma and that allows for interpretation of the results in these populations.

The timetable you submitted on May 22, 2025, states that you will conduct this trial according to the following schedule:

Trial Completion: 07/2028
Final Report Submission: 01/2029

Submit clinical protocols to your IND 125326 for this product. 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.

You must submit status reports of the progress of each clinical trial required under section 506(c) (listed above) to the NDA 180 days after the date of approval of this NDA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application’s ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted³.

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics*, to submit your 180-day reports.⁴

180-day reports must be clearly designated “**NDA 218785 180-Day AA PMR Progress Report.**”

FDA will consider the submission of your application’s ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

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

³ You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

⁴ FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at <https://www.fda.gov/about-fda/reports-manuals-forms/forms>.

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 these indications has orphan drug designation, you are exempt from this requirement.

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 (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 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, 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*.⁵

REPORTING REQUIREMENTS

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

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

⁵ <https://www.fda.gov/media/128163/download>.

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 website⁶.

If you have any questions, contact Megan Sybeldon, Regulatory Project Manager, at 240-402-4730 or Megan.Sybeldon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Deputy Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

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

⁶ <https://www.uspnf.com/>

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/

NICHOLAS C RICHARDSON
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