NDA 212608/S-006

SUPPLEMENT APPROVAL

Blueprint Medicines Corporation
Attention: Gemma Mandell, BSc
Senior Director, Regulatory Affairs
45 Sidney Street
Cambridge, MA 02139

Dear Ms. Mandell:

Please refer to your supplemental new drug application (sNDA) dated and received December 16, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ayvakit (avapritinib) film-coated tablets.

This Prior Approval supplemental new drug application provides for the following:

1. New indication for the treatment of adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM) and systemic mastocytosis with an associated hematological neoplasm (SM-AHN).

2. Two additional tablet strengths (25 mg and 50 mg), and manufacturing site, (b) (4)

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 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 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.

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

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 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).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 16, 2020, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212608/S-006**." Approval of this submission by FDA is not required before the labeling is used.

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.

[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.

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 Ayvakit (avapritinib) was approved on January 9, 2020, we have become aware of safety signals of intracranial hemorrhage and cognitive adverse reactions associated with avapritinib, which need to be further evaluated in ongoing clinical trials, such as the trial BLU-285-2202. 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 fully assess the signal of serious risks of intracranial hemorrhage and cognitive adverse reactions.

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 clinical trials (rather than a nonclinical or observational study) will be sufficient to fully assess a signal of serious risks of intracranial hemorrhage and cognitive adverse reactions.

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

4101-1 Conduct a pooled analysis of data from completed and on-going avapritinib trials, including Studies BLU-285-1101, BLU-285-2101, BLU-285-2202, and BLU-285-1303, to further characterize avapritinib-associated intracranial hemorrhage in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis. Include patient narratives with the onset and resolution date for each event, results of investigations (laboratory, imaging, other), avapritinib dose history and action taken, concomitant medications, patient comorbidities and outcome for intracranial hemorrhage events. Submit datasets, and patient narratives for intracranial hemorrhage events in the final report.

The timetable you submitted on June 8, 2021, states that you will conduct this study according to the following schedule:

Trial Completion:	06/2021
Final Report Submission:	12/2021

4101-2 Conduct a pooled analysis of data from completed and on-going avapritinib trials, including Studies BLU-285-1101, BLU-285-2101, BLU-285-2202, and BLU-285-1303, to further characterize avapritinib-associated cognitive adverse reactions (including memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, delirium, hallucination, mood altered, agitation, personality change, dementia, mental status changes, psychotic disorder, disorientation, mental impairment, and encephalopathy) in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis. Include patient narratives with the onset and resolution date for each event, results of investigations (laboratory, imaging, other), avapritinib dose history and action taken, concomitant medications, patient comorbidities and outcome of each event. Submit datasets, and patient narratives for serious cognitive adverse events in the final report.

The timetable you submitted on June 8, 2021, states that you will conduct this study according to the following schedule:

Trial Completion:	06/2021
Final Report Submission:	12/2021

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 124159, 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 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

[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.

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 COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4101-3 Complete Study BLU-285-2202, "An open-label, single-arm, Phase 2 study to evaluate efficacy and safety of avapritinib (BLU-285), a selective KIT mutation-targeted tyrosine kinase inhibitor, in patients with advanced systemic mastocytosis". Include an updated summary of safety, efficacy analyses, and datasets at the time of final clinical study report submission.

The timetable you submitted on June 8, 2021, states that you will conduct this study according to the following schedule:

Trial Completion:	01/2026
Final Report Submission:	12/2026

Submit clinical protocols to your IND 124159 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, contact Brittany Garr-Colón, MPH, Regulatory Project Manager, at (301) 796-6153 or via email at Brittany.Garr-Colon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Deputy Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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

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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.

/s/

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