NDA 212608/Original 1

NDA APPROVAL

Blueprint Medicines Corporation
Attention: Tanya Green, M.S.
Senior Director, Regulatory Affairs
45 Sidney Street
Cambridge, MA 02139

Dear Ms. Green:

Please refer to your new drug application (NDA) dated June 14, 2019, received June 14, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ayvakit (avapritinib) tablets, 100mg, 200mg, and 300mg, for oral use.

NDA 212608/Original 1 provides for the use of Ayvakit (avapritinib) tablets, 100mg, 200mg, and 300mg, for oral use, for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

As communicated to you on January 8, 2020, all future submissions to your application should specify the application number and all Original numbers to which each submission pertains.

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, Patient Package Insert) as well as annual reportable changes

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

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]

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 and carton and container labeling submitted on December 19, 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 *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**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Ayvakit was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues.

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.

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 known

[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.

serious risks of central nervous system (CNS) adverse reactions and intracranial hemorrhage.

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 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 known serious risks.

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

3781-1 Conduct an analysis characterizing avapritinib-associated CNS adverse reactions including but not limited to cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations including incidence, timing, appropriate diagnostic criteria, action taken with avapritinib, and outcome to provide additional data that may inform product labeling. Include patient-level data, clinical outcome assessments and pooled analyses of data from completed and on-going trials in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis, including trials BLU-285-1101, BLU-285-2101, and BLU-285-1303. Submit the analysis, datasets, the results of any related clinical outcome assessments, and patient narratives for CNS effects in the final report.

The timetable you submitted on January 8, 2020, states that you will conduct this trial according to the following schedule:

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

3781-2 Conduct an analysis characterizing avapritinib-associated intracranial hemorrhage, including incidence, timing, appropriate diagnostic criteria, action taken with avapritinib, predisposing concomitant medications and comorbidities and outcome to provide additional data that may inform product labeling. Include patient-level data and pooled analyses of data from completed and on-going trials in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis, including trials BLU-285-1101, BLU-285-2101, and BLU-285-1303. Submit the analysis, datasets,

and patient narratives for intracranial hemorrhage events in the final report.

The timetable you submitted on January 8, 2020, states that you will conduct this trial according to the following schedule:

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

3781-3 Complete a pharmacokinetic trial to determine an appropriate dose of avapritinib in patients with severe hepatic impairment in accordance with the FDA Guidance for Industry titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf.

The timetable you submitted on January 8, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2020
Trial Completion:	07/2023
Final Report Submission:	02/2024

Submit clinical protocol(s) to your IND 125379 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).**

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:

3781-4 Develop and submit the report of a valid companion diagnostic to detect PDGFRα D842V somatic variants for identifying patients with GIST who may benefit from avapritinib using clinical trial data from study BLU-285-1101 titled, "A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors", to inform product labeling. The analytical validation will include precision, limit of detection and accuracy studies for the PDGFRα D842V somatic variant indication. The clinical validation will be accomplished by a clinical bridging study comparing the nucleic acid-based in-vitro diagnostic device and the clinical trial enrollment assay.

The timetable you submitted on January 8, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2020

Submit clinical protocols to your IND 125379 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

Alternatively, you may submit a request for advisory comments 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]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with 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.[7]

[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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

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 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 Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

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

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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