



NDA 212608/S-020

SUPPLEMENT APPROVAL

Blueprint Medicines Corporation
Attention: Elisabeth Garrison, Pharm.D., M.S.
Associate Director, Global Regulatory Sciences (GRS) Strategy
45 Sidney Street
Cambridge MA 02139

Dear Dr. Garrison:

Please refer to your supplemental new drug application (sNDA) dated and received October 11, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ayvakit (avapritinib) tablets.

We also refer to our September 11, 2024, letter notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for avapritinib. This information pertains to the risk of thrombosis or other hormonally-associated adverse events related to estrogen used concomitantly with avapritinib.

This supplemental new drug application provides for revisions to the labeling for AVAKIT (avapritinib) tablets. The agreed upon changes to the language included in our September 11, 2024, letter are as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. Section 7 DRUG INTERACTIONS

a. 7.2 Effects of AYVAKIT on Other Drugs

Coadministration of AYVAKIT with ethinyl estradiol-containing contraceptives may increases the exposure of ethinyl estradiol, which may lead to increased risk of ethinyl estradiol-associated adverse reactions [redacted] (b) (4) [redacted] [see *Clinical Pharmacology (12.3)*].

If the patient is unable to use or tolerate an effective nonhormonal contraceptive or an effective hormonal contraceptive without estrogen, use a formulation of ethinyl estradiol containing 20 mcg or less unless a higher dose is necessary.

2. Section 8 USE IN SPECIFIC POPULATIONS

a. 8.3 Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose [*see Drug Interactions (7.2)*].

3. Section 12 CLINICAL PHARMACOLOGY

a. 12.3 Pharmacokinetics

Drug Interaction Studies

Hormonal Contraceptives: In a drug-drug interaction study of 15 subjects, coadministration of AYVAKIT 25 mg once daily with an oral contraceptive (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) resulted in a (b) (4) mean ethinyl estradiol AUC ratio of 1.15 (90% confidence interval [CI]: 1.04, 1.28) and a mean ethinyl estradiol C_{max} (b) (4) ratio of 1.46 (b) (4) (90% CI: 1.17, 1.81) (b) (4) relative to participants administered the oral contraceptive alone. This increase in (b) (4) ethinyl estradiol C_{max} (b) (4) may lead to an increased risk of ethinyl estradiol-related adverse events.

4. Section 17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose [*see Drug Interactions (7.2), Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose [*see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

5. Revise **PATIENT INFORMATION**

- a. Under the section, “**Especially tell your healthcare provider** if you take medicines that prevent blood clots” to read as:

Especially tell your healthcare provider if you take:

- estrogen-containing hormonal (b) (4) birth control (contraception)
- medicines that (b) (4) prevent blood clots

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.

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).

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>.

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 none of these criteria apply to your supplemental application, you are exempt from this requirement.

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*.³

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.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

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-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related 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).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

314.53(c)(2)(ii). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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 Stefanie McDaniel, Regulatory Health Project Manager, at Stefanie.McDaniel@fda.hhs.gov or (301) 796-2548.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert

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/

STEVEN J LEMERY
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