CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s000

OTHER REVIEW(S)
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 31, 2019
Requesting Office or Division: Division of Oncology 3 (DO3)
Application Type and Number: NDA 212608
Product Name and Strength: Ayvakit (avapritinib) Tablets, 100 mg, 200 mg, and 300 mg
Applicant/Sponsor Name: Blueprint Medicines Corp.
OSE RCM #: 2019-1281-2
DMEPA Safety Evaluator: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1  PURPOSE OF MEMORANDUM
The Applicant submitted revised container labels and carton labeling received on December 19, 2019 for Ayvakit. Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Ayvakit (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum.a

2  CONCLUSION
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/

JANINE A STEWART
12/31/2019 10:27:58 AM

CHI-MING TU
12/31/2019 10:29:58 AM
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 10, 2019
Requesting Office or Division: Division of Oncology 3 (DO3)
Application Type and Number: NDA 212608
Product Name and Strength: Ayvakit (avapritinib) Tablets, 100 mg, 200 mg, and 300 mg
Applicant Name: Blueprint Medicines Corp.
OSE RCM #: 2019-1281-1
DMEPA Safety Evaluator: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1  PURPOSE OF MEMORANDUM
The Applicant submitted revised container labels and carton labeling received on November 8, 2019 for Ayvakit. Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Ayvakit (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2  CONCLUSION
The revised container labels and carton labeling are unacceptable from a medication error perspective. The location of net quantity statement can be revised to promote the safe use of the product. Thus, we provide a recommendation to Blueprint Medicines Corp. in Section 3.

3  RECOMMENDATIONS FOR BLUEPRINT MEDICINES CORP.
We recommend the following be implemented prior to approval of this NDA:

   A. Relocate the net quantity statement away from the product strength, such as to the top right corner of the principal display panel. From post-marketing experience, the risk of

numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

a. Consider relocating the "Rx Only" statement to appear beneath the strength statement.
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/s/

JANINE A STEWART
12/10/2019 11:14:56 AM

CHI-MING TU
12/10/2019 12:11:27 PM
Memorandum

Date: December 3, 2019

To: Christy Osgood, MD, Clinical Reviewer
Division of Oncology 3 (DO3)
Idara Udoh, MS, Senior Regulatory Health Project Manager (DO3)
Afrouz Nayernama, Associate Director of Labeling

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O’Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ayvakit (avapritinib) tablets, for oral use

NDA: 212608

In response to DO3’s consult request dated July 12, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PP), and carton and container labeling for the original NDA submission for Ayvakit.

PI: OPDP’s comments on the proposed labeling are based on the draft PI received by electronic mail from DO3 (Idara Udoh) on November 15, 2019, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on December 2, 2019

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 14, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.
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/s/

ROBERT L NGUYEN
12/03/2019 01:05:16 PM
PATIENT LABELING REVIEW

Date: December 2, 2019

To: Steven Lemry, MD
   Acting Director
   Division of Oncology 3 (DOC3)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
   Team Leader, Patient Labeling
   Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
   Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (avapritinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 212608

Applicant: BluePrint Medicines Corporation
INTRODUCTION

On June 14, 2019, BluePrint Medicines Corporation submitted for the Agency’s review a New Drug Application (NDA) 212608 for TRADENAME (avapritinib) tablets, for oral use. The proposed indications are for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who have a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, such as the PDGFRA D842V mutation, regardless of prior therapy;

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 3 (DOC3) on July 9, 2019 and July 12, 2019, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for TRADENAME (avapritinib) tablets, for oral use.

MATERIAL REVIEWED

• Draft TRADENAME (avapritinib) tablets, for oral use PPI received on June 14, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 15, 2019.

• Draft TRADENAME (avapritinib) tablets, for oral use Prescribing Information (PI) received on June 14, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 15, 2019.

REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

• simplified wording and clarified concepts where possible
• ensured that the PPI is consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS
The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.
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/

SUSAN W REDWOOD
12/02/2019 01:14:26 PM

BARBARA A FULLER
12/02/2019 02:31:40 PM

LASHAWN M GRIFFITHS
12/02/2019 03:07:22 PM
Clinical Inspection Summary

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<tr>
<td>From</td>
<td>Yang-min (Max) Ning, M.D., Ph.D.</td>
</tr>
<tr>
<td></td>
<td>Aisha Johnson, M.D., M.P.H., M.B.A</td>
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<td></td>
<td>Kassa Ayalew, M.D., M.P.H.</td>
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<td>GCPAB/OSI/CDER/FDA</td>
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<tr>
<td>To</td>
<td>Christy Osgood, M.D.</td>
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<td></td>
<td>Ashley Ward, M.D.</td>
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<td></td>
<td>Idara Udoh, RPM</td>
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I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing, open-label study (BLU-285-1101) were submitted to the Agency in support of this New Drug Application (NDA) for avapritinib for the above proposed indications. Three clinical investigators, Dr. Robin Jones (Site 1101), Dr. Margaret Von Mehren (Site 2001), and Dr. Michael Heinrich (Site 2003), the study sponsor, and the contract research organization (CRO) which performed independent review of tumor assessment scans, were selected for clinical inspections.

The inspections verified the Applicant’s submitted clinical data with source records at the clinical investigator and CRO sites. There were no objectionable observations identified in the sponsor inspection. Based on the results of these inspections, the data derived from these clinical investigator sites and the CRO appear to be acceptable and supportive of this NDA for
avapritinib.

II. BACKGROUND

Blueprint Medicines Corporation, the sponsor for this NDA, seeks approval of avapritinib, a kinase inhibitor, for the treatment of unresectable or metastatic GIST who have a PDGFRα exon 18 mutation regardless of prior therapy. To support the application, the Sponsor submitted clinical data from the study BLU-285-1101 (NCT02508532), titled “A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors”. BLU-285 was the investigational drug name of avapritinib. This study had two parts: Part 1 for dose-escalation and Part 2 for dose-expansion. The study was initially designed to evaluate the safety and tolerability of increasing doses (Part 1) of avapritinib in patients with unresectable GIST or other relapsed or refractory solid tumors. Based on the encouraging initial antitumor activity and favorable tolerability, a new primary objective was introduced following initiation of Part 2 to assess the objective response rate (ORR) in two study populations: 1) patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy; 2) patients with unresectable or metastatic GIST who harbor PDGFRα exon 18 mutations, including PDGFRα D842V mutation, regardless of prior therapy.

Study subjects received avapritinib at a dose of 300 mg or 400 mg orally once daily (Part 2) in 28-day cycles until unacceptable toxicity, disease progression, or other criteria as specified in the study protocol. Tumor assessments were based on local assessments of computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, performed at baseline, every 2 cycles through Cycle 13, and thereafter every 3 cycles (e.g., C16D1, C19D1) until the end of treatment. All radiographic scans were also submitted to a central radiology laboratory for independent assessments of response and progression.

From 10/12/2015 through 11/16/2018, the study enrolled 237 subjects from 17 study sites, including 8 in the U.S., 8 in Europe, and 1 in Asia. Of the enrolled subjects, 43 were reported to have tumors harboring a PDGFRα exon 18 mutation and 121 to have received at least 3 prior lines of therapy. Clinical data from these two populations were used for efficacy analyses of avapritinib for the proposed indications.

Three clinical investigators, Dr. Robin Jones (Site 1101), Dr. Margaret Von Mehren (Site 2001), and Dr. Michael Heinrich (Site 2003), were selected for clinical inspection. These sites had a high number of enrollments relevant to other sites, raising a potential conflict of interest. Clinical inspections of the Sponsor and the CRO which performed central independent radiology review were also requested by the Review Division to evaluate the clinical trial oversight, data management, and reliability of independent assessment results.
III. RESULTS

1. Dr. Robin Jones, Clinical Investigator Site #1101
   Royal Marsden Hospital
   London, England

   This foreign clinical investigator was inspected on October 14-18, 2019 as a data audit for the study BLU-285-1101. This was the initial inspection of Dr. Jones. The study site enrolled 28 subjects, including three subjects (# ) consented in February 2019 (after the data cutoff). The first subject was enrolled on 1/11/2016. Nineteen subjects received study drug in Part 2, with four subjects (# ) reported to have tumors harboring a PDGFRα exon 18 mutation and fifteen subjects to have had at least one line of prior therapy. (Note that the submitted site-level data listings did not show subjects who received “at least 3 prior lines of therapy”). As of the data cutoff date, 9 of the 19 subjects remained on study treatment and 10 were discontinued due to disease progression, withdrawal, adverse event, or deaths. Of the 4 subjects with a PDGFRα exon 18 mutation, three remained on study treatment and one died from disease progression (Subject #)

   Source records reviewed during the inspection included the study protocol and amendments, informed consent forms, documentation of eligibility criteria, medical records, adverse events, treatment with the investigational product, visit data, laboratory results, case report forms (CRF), and related regulatory documents (e.g., Ethics Committee approvals and communications, training on the trial, financial disclosures, and delegation of authority).

   The inspection found adequate source documentation for all study subjects, with no significant deficiencies reported. No Form FDA 483 was issued. The submitted data were verifiable with source records at the study site. Note that the independent central tumor response data was not available for review at the site. There was no evidence of underreporting of adverse events. At the end of the inspection, a few identified discrepancies in source documentation were discussed with the investigator. These were: 1) the reported adverse event of mild ankle edema in Subject # should have a stop date in the CRF when it was mentioned in the source notes as not being present; 2) hair discoloration in Subject # was noted on but was not reported as an adverse event in the CRF until ; 3) a change in the local assessment of a tumor lesion measurement (from 49 mm to 52 mm) was found to have no date and initial as to who made the change in the source documentation. The Investigator acknowledged the identified discrepancies and stated that he would discuss and address the issues.

2. Dr. Margaret Von Mehren, Clinical Investigator Site #2001
   Fox Chase Cancer Center
   Philadelphia, PA 19111-2434

   This clinical investigator was inspected on October 2-11, 2019 as a data audit for the study BLU-285-1101. There was the second FDA inspection for this investigator. The previous
FDA inspection was conducted from 03/21/2002 through 04/03/2002 and the final compliance classification was Voluntary Action Indicated. This was associated with the identified deficiencies in the reporting of adverse events to the National Cancer Institute and to the Institutional Review Board (IRB).

The site screened 22 subjects and enrolled 21 of them into the study. Three of the enrolled subjects (#(b)(6)) had tumors harboring a PDGFRα exon 18 mutation and the rest of the subjects received at least one line of prior therapy. As of the data cutoff date, 6 subjects remained on study treatment and 15 were discontinued from study treatment due to disease progression, adverse events, consent withdrawal, or Investigator’s decision. For the three subjects with a PDGFRα exon 18 mutation, Subject (b)(6) remained on study treatment and Subjects (b)(6) were discontinued secondary to Investigator’s decision and disease progression, respectively.

Source records reviewed during the inspection included were not limited to the informed consent forms (ICFs), financial disclosure forms, FDA 1572-statement of investigators, study protocol and amendments, IRB’s approvals, training documents, subjects’ documents (e.g. concomitant medications, adverse events, medication diaries, laboratory assessments), drug accountability logs, and monitoring reports.

The inspection included review of all subjects’ source records and found that submitted data listings were verifiable with the source records, with no notable discrepancies or evidence of underreporting of adverse events. At the conclusion of the inspection, no Form FDA 483 was issued. The discussion items were: 1) multiple ECGs were obtained after the collection of laboratory samples, inconsistent with the order as specified in the protocol, which stated “ECG will be acquired within 10 minutes prior to the collection of blood sample”; 2) delayed reporting of a few serious adverse event (e.g., anemia in Subject (b)(6), nausea and vomiting in Subject (b)(6)) to the sponsor, which was related to the hospitalizations outside the study facility; 3) incomplete End of Treatment tests (e.g., no urinalysis performed for Subject (b)(6), no biomarker analysis for Subjects (b)(6)). The investigator acknowledged the findings, provided her explanation for each finding and related corrective actions.

3. Dr. Michael Heinrich, Clinical Investigator Site #2003
Oregon Health and Science University (OHSU)
Portland, OR 97239

This clinical investigator was inspected on August 12-16, 2019 as a data audit for the study BLU-285-1101. This was the first FDA inspection of the investigator. The site enrolled 36 into the study. Of them, four subjects (#(b)(6)) had tumors with a PDGFRα exon 18 mutation and the rest of the subjects received at least one line of prior therapy. As of the data cutoff date, 10 subjects remained on study treatment and 26 were discontinued due to disease progression, adverse events, or Investigator’s decision. For the four subjects with tumors positive for a PDGFRα exon 18 mutation, three remained on study treatment and one (Subject (b)(6)) discontinued from study treatment due to disease progression.
Source records were reviewed and compared with the data listings submitted by the sponsor for the site. The reviewed records included the study protocol and amendments, IRB’s approvals/correspondence, site monitoring, informed consent forms, subjects’ study records, investigational product handling and accountability, and related regulatory documents (e.g., Form FDA 1572s, financial disclosures, site’s retention of records).

The inspection found that the conduct of this study at this site was generally satisfactory. The sponsor’s data listings were consistent with the reviewed source data at the site. There was no under-reporting of adverse events. The inspection also verified that the investigator

At the end of this inspection, a Form FDA 483 (Inspectional Observations) was issued to the investigator. The listed observations included 1) “failure to provide informed consent materials in a language understandable to Subject #” and 2) “failure to follow the investigational plan in that one subject (# ) was enrolled in contradiction to exclusion criteria for a QT interval > 450, as well as missed electrocardiogram (ECG) assessments for two subjects (# ) as required by the protocol”.

In the Investigator’s written response to the Form FDA 483, he acknowledged the observations and provided his explanations as well as the corrective and preventive actions (CAPA). For Observation Item 1, the investigator admitted that Subject (Spanish-speaking) was not properly consented, which was reported as a protocol deviation after the issue was identified during a routine monitoring visit in . A CAPA was implemented to address the issue in April 2018. This CAPA required . The subject was re-consented on following the requirements for informed consent of non-English speaking patients using the OHSU short form in the subject’s native language (dated ). The CAPA was amended on July 1, 2019 to add . Documentation of the re-training was submitted with the investigator’s response. Regarding the Observation Item 2, the investigator stated that the identified issues occurred secondary to staff oversight. Subject had a QT interval of 457 milliseconds (ms) at screening based on a local ECG test. The value was not presented to the investigator for review. During the study (from April 2017 through the data cutoff in November 2018), this subject had no QT prolongation detected. The missed ECG assessments for Subject (Cycle 4 Day 1) and Subject (Cycle 1 Day -3) had been reported to the Institutional Review Board (IRB) on August 15, 2019 and acknowledged by the IRB on August 20, 2019. All ECGs that were not performed had been recorded as protocol deviations in the Investigational Site File. To address the issues, the investigator has conducted a re-training on the protocol’s requirements and implemented new measures, including a change to the screening workflow by adding a question "Has PI reviewed all screening procedures? Yes/No", use of a checklist of pre-dose procedures as required by
the protocol to confirm that all pre-dose procedures have been done at each study visit.

**Reviewer’s Comments:** The above investigator’s responses to the Form FDA 483 are considered adequate and acceptable. The reported QT interval of 457ms at the time of screening Subject [redacted] appears to be an isolated event given the available information. Of note, the study protocol allows continuation of study treatment without dosing interruption if a mild QT prolongation (e.g., 457ms) is detected in subjects who are receiving study treatment.

4. **CRO:**

This CRO was inspected on [redacted] to evaluate its independent radiology review (IRR) for the study BLU-285-1101 and verify of the reported data. The previous FDA inspection of this CRO was conducted on [redacted] and the final compliance classification was No Action Indicated.

The current inspection covered the study protocol, imaging review charter, and standard operating procedures (SOPs); selection, training and qualifications of radiology readers; quality assurance of the blinded reading process; monitoring of blinded image readers; data entry and database management; and overall reader compliance.

The inspection revealed that image readings at [redacted] were conducted by radiologists according to the review charter and study protocol. Imaging source data were verifiable at the CRO. A review of imaging case sets and corresponding records for 60 subjects from the CI Sites 2003 and 1101 found that tumor response data was consistent with Sponsor’s reported data to FDA, with no discrepancies reported. At the end of this inspection, no Form FDA 483 was issued.

5. **Sponsor: Blueprint Medicines Corporation**

45 Sidney Street
Cambridge, MA 02139

The sponsor inspection was conducted from August 28 through September 5, 2019 and evaluated the sponsor’s conduct, oversight, and management of the study BLU-285-1101 (conducted under IND 125379). This was the first FDA inspection of the sponsor.

Source records reviewed during the inspection included but were not limited to the organizational charts, standard operating procedures, safety plans, monitoring plans and reports, investigator/sponsor/CRO correspondence, vendor oversight plans, training records, investigator agreements, financial disclosure forms, electronic case report forms (eCRFs), adverse events, and test article accountability records. The three clinical investigators (Sites 1101, 2001, and 2003) as specified above were selected for data audit and record review. The agreement with the CRO [redacted] and related procedures and data management were also reviewed.
The inspection found no significant deficiencies, with no Form FDA 483 issued at the end of the inspection. The sponsor appeared to maintain adequate oversight and documentation of the study BLU-285-1101. The efficacy and safety data listings for the three investigator sites matched the sponsor’s source data, with no evidence of underreporting of adverse events and serious adverse events.

PRIMARY REVIEW:  {See appended electronic signature page}

Yang-min (Max) Ning, M.D., Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:  {See appended electronic signature page}

Aisha Johnson, M.D., M.P.H., M.B.A.  
Acting Team Lead  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:  {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 212608  
Review Division /Division Director/P Keegan  
Review Division /Medical Team Leader/A Ward  
Review Division /Project Manager/U Idara  
Review Division/Medical Officer/C Osgood  
OSI/Office Director/D Burrow  
OSI/DCCE/ Division Director/N Khin  
OSI/DCCE/Branch Chief/K Ayalew  
OSI/DCCE/Acting Team Leader/A Johnson  
OSI/DCCE/GCP Reviewer/YM Ning  
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague  
OSI/Database PM/Dana Walters

Reference ID: 4525946
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/

YANGMIN NING  
11/26/2019 02:24:08 PM

AISHA P JOHNSON  
11/26/2019 02:44:30 PM

KASSA AYALEW  
11/26/2019 04:26:18 PM
**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

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<td>Division of Oncology Products 2 (DOP2)</td>
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<td>Product Name, Dosage Form, and Strength:</td>
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<td>DMEPA Team Leader:</td>
<td>Chi-Ming (Alice) Tu, PharmD, BCPS</td>
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Reference ID: 4512583
1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed prescribing information (PI), container label and carton labeling submitted for Ayvakit (avapritinib) tablets for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

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<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Ayvakit (avapritinib) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas in the PI, carton labeling and container labels that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI, container label and carton labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Blueprint Medicines Corp. in Section 4.2 below.
4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. General Comments
      a. Replace “TRADENAME” with the conditionally acceptable name “Ayvakit” wherever it appears.
   2. How Supplied/Storage and Handling Section
      a. The storage temperature information is expressed inconsistently between the container label, carton labeling, and the PI. We defer to CMC to determine the correct storage temperature information. We recommend the storage temperature be consistent across all labels and labeling.

4.2 RECOMMENDATIONS FOR BLUEPRINT MEDICINES CORP.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)
   1. Replace “TRADENAME” with the conditionally acceptable name “Ayvakit” wherever it appears.
   2. Revise the statement from [b] to “Recommended Dosage: ...” to be consistent with the recommended dosage verbiage in the Prescribing Information.
   3. The use of graphic designs are discouraged on container labels and/or carton labeling because they can distract the reader from important information and add to label clutter. The graphic design should not compete with, interrupt, or distort important information. As proposed, the graphic design enhances the prominence of the such that it competes for prominence with the . Consider omitting, revising, or relocating the graphic design.
      a. Please note, if you choose to relocate the graphic design, we recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name, because the logo can often look like an additional letter in the proprietary name. In addition, there should be no intervening written, printed, or graphic matter between the proprietary name, established name, and product strength.
   4. The storage temperature information is expressed inconsistently between the container label, carton labeling, and the PI. Revise the temperature information to read consistently across the labels and labeling.
   5. Consider orienting text on side panels horizontally so all text on your proposed drug product’s square bottle have the same orientation.
B. Container Labels

1. As currently presented, the expiration date and the format for the expiration date are not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. As currently presented, the container label does not include a lot number statement. A Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Revise the container label to include a lot number expression.
   
   a. Ensure the lot number is clearly differentiated from the expiration date.
   b. Remove the "999999" statement from the container label to avoid confusion with lot numbers. As currently presented, "999999" may be misinterpreted as a lot number.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ayvakit received on August 16, 2019 from Blueprint Medicines Corp..

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Ayvakit</th>
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<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
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<tr>
<td><strong>Active Ingredient</strong></td>
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<td><strong>Indication</strong></td>
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<tr>
<td><strong>Route of Administration</strong></td>
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<tr>
<td><strong>Dosage Form</strong></td>
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<tr>
<td><strong>Strength</strong></td>
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<tr>
<td><strong>Dose and Frequency</strong></td>
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<td><strong>How Supplied</strong></td>
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<tr>
<td><strong>Storage</strong></td>
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<tr>
<td><strong>Container Closure</strong></td>
</tr>
</tbody>
</table>
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Ayvakit labels and labeling submitted by Blueprint Medicines Corp..

- Container label received on June 14, 2019
- Carton labeling received on June 14, 2019
- Prescribing Information (Image not shown) received on August 16, 2019

G.2 Label and Labeling Images

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

CHI-MING TU on behalf of JANINE A STEWART
10/29/2019 11:13:57 AM

CHI-MING TU
10/29/2019 11:14:27 AM