

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202429Orig1s016

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 24, 2017

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

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

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nicholas Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ZELBORAF (vemurafenib)

Dosage Form and Route: tablet for oral use

Application Type/Number: NDA 202429

Supplement Number: S-016

Applicant: Hoffman-La Roche, Inc.
c/o Genentech, Inc.

1 INTRODUCTION

On June 7, 2017, Hoffman-La Roche c/o Genentech, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 202429/S-016 for ZELBORAF (vemurafenib) tablet. The purpose of this submission is to update the Prescribing Information (PI) with efficacy and safety data for patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation based on the results from the Phase II pivotal study MO28072 (VE BASKET) entitled “An Open-label, Phase II Study of Vemurafenib in Patients with BRAF V600 Mutation-positive Cancers.”

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 Hematology Products (DHP) on August 2, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZELBORAF (vemurafenib) tablet.

2 MATERIAL REVIEWED

- Draft ZELBORAF (vemurafenib) tablet MG received on June 7, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 13, 2017.
- Draft ZELBORAF (vemurafenib) tablet Prescribing Information (PI) received on June 7, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 13, 2017.

3 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. In our review of the MG the target reading level is at or below an 8th grade 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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RUTH I LIDOSHORE
10/24/2017

NICHOLAS J SENIOR
10/24/2017

SHARON R MILLS
10/24/2017

LASHAWN M GRIFFITHS
10/24/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 18, 2017

To: Jennifer Lee, RPM
Division of Hematology Products 2 (DHP)

From: Nicholas Senior, PharmD, JD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for Zelboraf (vemurafenib)

NDA/BLA: 202429/Supplement 016

In response to revision division acronym consult request dated August 2, 2017, OPDP has reviewed the proposed product labeling (PI) for the supplement for Zelboraf (vemurafenib).

OPDP's comment on the proposed labeling is based on the draft PI received by electronic mail from review division DHP (Jennifer Lee) on October 13, 2017, and is provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

We have no comments at this time.

Thank you for your consult. If you have any questions, please contact name of OPDP reviewer at (240) 402-4256 or Nicholas.Senior@fda.hhs.gov.

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/s/

NICHOLAS J SENIOR
10/18/2017

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: August 24, 2017
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 202429/S-016
Product Name and Strength: Zelboraf (vemurafenib) tablets, 240 mg
Applicant/Sponsor Name: Hoffman-La Roche
Submission Date: June 7, 2017 and August 16, 2017
OSE RCM #: 2017-1096
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the proposed Prescribing Information (PI) for Zelboraf (vemurafenib) (Appendix A) to determine if it is acceptable from a medication error perspective. Hoffman-La Roche submitted a supplemental NDA 202429/S-016 to update the PI for Zelboraf with efficacy and safety data for patients with Erdheim-Chester Disease (ECD) that have BRAF V600 mutation. This supplemental NDA is based on results from a Phase II pivotal study MO28072.

2 CONCLUSION

We defer to the review team for analysis of the proposed changes to the various sections of the Prescribing Information. The proposed Prescribing Information is acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 16, 2017

PRESCRIBING INFORMATION

[Application 202429 - Sequence 0194 - 1.14.1 Draft Labeling -](#)

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/s/

NICOLE B GARRISON
08/24/2017

HINA S MEHTA
08/24/2017

CLINICAL INSPECTION SUMMARY

Date	August 23, 2017
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Patricia Oneal, M.D., Medical Officer Virginia Kwitkowski, Clinical Team Leader Jennifer Lee, Regulatory Project Manager Division of Hematology Products (DHP)
NDA	NDA 202429/S-016
Applicant	Hoffmann-La Roche, Inc.
Drug	ZELBORAF® (vemurafenib)
NME	No
Therapeutic Classification	Kinase inhibitor
Proposed Indication	Treatment of patients with Erdheim Chester Disease (ECD) with BRAF V600 mutation
Consultation Request Date	June 29, 2017 (signed)
Summary Goal Date	September 30, 2017
Action Goal Date	November 7, 2017
PDUFA Date	December 7, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

One clinical site (Drs. Hyman and Solit as co-principle investigators) was selected for inspection for Protocol MO28072, a Phase 2, open-label, multicenter, multinational, uncontrolled study exploring the efficacy and safety of vemurafenib in patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator. The study data derived from this clinical site are considered acceptable in support of the requested indication.

The preliminary classification for this site is Voluntary Action Indicated (VAI) due to failure to promptly report some non-serious adverse events and document all concomitant medications. Preliminary classifications are based on communications with the ORA investigator and Form FDA 483. Inspection classification becomes final when the Establishment Inspection Report is

received from the field, has been reviewed, and a letter is issued to the inspected entity. A clinical inspection summary addendum will be provided if review of the inspection report(s) indicates significant change in the classification for the inspection.

2. BACKGROUND

ZELBORAF® (vemurafenib) is an oral kinase inhibitor approved in 2011 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. The sponsor subsequently conducted a Phase 2, multiple-cohort, open-label study (MO28072) of vemurafenib in patients with cancers other than melanoma in which the BRAF V600 mutation is present to evaluate the efficacy of vemurafenib. The study enrolled seven cohorts of patients with different cancers including patients with Erdheim Chester disease (ECD) and Langerhans cell histiocytosis (LCH) in Cohort 7a.

The proposed indication for Zelboraf® (vemurafenib) is for the treatment of patients with Erdheim Chester Disease (ECD) with BRAF V600 mutation. The Agency granted Breakthrough Therapy designation for Zelboraf on April 20, 2017 for the treatment of patients with ECD with BRAF V600 mutation.

The sponsor has submitted the Phase 2 study results, with a focus on the ECD and ECD/LCH cohort to support the proposed indication. CDER DHP requested one clinical site for inspection based on total number of patients enrolled, reasons for discontinuations (withdrawal of patient consent), and death reported at the site.

Study MO28072

Study MO28072 was an open-label, multicenter, multinational, uncontrolled Phase 2 study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best treatment option in the opinion of the Investigator. The study included seven cohorts of patients with different cancers including: Cohort 1: Non-small cell lung cancer (NSCLC); Cohort 2: Ovarian cancer; Cohort 3: Colorectal cancer; Cohort 4: Cholangiocarcinoma / cancer of the biliary tract; Cohort 5: Breast cancer; Cohort 6: Multiple myeloma (MM); Cohort 7: Solid tumors other than the above. Cohort 7a enrolled patients with Erdheim Chester disease (ECD) and Langerhans cell histiocytosis (LCH). Patients with BRAF V600 mutation-positive cancers were identified through mutation analysis assays as routinely performed at each participating site according to their local procedure.

The primary objectives of the study were to evaluate the efficacy of vemurafenib in patients with cancers harboring BRAF V600 mutations as response rate (RR) at Week 8 determined by the Investigator using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST, version 1.1) or International Myeloma Working Group (IMWG) uniform response criteria and to identify tumor types for further development.

The primary efficacy endpoint is response rate at Week 8, as assessed by the Investigator using RECIST, version 1.1 for patients with solid tumors. Responders at Week 8 will be defined based on tumor assessment status of complete response (CR) or Partial response (PR) at Week 8.

The study main eligibility criteria included patients with histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) that harbor a BRAF V600 mutation and were refractory to standard therapy or for which standard or curative therapy did not exist or were not considered appropriate by the Investigator. Additional inclusion criteria for patients with ECD and ECD/LCH (Cohort 7a) included patients with non-measurable disease according to RECIST v1.1 if in the opinion of the Investigator the tumor response were reliably morphologically evaluated. Patients with concurrent ECD and LCH and patients with ECD and/or LCH and active or untreated CNS involvement were also eligible.

Patients were to receive continuous oral doses of vemurafenib 960 mg twice daily. For each of the cohorts, the study was divided into two stages. Stage I of the study was complete when 7 patients with measurable disease were enrolled and completed a minimum of 8 weeks of treatment, developed progressive disease (PD), were prematurely withdrawn from the study, or died, whichever occurred first. Dependent upon the response rate of patients completing Stage I, more patients could be enrolled to Stage II. The study consists of a Screening Period, a Treatment Period, an End of Treatment Visit occurring when study medication is discontinued for any reasons, a Safety Follow-Up Visit occurring 28 days after the last dose of study medication and a Survival Follow-Up Period lasting for a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent, or are lost to follow-up (whichever occurs first) to monitor survival status.

The study enrolled 208 subjects from 25 clinical sites in United States, France, Spain, Germany, and the United Kingdom. Cohort 7a included 22 patients with ECD and 4 patients with LCH. The study enrolled the first patient on April 11, 2012 and the last patient completed the last study visit on October 27, 2016. The database cut-off date of the submission was January 12, 2017.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
David Hyman, MD David Solit, MD Memorial Sloan-Kettering Cancer Center 300 East 66 th Street, Box 22 New York, NY 10065	Site# 244213 Protocol MO28072 Subjects=15	July 27, 28, 31, and August 1, 2017	Pending Preliminary classification VAI

Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

David Hyman, M.D. and David Solit, MD (Site# 244213, New York, NY)

The site screened 49 subjects and enrolled 47 subjects including the (b) (6) subjects with ECD for Study Protocol MO28072. An audit of all (b) (6) subjects' records with ECD was conducted. Among the (b) (6) subjects with ECD, (b) (6) subjects completed the study, and (b) (6) subjects discontinued from the study. The reasons for discontinuations in (b) (6) subjects were withdrawal by subject (b) (6), lost to follow-up ((b) (6) and (b) (6) (b) (6)). The discontinuation data listing provided in the NDA was verified by review of source documents during the inspection.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, electronic files, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint as requested were verifiable at the study site. No under-reporting of serious adverse events were noted.

However, the following observations were noted with a Form FDA 483 issued by the field investigator:

1. Failure to report promptly to the sponsor adverse events that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

Specifically, the following adverse events were documented in subject source records, but were not recorded in the subjects' electronic data capture (EDC)/electronic case report forms (eCRF's):

- Subject (b) (6) sore throat
- Subject (b) (6) dizziness
- Subject (b) (6) diarrhea and akathisia

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, some concomitant medications including pain medication, antibiotics, or sleeping medications were not included in eCRFs for (b) (6) subjects (b) (6)

3. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, protocol-required procedures were not followed for (b) (6) subjects for timely reporting of serious adverse events. According to the IRB-approved study protocol, any serious adverse event or non-serious adverse event of special interest must be reported to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following deviations from the protocol were observed:

- Subject (b) (6): Squamous cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this serious adverse event (SAE) on (b) (6), via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Keratocanthoma was noted in this subject's source records with a date of onset of (b) (6). This SAE was reported on (b) (6). Gangliocytic paraganglioma was also noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Basal cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6). Basal cell carcinoma was noted an additional time in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Squamous cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Basal cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6).

OSI Reviewer's comments:

The above observations were shared with DHP. The underreported adverse events were considered to be non-serious adverse events and the missed concomitant medications are supportive medications. For tumor adverse event reporting, most events were reported within 1 or 2 weeks after the site received the pathology reports except one event was reported 3 month

later. These observations appear unlikely to have significant impact on the overall efficacy and safety of the study.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the above observations. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

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