DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114/S-004

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT/COMMITMENT

Novartis Pharmaceuticals, Corporation
Attention: Amita Chaudhari, M.Sc.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Chaudhari:

Please refer to your supplemental New Drug Application (sNDA) dated May 22, 2015, received May 22, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Mekinist (trametinib) tablets; 0.5 mg, 2.0 mg.

This "Prior Approval" supplemental new drug application provides regular approval of trametinib, in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test and to remove the statement from the currently approved indication "This indication is based on the demonstration of durable response rate [see Clinical Studies (14.1)]. Improvement in disease-related symptoms or overall survival has not been demonstrated for MEKINIST in combination with dabrafenib."

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the 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 titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

SUBPART H FULFILLED

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills the below postmarketing requirement (PMR) made under 21 CFR 314.510.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) 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.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated May 22, 2015, containing the final report for the following postmarketing requirement listed in the January 9, 2015, approval letter.

2117-1 To submit an efficacy supplement containing the final report, including summary analyses, datasets, and revised labeling based on the results of the ongoing MEK115306 trial, "A Phase III, Randomized, Double-Blinded Study, Comparing the Combination of the BRAF inhibitor, Dabrafenib and the MEK inhibitor, Trametinib to Dabrafenib and Placebo as First-Line Therapy in Subjects with unresectable (Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-Positive Cutaneous Melanoma." Enrollment of approximately 340 patients is expected. The primary endpoint is progression-free survival. Overall survival is a key secondary endpoint.

We have reviewed your submission and conclude that the above requirement was fulfilled.

FULFILLMENT OF POSTMARKETING COMMITMENT

Postmarketing Commitment Subject to Reporting Requirements Under Section 506B

2117-2 Complete and submit the final report, including datasets, for the ongoing MEK116513 trial, "A Phase III, Randomised, Open-Label Study Comparing the Combination of the BRAF Inhibitor Dabrafenib and the MEK Inhibitor Trametinib to the BRAF Inhibitor Vemurafenib in Subjects with Unresectable (Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-Positive Cutaneous Melanoma." Enrollment of approximately 694 patients is expected. The primary endpoint is overall survival.

We have reviewed your submission and conclude that the above commitment was fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our January 8, 2014, letter. We also remind you that there are postmarketing requirements listed in our May 29, 2013, approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call Norma Griffin, Lead Regulatory Health Project Manager, at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
11/20/2015