DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202429

NDA APPROVAL

Hoffmann-La Roche Inc.
Attention: Linda J. Burdette, Ph.D.
Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Burdette:

Please refer to your New Drug Application (NDA) dated April 27, 2011, received April 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zelboraf (vemurafenib) Tablet, 240mg.

We acknowledge receipt of your amendments dated April 28; May 6, 17, 23, 27 (2); June 1 (2), 2, 3, 7, 14, 15, 20, 22, 24, 30 (3); July 5, 11, 12, 15, 19 (3), 20, 25, 29; August 3, 4, 5, 8, and 11, 2011.

This new drug application provides for the use of Zelboraf (vemurafenib) Tablet, 240 mg for the treatment of unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation as detected by an FDA-approved test.

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 text.

Based on the stability data provided in your application, the drug product is granted a twelve (12) month expiry when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF). As agreed, validation batches M0020, M0021 and M0022 only are granted a twenty-four (24) month expiry at USP controlled room temperature provided you submit quarterly (every three months) stability updates for these three batches, as general correspondences to the NDA, through the 24-month expiry.

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, Medication Guide). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202429**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Zelboraf (vemurafenib) Tablet was not referred to an FDA advisory committee because the benefit/risk profile of Zelboraf (vemurafenib) Tablet is clearly favorable for the proposed indication.

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.

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 identify unexpected serious

risks from the effects of inhibition of human CYP2C8 and CYP2B6 by Zelboraf (vemurafenib) Tablet.

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 this serious risk.

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

1803-1 Perform an *in vitro* screen to determine if vemurafenib is an inhibitor of human CYP2C8 and CYP2B6. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

The timetable you submitted on July 19, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2011
Study Completion Date:	01/2012
Final Report Submission:	03/2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks from longer duration of exposure to Zelboraf (vemurafenib) Tablet, an increase in secondary malignancies with Zelboraf (vemurafenib) Tablet, drug-drug interactions with Zelboraf (vemurafenib) Tablet, and the effect of severe hepatic impairment on the pharmacokinetics of Zelboraf (vemurafenib) Tablet.

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

1803-2 Submit the final analysis of safety in the ongoing trial (Protocol NO25026:BRIM3) to provide the potential for new safety signals from longer duration of exposure.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2009 (submitted)
Trial Completion Date:	03/2014
Final Report and Datasets Submission:	10/2014

1803-3 Submit an analysis of secondary malignancies for the proposed adjuvant melanoma trial [G027826: Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically-Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence] annually and one year after the last patient has completed clinical trial treatment.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	08/2011
Final Protocol Submission:	02/2012
Interim Report Submission:	02/2013
Interim Report Submission:	02/2014
Interim Report Submission:	02/2015
Interim Report Submission:	02/2016
Interim Report Submission:	02/2017
Trial Completion Date:	03/2017
Final Report Submission:	09/2017

1803-4 Follow-up for secondary malignancies from the planned papillary thyroid cancer trial [N025530: An Open-Label, Multi-Center Phase II Study of the BRAF Inhibitor RO5185426 in Patients with Metastatic or Unresectable Papillary Thyroid Cancer (PTC) positive for the BRAF V600 Mutation and Resistant to Radioactive Iodine] annually and one year after the last patient has completed clinical trial treatment.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Protocol amendment* submission:	11/2011
**Study NO25530 is ongoing*	
Interim Report Submission:	11/2012
Interim Report Submission:	11/2013
Interim Report Submission:	11/2014
Interim Report Submission:	11/2015
Trial Completion Date:	08/2015
Final Report Submission:	02/2016

1803-5 Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of vemurafenib.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	02/2012
Final Protocol Submission:	07/2012
Trial Completion Date:	04/2014
Final Report and Datasets Submission:	10/2014

1803-6 Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of vemurafenib.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	02/2012
Final Protocol Submission:	07/2012
Trial Completion Date:	04/2014
Final Report and Datasets Submission:	10/2014

1803-7 Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	05/2012
Final Protocol Submission:	09/2012
Trial Completion Date:	02/2017
Final Report and Datasets Submission:	08/2017

Submit the protocols to your IND 073620, with a cross-reference letter to this NDA. Submit 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:

1803-8 Submit updated overall survival results from the ongoing trial (Protocol NO25026:BRIM3) with a minimum follow-up of 24 months after the last patient was enrolled into the trial.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule

Final Protocol Submission:	09/2009 (submitted)
Trial Completion Date:	12/2012
Final Report and Datasets Submission:	07/2013

1803-9 Develop an Investigational Use Only, Companion Diagnostic (IUO CoDx) that reliably detects V600K BRAF mutation in patients with unresectable or metastatic melanoma and conduct an open-label single arm trial with overall response rate and duration of response as the primary endpoints in this population as determined by the diagnostic test.

The timetable you submitted on July 19, 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	06/2012
Final Protocol Submission*:	10/2012
**To coincide with completion of 1 year prework for IUO development*	
Trial Completion Date:	01/2015
Final Report Submission:	07/2015

1803-10 Assess changes in NRAS mutation status at both baseline and disease progression in biopsy accessible lesions in patients with advanced melanoma positive for the V600E BRAF mutation who have been treated with vemurafenib. This assessment should include all patients with available biopsy specimens and may be derived from completed and ongoing trials [see below for trial ID number and title*] in patients treated with vemurafenib.

*PLX06-02: A Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX4032 in Patients with Solid Tumors
*NP22657: An Open-Label, Multi-Center, Phase II Study of Continuous Oral Dosing of RO5185426 in Previously Treated Patients With Metastatic Melanoma
*NO25026: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine

*NP25163: A Phase I, Randomized, Open-label, Multi-center, Multiple Dose Study to Investigate the Pharmacokinetics and Pharmacodynamics of RO5185426 Administered as 240 mg Tablets to Previously Treated BRAF V600E Positive Metastatic Melanoma Patients

*NP25396: A Phase I, Randomized, Open-label, Multi-center, Two Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960 mg RO5185426 Twice Daily to $BRAF^{V600E}$ Positive Metastatic Melanoma Patients

The timetable you submitted on July 19, 2011 states that you will conduct these trials according to the following schedule:

Trial Completion Date:	05/2012
Final Report Submission:	09/2012

Submit clinical protocols to your IND 73620 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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 package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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 Theresa Ferrara, Regulatory Project Manager, at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
08/17/2011