



NDA 206192

NDA APPROVAL

Genentech, Inc.
Attention: Sarah Wayson, Ph.D.
Regulatory Program Management
One DNA Way, MS 241A
South San Francisco, CA 94080-4990

Dear Dr. Watson:

Please refer to your New Drug Application (NDA) dated December 11, 2014, received December 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cotellic (cobimetinib), tablet for oral use, 20 mg.

We also refer to our approval letter dated November 10, 2015, which contained the following errors: the postmarketing requirement 2996-2 replaced the phrase “randomized controlled clinical trials using cobimetinib” with “randomized controlled and open label clinical trial(s) using cobimetinib” as the open label language was inadvertently not included.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain November 10, 2015, the date of the original approval letter.

We acknowledge receipt of your amendments dated December 19, 2014; December 23, 2014; January 6, 2015; January 8, 2015(2); February 2, 2015; February 4, 2015; February 6, 2015; February 10, 2015; February 18, 2015 (2); March 2, 2015; March 10, 2015; March 12, 2015; March 16, 2015; March 18, 2015; March 19, 2015; March 23, 2015; March 30, 2015 (2); April 1, 2015; April 6, 2015 (2); April 8, 2015; April 30, 2015; May 7, 2015; May 8, 2015; May 14, 2015 (2); May 15, 2015; May 19, 2015; May 22, 2015; May 27, 2015; June 8, 2015; June 15, 2015; July 1, 2015; October 13, 2015; October 16, 2015; October 27, 2015; October 29, 2015; October 30, 2015; November 2, 2015 (2); November 3, 2015, November 4, 2015; November 5, 2015 (2); November 6, 2015 (2); and November 9, 2015 (3).

This new drug application provides for the use of COTELLIC for the treatment, of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib. COTELLIC is not indicated for treatment of patients with wild-type BRAF melanoma

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 text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, 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 patient package insert). 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 immediate container labels that are identical to the enclosed carton and immediate container labels submitted on November 6, 2015, 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 *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 206192.**” 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.

Please submit one market package of the drug product when it is available to the following address:

Meredith Libeg
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2326
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** if shipping via United States Postal Service (USPS).
Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

DATING PERIOD

The shelf life for Cotellic shall be 30 months when stored below 30°C (86°F).

ADVISORY COMMITTEE

Your application for COTELLIC was not referred to an FDA advisory committee because this drug is not the first in its class; the safety profile is similar to that of other drugs approved for this indication; the clinical trial design is acceptable; and the evaluation of the safety data when used in the treatment of BRAF V600 mutation positive metastatic melanoma did not raise significant safety or efficacy issues that were unexpected in the intended population, and outside expertise was not necessary.

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 assess a known serious risk of ocular toxicity with Cotellic (cobimetinib) tablets, and assess a signal of a serious risk of toxicity from drug over-exposure due to impaired hepatic function on the pharmacokinetics of Cotellic (cobimetinib) tablets.

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 these serious risks.

Finally, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to assess a known serious risk of ocular toxicity with Cotellic (cobimetinib) tablets, and assess a signal of a serious risk of toxicity from drug over-exposure due to impaired hepatic function on the pharmacokinetics of Cotellic (cobimetinib) tablets.

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

2996-1 Complete a clinical pharmacokinetic trial to determine the appropriate dose of cobimetinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on November 9, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 30, 2016

2996-2 Provide integrated safety analyses from an adequate number of randomized controlled and open label clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alteration required to minimize the impact of retinal pigmented epithelial detachments. This will include safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

The timetable you submitted on November 9, 2015, states that you will conduct this analysis according to the following schedule:

Final Proposal Submission: December 31, 2016
Trial Completion Date: September 30, 2020
Final Report Submission: December 31, 2020

Submit the protocol(s) to your IND 109307, with a cross-reference letter to this NDA. Submit all final report(s) 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:

2996-3 Submit the clinical report at the time of the final analysis of Trial GO28141, A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus Cobimetinib (GDC-0973) in Previously Untreated BRAFV600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma (coBRIM) to update the label with mature overall survival data.

The timetable you submitted on November 9, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 30, 2016

Submit clinical protocols to your IND 109307 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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 study 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, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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>).

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. 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).

OTHER COMMITMENTS

In accordance with your submission on November 9, 2015, we remind you to submit to CDRH by June 30, 2016, a PMA supplement for the FDA-approved Roche cobas 4800 BRAF Mutation test, to revise the instructions for use to include an updated indications for use statement and updated clinical section to reference the detection of V600K mutations in the trial that supported the FDA approval of cobimetinib with vemurafenib for patients with unresectable or metastatic melanoma with BRAF V600E and V600K mutations.

Submission Timeline: June 30, 2016

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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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 within two weeks of receipt of this communication.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Meredith Libeg, Senior Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

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

Enclosure(s):
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
11/10/2015

¶