DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203388/S-005
NDA 203388/S-006
NDA 203388/S-007
NDA 203388/S-008

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENT

Genentech, Inc.
Attention: Moema Fernandes, Pharm.D.
Regulatory Program Management
1 DNA Way, MS 241-B
South San Francisco, CA 94080

Dear Dr. Fernandes:

Please refer to your Supplemental New Drug Applications (sNDAs) for supplements 5, 6, 7 and 8 dated November 21, 2014, received November 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Erivedge® (vismodegib) capsule, 150 mg.

We acknowledge receipt of your amendments to supplements 5, 6, 7 and 8 dated March 12, 2015, April 13, 2015, May 6, 2015, May 19, 2015, and May 20, 2015.

Supplement 5: This "Prior Approval" supplemental new drug application provides for an update to the HIGHLIGHTS OF PRESCRIBING INFORMATION, Boxed Warning, WARNINGS AND PRECAUTIONS, Embryo-Fetal Toxicity (5.1), Blood Donation (5.2), Semen Donation (5.3), USE IN SPECIFIC POPULATIONS, Pregnancy (8.1), Lactation (8.2), Females and Males of Reproductive Potential (8.3) and Hepatic Impairment (8.7), and CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3), and PATIENT COUNSELING INFORMATION subsections of the package insert, to incorporate the results from study GP27839 entitled, "A Phase Ib, Open-Label Pharmacokinetics and Safety Study of the Hedgehog Pathway Inhibitor Vismodegib in Patients with Advanced Solid Malignancies Including Hepatocellular Carcinoma with Varying Degrees of Renal or Hepatic Function," in fulfillment of PMR 1862-4. This supplement also provides for an update to the semen information in the medication guide with the results from study GP27839.

Supplement 6: This "Prior Approval" supplemental new drug application proposed to update the ADVERSE REACTIONS, Clinical Trial Experience (6.1) subsection of the package insert and to list the most common side effects in the medication guide. FDA determined that there was insuffient information to support the requested changes to section 6.1, so the proposed edits to this section were rejected. However, the list of the most common side effects was updated to include information on amenorrhea in the medication guide.

Supplement 7: This "Prior Approval" supplemental new drug application provides for an update to the DRUG INTERACTIONS, and the CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3) subsections of the package insert to incorporate the results from study GP28465, entitled, "A Clinical Drug-Drug Interaction Study to Evaluate the Effect of a Proton Pump Inhibitor, a Combined P-gp/CYP3A4 Inhibitor, and a CYP2C9 Inhibitor on the Pharmacokinetics of Vismodegib," in fulfillment of PMR 1862-7.

Supplement 8: This "Prior Approval" supplemental new drug application provides for an update to the USE IN SPECIFIC POPULATIONS, Renal Impairment (8.8) and the CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3) subsections of the package insert, to include the latest clinical pharmacology data and other data previously submitted on October 11, 2013 in support of the release from PMR 1862-5.

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 and with the minor editorial revision listed below.

> Removed "at least" from the HIGHLIGHTS OF PRESECRIBING INFORMATION, Warnings and Precautions, Blood Donation subsection to maintain consistency with the Full Prescribing Information.

WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015.

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, text for the Medication Guide), 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).

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 none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have also reviewed the results from study GP27839, submitted with supplement 5 to fulfill PMR 1862-4, and study GP28465, submitted with supplement 7 to fulfill PMR 1862-7. Postmarketing Requirements 1862-4 and 1862-7 are listed in the January 30, 2012, approval letter, as:

1862-4 To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function–Study Design, Data Analysis and Impact on Dosing and Labeling". The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the trial should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

1862-7 To conduct a drug-drug interaction clinical trial in healthy volunteers to evaluate if gastric pH elevating agents alter the bioavailability and impact the steady-state exposure of vismodegib. The trial may be conducted in a gated manner, first evaluating the effect of proton pump inhibitors (PPIs) on the steady state exposure of vismodegib. In the event that concomitant administration of PPIs has a large impact on vismodegib steady state exposure, H2 antagonists and antacids will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect PK differences. The trial results should allow for a determination on how to dose vismodegib with regard to gastric pH elevating agents.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that there are still postmarketing requirements and commitments listed in the January 30, 2012, approval letter that are 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Ms. Karen Boyd, Senior Regulatory Project Manager, at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Jeffery Summers, M.D.
Deputy Director for Safety
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/

JEFFERY L SUMMERS
05/21/2015