NDA 213721/S-011

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENTS/COMMITMENT

Genentech, Inc.
Attention: Ruina Li, M.S.
Regulatory Program Management
1 DNA Way MS# 451A
South San Francisco, CA 94080-4990

Dear Ms. Li:

Please refer to your supplemental new drug application (sNDA) dated and received February 1, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for GAVRETO (pralsetinib) capsule.

This Prior Approval sNDA provides for updates related to use with (CYP)3A and P-gp inhbibitors and CYP3A inducers (Sections 2.4, 2.5, 7.1 and 12.3) in the U.S. Prescribing Information label and Patient Information.

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.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 (which includes new salts and new fixed combinations), 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 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/COMMITMENT

We have received your submission dated February 1, 2023, reporting on the following postmarketing requirements/commitment listed in the September 4, 2020, (NDA 213721), and December 1, 2020, (NDA 214701) approval letters.

3916-2 Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of a moderate CYP3A inhibitor on the pharmacokinetics of pralsetinib, assess the magnitude of increased pralsetinib exposure, and inform appropriate dosing strategies for safe coadministration of pralsetinib with moderate CYP3A inhibitors. Design and conduct the study in accordance with the FDA Guidances for Industry titled, "*In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" and Physiologically Based Pharmacokinetic Analyses – Format and Content*". Submit the model with the final report. The results from this study may inform product labeling.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3916-3 Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of a combined P-gp and moderate CYP3A inhibitor on the pharmacokinetics of pralsetinib, assess the magnitude of increased pralsetinib exposure, and inform appropriate dosing strategies for safe coadministration of pralsetinib with combined Pgp and moderate CYP3A inhibitors. Design and conduct the study in accordance with the FDA Guidances for Industry titled, "*In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions and Physiologically Based Pharmacokinetic Analyses – Format and Content*". Submit the model with the final report. The results from this study may inform product labeling.

3916-5 Conduct a clinical drug-drug interaction study to evaluate the effect of repeat doses of a P-gp inhibitor on the pharmacokinetics of pralsetinib and to inform appropriate dosing strategies for safe coadministration of pralsetinib with P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled: "*Clinical Drug Interaction Studies - Cytochrome P450 Enzyme and Transporter-Mediated Drug Interactions". Submit the datasets with the final report. The results from this study may inform product labeling.*

3916-10 Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of a moderate CYP3A inducer on the pharmacokinetics of pralsetinib, assess the magnitude of decreased pralsetinib exposure, and inform appropriate dosing strategies for coadministration of pralsetinib with moderate CYP3A inducers. Design and conduct the study in accordance with the FDA Guidances for Industry titled, "*In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" and "Physiologically Based Pharmacokinetic Analyses – Format and Content"* . Submit the model with the final report. The results from this study may inform product labeling.

3959-6 Conduct a rodent fertility study investigating treated male rats (vehicle control and high dose only) mated to untreated female rats to evaluate the potential for pralsetinib to impair male fertility.

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

We remind you that there are postmarketing requirements and postmarketing commitments listed in the September 4, 2020 (NDA 213721), and December 1, 2020 (NDA 214701) approval letters that are still open.

We remind you that accelerated approval PMR 3916-1 listed in the September 4, 2020, approval letter and accelerated approval PMRs 3959-1 and 3959-2 listed in the December 1, 2020, are still open. Pursuant to 21 CFR 314.510 (Subpart H), continued approval of the drug is contingent upon verification and description of clinical benefit and completion of the clinical trial for PMRs 3916-1, 3959-1, 3959-2.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Jacqueline Glen, Regulatory Health Project Manager, at Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO 2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIN A LARKINS
06/30/2023 11:30:49 AM
Supervisory Associate Director as designated signatory authority for Dr. Harpreet Singh