



NDA 213721

ACCELERATED APPROVAL

Blueprint Medicines Corporation
Attention: Megan Sanchez, MPH
Director, Regulatory Affairs
45 Sidney Street
Cambridge, MA 02139

Dear Ms. Sanchez:

Please refer to your new drug application (NDA) dated and received, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gavreto (pralsetinib), 100 mg capsules.

This new drug application provides for the use of Gavreto (pralsetinib) capsules, 100 mg, for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We note that your September 4, 2020, submission includes final printed labeling (FPL) for your Prescribing Information and Patient Package Insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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, text for the Patient Package Insert. Information on submitting

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on August 18, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 213721.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Gavreto was not referred to an FDA advisory committee because this drug is not the first in its class.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 3, 2020. This requirement, along with required completion dates, is listed below.

- 3916-1 Submit the final report, including datasets, from an ongoing clinical trial to verify and further characterize the clinical benefit of pralsetinib for the treatment of patients with 1) treatment-naïve RET fusion-positive NSCLC and with 2) RET fusion-positive NSCLC who have previously received platinum chemotherapy to provide a more precise estimation of the BICR-assessed overall response rate and duration of response after all responders in the population of patients with treatment-naïve NSCLC (approximately 120 patients) have been followed for at least 12 months from the date of initial response (or until disease progression, whichever

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>.

comes first) and after all responders in the population of patients with NSCLC previously treated with platinum therapy (87 patients) have been followed for at least 6 months.

Final Protocol Submission: 07/2020 (completed)

Trial Completion: 04/2022

Final Report Submission: 10/2022

Submit clinical protocols to your IND 143094 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement 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.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(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 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 signal of a serious risk of gastrointestinal perforations and fistulas in patients administered pralsetinib and to determine appropriate dosage adjustments when pralsetinib is co-administered with moderate CYP3A inhibitors and combined P-gp and moderate CYP3A inhibitors.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

- 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.

The timetable you submitted on September 3, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 09/2021
Final Protocol Submission: 12/2021
Study Completion: 06/2022
Final Report Submission: 08/2022

- 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 P-gp 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.

The timetable you submitted on September 3, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 09/2021
Final Protocol Submission: 12/2021
Study Completion: 06/2022
Final Report Submission: 08/2022

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased adverse events of pralsetinib associated gastrointestinal perforations and fistulas and to determine appropriate dose adjustments when pralsetinib is administered to patients with moderate or severe hepatic impairment or coadministered with P-gp inhibitors, substrates of CYP enzymes and transporter substrates.

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

- 3916-4 Conduct a comprehensive analysis evaluating and characterizing the incidence, clinical presentation, management, and outcome of the potential serious risk of pralsetinib associated gastrointestinal perforations and fistulas. Submit an integrated final report containing data from patient-level and pooled analyses of on-going and completed clinical trials, post-marketing reports and/or literature reports and a comprehensive pharmacovigilance assessment for this potential serious risk. The results from this report may inform product labelling.

The timetable you submitted on September 3, 2020, states that you will conduct this trial according to the following schedule:

Final Report Submission: 08/2026

- 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-](#)

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

[Mediated Drug Interactions](#)". Submit the datasets with the final report. The results from this study may inform product labeling.

The timetable you submitted on September 3, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 02/2021
Final Protocol Submission: 05/2021
Study Completion: 12/2021
Final Report Submission: 04/2022

- 3916-6 Conduct a clinical drug interaction study to evaluate the effect of repeat doses of pralsetinib on the pharmacokinetics of transporter substrates of P-gp, BCRP, OATP1B1, OATP1B3, MATE-1, and MATE-2K, assess the magnitude of exposure change, and inform appropriate dosing strategies for coadministration of pralsetinib with these transporter substrates. 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 final report. The results from this study may inform product labeling.

The timetable you submitted on September 3, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 04/2021
Final Protocol Submission: 07/2021
Study Completion: 08/2024
Final Report Submission: 03/2025

- 3916-7 Conduct a clinical drug interaction study to evaluate the effect of repeat doses of pralsetinib on the pharmacokinetics of sensitive substrates of CYP3A4/5, CYP2C8, and CYP2C9, assess the magnitude of exposure change, and inform appropriate dosing strategies for safe coadministration of pralsetinib with sensitive substrates of CYP3A4/5, CYP2C8, and CYP2C9. 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.

The timetable you submitted on September 3, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 04/2021
Final Protocol Submission: 07/2021
Study Completion: 08/2024
Final Report Submission: 03/2025

- 3916-8 Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of pralsetinib in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "[Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling](#)". Submit the datasets with the final report. The results from this trial may inform product labeling.

The timetable you submitted on September 3, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 05/2021
Trial Completion: 03/2024
Final Report Submission: 09/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁴

Submit clinical protocol(s) to your IND 143094 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and 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

⁴ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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:

- 3916-9 Submit the final report including datasets from a multi-center, randomized trial comparing pralsetinib to physician's choice of platinum-based chemotherapy treatment regimens based on standard of care treatment for the first-line treatment of RET fusion-positive, metastatic non-small cell lung cancer. The results from this trial may inform product labeling.

The timetable you submitted on September 3, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2019 (completed)
Trial Completion: 12/2025
Final Report Submission: 06/2026

- 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.

The timetable you submitted on September 3, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 09/2021

Final Protocol Submission: 12/2021

Study Completion: 06/2022

Final Report Submission: 08/2022

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 143094 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 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

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.⁵

⁵ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

REPORTING REQUIREMENTS

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

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.

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert
- Container Labeling

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/

MARC R THEORET
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