DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022068/S-026

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Omer Munir, RPh
Sr. Associate Director, Global Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Munir:

Please refer to your Supplemental New Drug Application (sNDA) dated July 13, 2017, received July 13, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tasigna® (nilotinib) oral capsules; 200mg; 150 mg.

This Prior Approval supplemental new drug application provides for updates to the package insert (PI) with information which allows for eligible patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) who have received Tasigna for a minimum of 3 years and achieved a sustained molecular response (MR4.5) and patients with Ph+ CML-CP resistant or intolerant to imatinib who have received Tasigna for at least 3 years and have achieved a sustained molecular response (MR4.5) to be considered for treatment discontinuation.

## 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.

## WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

## 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 and

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 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 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 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.

Since Tasigna® (nilotinib; AMN107) was approved on October 29, 2007, we have become aware of changes in the risk of resistance for patients who discontinue nilotinib in clinical trials We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 the unexpected serious risk of long-term safety of patients who discontinue Tasigna.

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:

PMR 3323-1 Characterize the risk of relapse after treatment discontinuation of Tasigna in patients who have achieved a molecular response (MR 4.5). Submit final trial reports and datasets for trials CAMN107A2408 and CAMN10712201 with a minimum of 60 months of follow-up.

The timetable you submitted on December 21, 2017 states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Trial Completion (Trial 2408): | 01/2020 |
| Trial Completion (Trial 12201): | 01/2020 |
| Interim (3 year) report 1: | 07/2018 |
| Interim (4 year) report 2: | 06/2019 |
| Final (5 year) Report Submission: | 10/2020 |

PMR 3323-2 Characterize the potential risk of resistance to treatment after discontinuation of Tasigna by collecting and reporting information on late relapses, loss of response, and occurrence of mutations (risk of developing resistance), on a yearly basis from trials CAMN107A2408 and CAMN10712201. Provide gene expression profile information for patients that relapse from treatment-free period compared to patients who relapse on treatment in the 5-year trial reports. Submit annual summaries with the annual post-marketing reporting and submit cumulative 3, 5, and 10 year reports.

The timetable you submitted on December 21, 2017 states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission (amendment) Trial A2408: | 05/2018 |
| Draft Protocol Submission (amendment) Trial I2201: | 05/2018 |
| Final Protocol Submission (amendment) Trial A2408 Submission: | 01/2019 |
| Final Protocol Submission (amendment) Trial I2201 Submission: | 01/2019 |
| Interim follow-up report 1 (year 3): | 07/2018 |
| Interim follow-up report 2 (year 4): | 06/2019 |
| Interim follow-up report 3 (year 5): | 10/2020 |
| Interim follow-up report 4 (year 6) | 10/2021 |
| Interim follow-up report 5 (year 7): | 10/2022 |
| Interim follow-up report 6 (year 8): | 10/2023 |
| Interim follow-up report 7 (year 9): | 10/2024 |
| Extension Trial Completion (Trial A2408): | 02/2025 |
| Extension Trial Completion (Trial I2201): | 02/2025 |
| Final Report (10 year) Submission: | 02/2026 |

PMR 3323-3 Characterize safety for patients who are still in remission or experienced loss of major molecular response and restarted Tasigna in trials CAMN107A2408 and CAMN10712201. Assess mortality, late adverse events, incidence of pancreatitis, diabetes, arterial vascular disease, and other comorbid conditions. Submit annual summaries with the annual post-marketing reporting and submit cumulative 3, 5, and 10 year reports.

The timetable you submitted on December 21, 2017 states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission Trial A2408 (amendment): | 05/2018 |
| Draft Protocol Submission Trial I2201 (amendment): | 05/2018 |
| Final Protocol Submission Trial A2408(amendment): | 01/2019 |
| Final Protocol Submission Trial I2201 (amendment): | 01/2019 |
| Interim follow-up report 1 (year 3): | 07/2018 |
| Interim follow-up report 2 (year 4): | 06/2019 |
| Interim follow-up report 3 (year 5) | 10/2020 |
| Interim follow-up report 4 (year 6): | 10/2021 |
| Interim follow-up report 5 (year 7): | 10/2022 |
| Interim follow-up report 6 (year 8): | 10/2023 |
| Interim follow-up report 7 (year 9): | 10/2024 |
| Extension Trial Completion (Trial A2408): | 02/2025 |
| Extension Trial Completion (Trial I2201): | 02/2025 |
| Final Trial Report Submission: | 02/2026 |

Submit the protocol(s) to your IND 69764, with a cross-reference letter to this NDA/. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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.

## 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:

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

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.

## 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 Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

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/s/

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ALBERT B DEISSEROTH
12/22/2017