NDA 202806/S-025

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENT

Novartis Pharmaceuticals Corporation
Attention: Carolyn Zhu, Pharm.D.
Senior Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Zhu:

Please refer to your supplemental new drug application (sNDA) dated and received August 24, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tafinlar (dabrafenib) capsules.

We acknowledge receipt of your major amendment dated January 19, 2023, which extended the goal date by three months.

This Prior Approval sNDA provides for the use of Tafinlar (dabrafenib) capsules for the treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information 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 *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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated August 24, 2022, reporting on the following postmarketing requirement listed in the June 22, 2022, approval letter.

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

4298-2 Develop age appropriate pediatric formulations (dabrafenib dispersible tablets for oral suspension, and trametinib powder for oral solution), and evaluate these in Study CDRB436G2201 (“Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)”).

4298-3 Conduct Study CDRB436G2201 (“Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma [HGG]”) to confirm safety and efficacy in pediatric patients with glioma one year of age and above.

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

We remind you that there is a postmarketing requirement and a postmarketing commitment listed in the June 22, 2022, approval letter that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 the known serious risks of new primary malignancies, cardiomyopathy, and ocular toxicities and identify the unexpected serious risks of long-term adverse effects on growth and development including growth plate abnormalities in pediatric patients.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these known serious risks, and to identify these unexpected serious risks.

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

4424-1 Conduct comprehensive safety analyses from ongoing trials to further assess the serious risks of dabrafenib in combination with trametinib, including but not limited to new primary malignancies (cutaneous and non-cutaneous), cardiomyopathy, and ocular toxicities, in pediatric patients with BRAFV600E mutant low grade glioma over a sufficient period of follow-up time to further characterize these risks. The report should include appropriate monitoring and risk mitigation strategies.

The timetable you submitted on March 15, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	09/2023
Final Protocol Submission (Analysis Plan):	12/2023
Study Completion:	11/2026
Final Report Submission:	05/2027

4424-2 Conduct an integrated safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects including but not limited to growth plate abnormalities of dabrafenib in combination with trametinib on growth and development in a sufficient number of pediatric patients. Monitor patients for growth and development using age-appropriate screening tools. Include evaluations of growth as measured by height, weight, height velocity and height standard deviation scores, age at menarche if applicable (females) and Tanner stage. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

The timetable you submitted on March 15, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	09/2023
Final Protocol Submission (Analysis Plan):	12/2023
Trial Completion:	11/2026
Final Report Submission:	05/2027

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]

Submit clinical protocol(s) to your IND 117898 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

[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.

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:

4424-3 Complete Study CDRB436G2201, entitled “Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)”, and provide the final analysis for overall survival (OS) and progression free survival once all patients with LGG have been followed for at least 2 years. Include an analysis of change in visual acuity over the course of treatment with dabrafenib and trametinib for patients who enrolled on the study due to impaired vision.

The timetable you submitted on March 15, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	03/2023
Final Protocol Submission (Analysis Plan):	04/2023
Study Completion:	04/2023
Final Report Submission:	10/2023

Submit the datasets with the final report submission.

4424-4 Commitment to support the availability of an in vitro diagnostic device, through an appropriate analytical and clinical validation study using clinical trial data that demonstrates the device is essential to the safe and effective use of dabrafenib in combination with trametinib (D+T) for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

The timetable you submitted on March 15, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2025

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 117898 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/subjects 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. 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.*[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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

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).

If you have any questions, call Raniya Ali Al-Matari, Regulatory Health Project Manager, at 301-796-1755.

Sincerely,

{See appended electronic signature page}

Nicole Drezner, M.D.
Acting Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

NICOLE L DREZNER
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