BLA 761128

BLA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Amanda Bright, PharmD
Global Program Regulatory Manager
One Health Plaza, Bldg. 337
East Hanover, NJ 07936

Dear Dr. Bright:

Please refer to your biologics license application (BLA) dated May 16, 2019, received May 16, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for ADAKVEO® (crizanlizumab-tmca) injection, for intravenous use.

LICENSING

We have approved your BLA for ADAKVEO (crizanlizumab-tmca) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ADAKVEO under your existing Department of Health and Human Services U.S. License No. 1244. ADAKVEO is indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture crizanlizumab-tmca drug substance at Novartis Pharma AG in Basel, Switzerland. The final formulated drug product will be manufactured, filled, labeled, and packaged at Novartis Pharma Stein AG in Stein, Switzerland. You may label your product with the proprietary name, ADAKVEO, and market it at a strength of 100 mg per 10 mL (10 mg/mL) in a single-dose vial for injection.

DATING PERIOD

The dating period for ADAKVEO shall be 15 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4).

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ADAKVEO to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of ADAKVEO, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

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, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert). 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 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 November 1, 2019, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761128**." Approval of this submission by FDA is not required before the labeling is used.

[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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ADVISORY COMMITTEE

Your application for ADAKVEO was not referred to an FDA advisory committee because the evaluation of the application did not raise significant safety or efficacy issues that were unexpected in the intended population.

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(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 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 a signal of serious risk of neutralizing antibodies activity associated with use of crizanlizumab-tmca.

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 studies:

3741-1 Develop and validate a neutralizing antibody assay (NADA) to test confirmed anti-drug antibody positive samples from studies CSEG101 A2102, A2202 and A2301. The assay should be capable of detecting

NADA responses in the presence of crizanlizumab levels that are expected to be present in the serum at time of subject sampling.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Final Report Submission: 12/2020

3741-2 Assess neutralizing anti-drug antibody (NADA) responses with a validated NADA assay. NADA response will be evaluated in all confirmed ADA positive samples from studies CSEG101 A2102, A2202 and the primary analysis of A2301.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Study Completion: 12/2025
Final Report Submission: 12/2025

Provide a final report and include information on the level of crizanlizumab in each sample at each sampling point.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of infusion related reactions and of immunogenicity, and signals of serious risk of bleeding complications and infections

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

3741-3 Complete Study A2202: Phase 2 Multicenter, Open-Label Study to Assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/Hydroxycarbamide, in Sickle Cell Patients with Vaso-Occlusive Crisis (SOLACE-adults) and evaluate the serious risks of infusion related reactions, bleeding complications, and infections.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Interim Report (Primary Analysis Report): 12/2019
Trial Completion: 06/2025
Final Report Submission: 12/2025

In the primary analysis report include an updated evaluation of infusion related reactions, effects on hemostasis, bleeding complications, and infection.

In the final report submission, include full summary analysis (updated description of safety and efficacy data) and datasets at the time of the final report submission or earlier if trial is completed earlier.

3741-4 Complete Study B2201: Phase II, Multicenter, Open-label study to Access Appropriate Dosing and to Evaluate Safety of Crizanlizumab, with or without Hydroxyurea in Sequential, Descending Age Groups of Pediatric Sickle Cell Disease Patients with Vasoocclusive Crises and evaluate the serious risks of infusion related reactions, bleeding complications, and infections.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Interim Report (Primary Analysis Report):	03/2023
Trial Completion:	06/2025
Final Report Submission:	12/2025

In the primary analysis report include an updated evaluation of infusion related reactions, bleeding complications, and infection, and any information on efficacy.

In the final report submission, include full summary analysis (updated description of safety and efficacy data) and datasets at the time of the final report submission.

3741-5 Complete Study A2301 of Crizanlizumab in Adolescents and Adults (≥ 12 years of age), a randomized, comparative dose study that compares 7.5 mg/kg dosing and 5.0 mg/kg dosing versus placebo. Assess the serious risks of infusion related reactions, bleeding complications, and infections.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Interim Report (Primary Analysis Report):	12/2025
Trial Completion:	06/2029
Final Report Submission:	12/2029

In the primary analysis report include an updated evaluation of infusion related reactions, bleeding complications, and infection, and any information on efficacy.

In the final report submission, include full summary analysis (updated description of safety and efficacy data) and datasets at the time of the final report submission.

3741-6 Assess immunogenicity of crizanlizumab, including anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) in all crizanlizumab-treated subjects in Study A2301. Evaluate the effect of immunogenicity on pharmacokinetics, pharmacodynamics, safety and efficacy of crizanlizumab.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Trial Completion:	12/2025
Final Report Submission:	12/2025

In the primary analysis report include the complete immunogenicity data set, information on the drug product lots administered to each patient, the ADA status and titers, the NADA status and the level of each patient's test sample at the specific sampling point.

Submit clinical protocol(s) to your IND 110752 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. 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 601.70 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 601.70 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 601.70. 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:

3741-7 Demonstrate whether crizanlizumab induces myeloid cell-dependent effector functions using (b) (4) If cell-dependent effector functions are identified as confirmed or potential activities for crizanlizumab, develop and implement an appropriate control strategy, that monitors antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Final Report Submission: 02/2020

3741-8 Submit an Integrated Summary of Immunogenicity that describes the totality of the immunogenicity program, as recommended in Section VIII Documentation of the 2019 FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection.

The timetable you submitted on November 14, 2019 states that you will conduct this trial according to the following schedule:

Study Completion: 12/2025
Final Report Submission: 12/2025

Submit the ISI report to eCTD Section 5.3.5.3 Reports of Analysis of Data from More than One Study

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3741-9 Perform real-time shipping validation studies, per "(b) (4) ", to support the stability of crizanlizumab drug product vials from the drug product manufacturing facility in Switzerland to the US.

The timetable you submitted on November 14, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2020

3741-10 Re-evaluate and, as applicable, revise the release and stability specifications for crizanlizumab drug substance (DS) and drug product (DP) based on the product quality attribute test results of clinical batches used in clinical studies.

The timetable you submitted on November 14, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2025

3741-11 Develop an endotoxin detection method capable of detecting endotoxin from crizanlizumab DP release samples.

The timetable you submitted on November 14, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2020

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 110752 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. 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**."

REQUEST FOR SUPPLEMENT

Revise the label for ADAKVEO label to include the updated immunogenicity information at the time of the final report submission for PMC 3741-8.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Patient Package Insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[5] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[6]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

[6] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Michael Gwathmey, Regulatory Project Manager, at (301) 796-8498.

Sincerely,

{See appended ele9ctronic signature page}

Marc R. Theoret, MD
Deputy Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or 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/

MARC R THEORET
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