BLA 761315

BLA APPROVAL

Novo Nordisk Inc.
Attention: Ge (Larry) Bai, PhD
Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Dr. Bai:

Please refer to your biologics license application (BLA) dated and received August 24, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Alhemo (concizumab-mtci) injection.

We acknowledge receipt of your resubmission dated June 20, 2024, which constituted a complete response to our April 24, 2023, action letter.

LICENSING

We have approved your BLA for Alhemo (concizumab-mtci) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Alhemo, under your existing Department of Health and Human Services U.S. License No. 1261. Alhemo is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and hemophilia B (congenital factor IX deficiency) with FIX inhibitors.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture concizumab-mtci drug substance (b) (4). The final formulated drug product will be manufactured and filled at Novo Nordisk A/S, Kalundborg, Denmark, (FEI: 3002807751) and assembled, labelled and packaged at Novo Nordisk A/S, Værlose, Denmark (FEI: 3015545250). You may label your product with the proprietary name, Alhemo, and market it in the following:

- 60 mg/1.5 mL (40 mg/mL) in a single-patient-use prefilled pen
- 150 mg/1.5 mL (100 mg/mL) in a single-patient-use prefilled pen
- 300 mg/3 mL (100 mg/mL) in a single-patient use-prefilled pen

DATING PERIOD

The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for Alhemo drug product shall be 24 months from the date of manufacture when stored at 2-8 °C including an in-use period of 4 weeks below 30°C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Alhemo 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 Alhemo, or in the manufacturing facilities, will require the submission of information to your BLA 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 with minor editorial revisions listed below and reflected in the enclosed labeling with minor editorial revisions listed below and reflected in the enclosed labeling:

Deletion of bullets for single-item listings in the Highlights section (Contraindications and Adverse Reactions).

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide). Information on submitting SPL files using

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

eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[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 enclosed carton and container labeling, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761315**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Alhemo was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class, and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761315. All correspondences related to this voucher should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351(a) of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

[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.

- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the PRV may be transferred, but each person to whom the PRV is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the PRV was transferred.

- FDA may revoke the PRV if the rare pediatric disease product for which the PRV was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a PRV must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
    - the estimated demand in the U.S. for the product, and
    - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

We remind you of your postmarketing commitments:

4761-1: Conduct adequate analytical and clinical validation testing to establish an FDA cleared or approved in-vitro diagnostic device to accurately and reliably detect concizumab concentration in human 3.2% citrated plasma that is safe and effective for concizumab dose adjustment decisions 4 weeks after initiation of treatment with concizumab in patients with Hemophilia A and B with inhibitors. The final report should include the results of the validation studies to inform product labeling.

The timetable you submitted on December 20, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2025

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

We remind you of your postmarketing commitments:

4761-2: To implement the change (b) (4) in the concizumab drug product (DP). The final report includes updates to the concizumab DP manufacturing process and all supporting studies of the pre- and post-change concizumab DP will be reported per 21 CFR 601.12.

The timetable you submitted on November 22, 2024, states that you will conduct this study according to the following schedule:

Final report submission date: 10/2027

4761-3: To commit to re-evaluate the shelf-life (b) (4) after sufficient release and stability data from is collected no later than 3 years post-approval to support the concizumab-mtci drug product lifecycle. The revised shelf-life (b) (4) and adequate justifications will be reported per 21 CFR 601.12.

The timetable you submitted on December 10, 2024, states that you will conduct this study according to the following schedule:

Final report submission date: 04/2028

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]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 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 at 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:

[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

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

REQUESTED ENHANCED PHARMACOVIGILANCE

We request that for Alhemo you submit all serious and non-serious domestic and foreign cases of thromboembolic events as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)) through the 5th year following initial U.S. approval.

We request that you provide a separate narrative summary analysis of thromboembolic events reported with Alhemo as part of your required periodic safety reports (e.g., periodic adverse experience report (PAER) required under 21 CFR 600.80(c)(2)), quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following initial U.S. approval date.

Your analysis should include interval and cumulative data relative to the date of approval of Alhemo. Your analysis should provide an assessment of causality, with documentation of indication (including all labeled and off-label use), temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

POST APPROVAL FEEDBACK MEETING

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.

If you have any questions, please contact Rolanda Bailey, Regulatory Project Manager, at (240) 402-5631 or email at Rolanda.Bailey@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and 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/

NORMAN L STOCKBRIDGE
12/26/2024 04:35:41 PM
Signed on behalf of Lisa Yanoff.