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Our STN: BL 125772/0

BLA APPROVAL
November 22, 2022

CSL Behring LLC
Attention: Poorva Chiddarwar
1020 First Avenue
P.O. Box 61501
King of Prussia, PA 19406-0901

Dear Ms. Chiddarwar:

Please refer to your Biologics License Application (BLA) received on March 24, 2022, submitted under section 351(a) of the Public Health Service Act (PHS Act) for etranacogene dezaparvovec-drlb.

LICENSING

We have approved your BLA for etranacogene dezaparvovec-drlb effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, etranacogene dezaparvovec-drlb under your existing Department of Health and Human Services U.S. License No. 1767. Etranacogene dezaparvovec-drlb is indicated for treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT02396342; NCT03489291 and NCT03569891.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture the etranacogene dezaparvovec-drlb drug substance and drug product at uniQure, Inc., 113 Hartwell Avenue, Lexington, MA, USA, and to perform the final drug product labeling and packaging at CSL Behring (b)(4)

You may label your product with the proprietary name HEMGENIX and market it in single-use glass vials containing 10 mL extractable volume at a concentration of 1×10^{13} genomic copies per mL.

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for etranacogene dezaparvovec-drlb shall be 24 months from the date of manufacture when stored at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (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 required to submit lot release protocols for future lots of etranacogene dezaparvovec-drlb to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). 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.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, 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 the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at <https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations> :

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging, or labeling of etranacogene dezaparvovec-drlb, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert under amendment 80, dated November 22, 2022 and the draft carton and container labels submitted under amendment 80, dated November 22, 2022.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via 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 Package Inserts submitted on November 22, 2022. 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* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on November 22, 2022, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm333969.pdf>.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125772/0 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry Providing Submissions in Electronic Format —Postmarketing Safety Reports at <https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm458559.pdf> and FDA's Adverse Event reporting System website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>. For information on distribution reporting, please refer to the guidance for industry Electronic Submission of Lot Distribution Reports at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>.

PEDIATRIC REQUIREMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify an

unexpected serious risk of bleeding due to failure of expected pharmacological action of HEMGENIX in the presence of pre-existing anti-AAV5 neutralizing antibodies (NAb). Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk. Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

1. To validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher.

We acknowledge the timetable you submitted on November 21, 2022, which states that you will conduct this study according to the following schedule:

Assay and methodology for reportable titers up to 1:1100

Study Report Submission: February 10, 2023

Assay and methodology for reportable titers \geq 1:1100 including above 1:1400

Final Study Report Submission: May 31, 2023

2. A postmarketing study to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of HEMGENIX and pre-existing anti-AAV5 NAb to the capsid of HEMGENIX with a validated assay (required in PMR 1). The study will evaluate at least 35 Hemophilia B patients treated with HEMGENIX, to include at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 NAb titers. The assessment will compare pre- and post-treatment annualized bleeding rates (ABRs), with a lead-in period, to establish the patients' baseline ABR on routine treatment, and 18-month follow-up after HEMGENIX administration.

We acknowledge the timetable you submitted on November 18, 2022, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 10, 2023

Study Completion Date: December 31, 2028

Final Report Submission: May 31, 2029

Please submit the protocols to your IND 16248, with a cross-reference letter to this BLA, STN BL 125772/0 explaining that the protocols and other relevant information were submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a

supplement to this BLA, STN BL 125772/0. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 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. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at <http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>. We will consider the submission of your annual report under section 506B of the FDCA 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 section 505(o) and 21 CFR 601.70. We remind you that to comply with section 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 periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

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

We acknowledge your written commitments as described in your letters of November 7 and 16, 2022 as outlined below:

3. CSL Behring commits to validate a suitable method for release testing of etranacogene dezaparvovec-drlb drug product for (b)(4) . A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria as a “PMC Submission – Final Study Report.”

Final Report Submission: December 31, 2023

4. CSL Behring commits to validate (b)(4) for release testing of etranacogene dezaparvovec-drlb drug product for (b)(4) . A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria as a “PMC Submission – Final Study Report.”

Final Report Submission: December 31, 2023

5. CSL Behring commits to include (b)(4) assay for release testing of etranacogene dezaparvovec-drlb drug product. A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria as a “PMC Submission – Final Study Report.”

Final report submission: July 30, 2023

6. CSL Behring commits to perform a long-term leachables study of the intended drug product (b)(4) container closures at the intended storage conditions. A final leachables report will be submitted as a “PMC Submission – Final Study Report.”

Final report submission: April 30, 2024

7. CSL Behring commits to complete (b)(4) validation for (b)(4) assays. A final report will be submitted as a “PMC Submission – Final Study Report.”

Final report submission: December 31, 2022

8. CSL Behring commits to re-evaluate the acceptance criteria for release testing of etranacogene dezaparvovec-drlb drug substance and drug product based on

manufacturing experience when additional data from (b)(4) drug substance and (b)(4) drug product commercial batches are available and revise if appropriate. A final acceptance criteria report after re-assessment will be submitted as a “PMC Submission-Final Study Report.”

Final report submission: June 30, 2024

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125772/0. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

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, please contact the Regulatory Project Manager for this application.

Sincerely,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research