Our STN: BL 125785/0

BLA APPROVAL
January 16, 2024

Vertex Pharmaceuticals Inc
Attention: Brett Richardson
50 Northern Avenue
Boston, MA 02210

Dear Brett Richardson:

Please refer to your Biologics License Application (BLA) received March 31, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for exagamglogene autotemcel.

With the issuance of this approval letter, we have administratively closed BLA STN 125785. Future correspondence and submissions should be addressed to the original BLA STN 125787 for this biological product.

LICENSING

We have approved your BLA for exagamglogene autotemcel effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, exagamglogene autotemcel under your existing Department of Health and Human Services U.S. License No. 2279. Exagamglogene autotemcel is indicated for the treatment of patients aged 12 years and older with transfusion-dependent ß-thalassemia (TDT).

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 03655678 and 04208529.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture exagamglogene autotemcel drug substance and drug product at (b) (4)

You may label your product with the proprietary name CASGEVY and market it in 20 mL vials containing 4 to 13 × 10^6 CD34+ cells/mL frozen in 1.5 to 20 mL of solution. The minimum dose is 3 × 10^6 CD34+ cells per kg of body weight, which may be contained within multiple vials.

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 exagamglogene autotemcel shall be 18 months from the date of manufacture when stored in the vapor phase of liquid nitrogen at ≤ -135°C (≤ -211°F). The date of manufacture shall be defined as the date of final formulation of the drug product. The dating period for the SPY101 gRNA shall be (b) (4) when stored at (b) (4). The dating period for Cas9 shall be (b) (4) when stored at (b) (4).

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of exagamglogene autotemcel 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 125787 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 exagamglogene autotemcel, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft content of labeling including Package Insert and Patient Package Insert submitted under amendment 92, dated January 16, 2024 and the draft carton and container labels submitted under amendment 79, dated December 18, 2023.

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, 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 Insert and Patient Package Insert submitted on January 16, 2024. 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 package and container labels submitted on December 18, 2023, 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 BL STN 125787 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
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10903 New Hampshire Ave.
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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. In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for secondary malignancies and off-target effects following genome editing as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). 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/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports and FDA's Adverse Event reporting System website at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at https://www.fda.gov/vaccines-blood-biologics/lot-release/lot-distribution-database-ldd.

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/POSTMARKETING COMMITMENTS

Refer to BL STN 125787/57 for postmarketing requirements or commitments related to exagamglogene autotemcel.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, and annual reports should be addressed to BL STN 125787/0.

Sincerely,

Nicole Verdun, MD
Director
Office of Therapeutic Products
Center for Biologics Evaluation and Research