Our STN: BL 125771/0

BLA APPROVAL
Februray 22, 2023

Bioverativ Therapeutics, Inc.
Attention: Hei-Jen Sun, PhD
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Sun:

Please refer to your Biologics License Application (BLA) received June 30, 2022, submitted under section 351(a) of the Public Health Service Act (PHS Act) for antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl.

LICENSING

We have approved your BLA for antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl under your existing Department of Health and Human Services U.S. License No. 2078. Antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl is indicated for use in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes; (2) On-demand treatment and control of bleeding episodes; and (3) Perioperative management of bleeding.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 04161495, 04759131, 04644575, 05042440, and 04770935.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl drug substance at (b) (4) (b) (4) The final formulated product will be manufactured and filled at (b) (4) (b) (4) and, labeled and packaged at (b) (4) (b) (4) (b) (4) The diluent, Sterile Water for Injection, will be manufactured at (b) (4) You may label your product with the proprietary name ALTUVIIIO and market it in nominal doses of 250, 500, 750, 1000, 2000, 3000 or 4000 IU/vial.

ADVISORY COMMITTEE

We did not refer your application to an 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 antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl shall be 48 months from the date of manufacture when stored at 5 ± 3°C in primary packaging and secondary packaging. Within this period of 48 months, the product may be stored for up to 6 months at room temperature (not to exceed 30 °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.

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl 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 antihemophilic factor (Recombinant), Fc-VWF-XTEN fusion protein-ehtl, 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, Patient Package Insert and Instructions for Use submitted under amendment 37, dated February 16, 2023 and the draft carton and container labels submitted under amendment 30, dated February 30, 2023.

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, Patient Package Insert, Instructions for Use** on February 16, 2023. 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 February 1, 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/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125771 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.

For information on the postmarketing safety reporting requirements for combination products as described in 21 CFR 4, Subpart B, and the dates by which combination product applicants must comply with these requirements, please refer to the Postmarketing Safety Reporting for Combination Products webpage available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letters of February 08 and 14, 2023, as outlined below:

1. Bioverativ commits to add an upper limit to the (b) (4) acceptance criteria in the Drug Substance specification and to implement lot testing starting with the 2024 Drug Substance campaign.

   Final Report Submission: March 29, 2024

2. Bioverativ commits to add a test for (b) (4) to the Drug Substance specification and to implement lot testing starting with the 2024 Drug Substance campaign.

   Final Report Submission: March 29, 2024

3. Bioverativ commits to develop a Drug Substance specification to control (b) (4) and to implement lot testing starting with the 2024 Drug Substance campaign.

   Final Report Submission: March 29, 2024

4. Bioverativ commits to include (b) (4) as an identification test for Drug Substance release and to implement lot testing starting with the 2024 Drug Substance campaign.

   Final Report Submission: March 29, 2024

5. Bioverativ commits to develop and include a Drug Substance release specification to control (b) (4) and to implement lot testing starting with the Q3 2024 campaign batches.

   Final Report Submission: June 28, 2024

6. Bioverativ commits to include Drug Product release specifications for total protein and specific activity and to implement lot testing starting with the Q2 2024 campaign batches.

   Final Report Submission: March 29, 2024

7. Bioverativ commits to develop and include Drug Product release specifications to control for individual excipients (polysorbate 80, arginine, histidine, calcium, sucrose) and to implement lot testing starting with the Q3 2024 campaign batches.

   Final Report Submission: June 28, 2024.

We acknowledge that you have committed to submit Module 3 updates for each of these Postmarketing Commitments by the time of their respective final report submission. We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125771. 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;
- a description of what has been accomplished to fulfill the non-section 506B PMC; and,
- a summary of 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