Our STN: BL 125795/0

BLA APPROVAL
November 9, 2023

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Michael Cronin, PharmD
Senior Director, Global Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Dr. Cronin:

Please refer to your Biologics License Application (BLA) received March 17, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for ADAMTS13, recombinant-krhn.

LICENSING

We have approved your BLA for ADAMTS13, recombinant-krhn effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ADAMTS13, recombinant-krhn under your existing Department of Health and Human Services U.S. License No. 1898. ADAMTS13, recombinant-krhn is indicated for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 02216084; 03393975; and 04683003.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ADAMTS13, recombinant-krhn drug substance at Takeda Manufacturing (b) (4). The final formulated product will be manufactured, filled, lyophilized, labeled, and packaged at the Takeda Manufacturing (b) (4). The diluent, sterile Water for Injection, will be manufactured at (b) (4). The co-packaged combination product, which contains the package insert, lyophilized ADAMTS13, recombinant-krhn drug product (500 IU or 1500 IU), sterile Water for Injection diluent, BAXJECT II Hi-Flow Needleless Transfer Device, (b) (4) Winged Infusion Set, (b) (4) syringe (10 mL or 20 mL, respectively), and alcohol swab (pack of 2), will be assembled at Takeda Manufacturing (b) (4).

You may label your product with the proprietary name ADZYNMA and market it in nominal dosage strengths of 500 IU/vial and 1500 IU/vial.

ADVISORY COMMITTEE

We did not refer your application to the Blood Products 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 ADAMTS13, recombinant-krhn shall be 36 months from the date of manufacture when stored at 2-8°C or at room temperature not to exceed 30°C for a period up to 6 months. 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 expiration date for the packaged product, ADAMTS13, recombinant-krhn plus diluent, sterile Water for Injection, shall be dependent on the shortest expiration date of any component.

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of ADAMTS13, recombinant-krhn 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 ADAMTS13, recombinant-krhn, 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 67 (sequence 0068), dated November 6, 2023, and the draft carton and container labels submitted under amendment 59 (sequence 0060), dated October 20, 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, and Instructions for Use, submitted on November 6, 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 October 20, 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 125795/0 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. In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for all adverse events involving the development of antibodies to ADAMTS13, regardless of label status or seriousness, as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). ADAMTS13 antibody reports must be submitted as 15-day expedited reports for 3 years following the date of product licensure. 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.

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.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher (PRV), as provided under section 529 of the FDCA. This PRV has been assigned a tracking number, PRV BLA 125795/0. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 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**."
- 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 website 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 PRV Program webpage available at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letters of October 17, 2023 (amendment 57; sequence 0058), and October 31, 2023 (amendment 64; sequence 0065) as outlined below:

1. Takeda commits to perform and provide data from (b) (4) . This will include:
   a. (b) (4) to monitor the potential occurrence of any (b) (4) ,
   b. monitoring process parameters and in-process controls, and
   c. release and stability testing of (b) (4) Drug Product (DP) lots manufactured from DS batches derived from the (b) (4) .

   The results will be submitted as a "Postmarketing Study Commitment – Final Study Report" by August 31, 2027.

   Final Study Report Submission: August 31, 2027

2. Takeda commits to perform the analysis of cumulative organic leachables from the manufacturing process and storage in (b) (4) Drug Product (DP) lots representative of each product strength, lot (b) (4) (500 IU/vial) and lot (b) (4) (1500 IU/vial), at the remaining stability study time points under the long-term storage condition at 2°C to 8°C until the intended DP shelf life of 36 months is reached and at the maximal in-use storage time of reconstituted product until administration to patient, and to perform toxicological assessment of respective leachable levels.

The results will be submitted in the 2024 and 2025 Annual Reports for the 24-month and 36-month time points, respectively.

3. Takeda commits to reanalyze the (b) (4) release data for (b) (4) from (b) (4) additional (b) (4) campaigns: (b) (4) at the (b) (4) facility and perform statistical analysis of data and propose amended interim rADAMTS13 (b) (4) release and stability acceptance criteria for (b) (4). The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment as a ”Postmarketing Study Commitment – Final Study Report” by January 31, 2024.

   Final Study Report Submission: January 31, 2024

4. Takeda commits to reanalyze the (b) (4) data for (b) (4) following the completion of the (b) (4) campaign to be produced no later than 2026 at the (b) (4) facility. Data analysis will include release and stability data generated on (b) (4) batches manufactured at the (b) (4) facility and placed on stability prior to the 2026 (b) (4) campaign; release data from the 2026 (b) (4) campaign; (b) (4) stability from the same 2026 (b) (4) campaign; and statistical analysis of all data from batches manufactured at this facility and propose amended final rADAMTS13 (b) (4) release and stability acceptance criteria for (b) (4). The results will be submitted as a Prior Approval Supplement (PAS), specifying the submission in fulfillment of a ”Postmarketing Study Commitment – Final Study Report” by August 31, 2027.

   Final Study Report Submission: August 31, 2027

5. Takeda commits to reanalyze Drug Product (DP) data for Specific Activity upon completion of stability studies for PPQ DP lots at the intended stability storage conditions (36 months at 2-8°C including 6 months at +30°C) and propose amended interim rADAMTS13 Specific Activity release and stability acceptance criteria for DP. The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of “Postmarketing Study Commitment – Final Study Report” by January 31, 2025.

   Final Study Report Submission: January 31, 2025

6. Takeda commits to reanalyze Drug Product (DP) release and stability data for Specific Activity once a minimum of 12 months stability data have been generated from specified DP lots as follows. Analysis will incorporate additional release and stability data from (b) (4) DP lots (consisting of (b) (4) 500 IU/vial and (b) (4) 1500 IU/vial) manufactured from each of the following (b) (4). If appropriate, Takeda

will propose amended interim rADAMTS13 Specific Activity release and stability acceptance criteria for DP. The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of "Postmarketing Study Commitment – Final Study Report" by December 31, 2025.

Final Study Report Submission: December 31, 2025

7. Takeda commits to reanalyze Drug Product (DP) data for Specific Activity upon completion of stability studies for DP lots manufactured from the (b) (4) campaigns under PMC 3, specifically those DP lots manufactured from the (b) (4) campaigns, at the intended stability storage conditions (36 months at 2-8°C including 6 months at +30°C) and propose amended final rADAMTS13 Specific Activity release and stability acceptance criteria for DP, if appropriate. The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of "Postmarketing Study Commitment – Final Study Report" by June 30, 2030.

   Final Study Report Submission: June 30, 2030

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125795/0. 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,

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