Our STN: BLA 125795/73

NOTIFICATION
SAFETY LABELING CHANGE
POSTMARKETING REQUIREMENT
February 5, 2026

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Michael Cronin, PharmD
125 Binney Street
Cambridge, MA 01242

Dear Dr. Cronin:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for ADAMTS13, recombinant-krhn [ADZYNMA].

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and licensed biological product applications to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since ADZYNMA was approved on November 9, 2023, we have become aware of postmarketing adverse event reports of neutralizing antibodies to ADAMTS13, including one death, in congenital thrombotic thrombocytopenic purpura (cTTP) patients treated with ADZYNMA. For additional information, please see CBER safety communication titled, "FDA Investigating Death Due to Neutralizing Antibodies to ADAMTS13 following Adzynma Treatment of Congenital Thrombotic Thrombocytopenic Purpura," and a posting at July - September 2025: Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS). We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and discussed during the February 5, 2026 teleconference, we believe that the new safety information should be included in the labeling for ADZYNMA as follows (additions are underlined, and deletions are in strikethrough):

HIGHLIGHTS:

RECENT MAJOR CHANGES

Boxed Warning	month/year
Warnings and Precautions (5.2)	month/year

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

BOXED WARNING
WARNING: NEUTRALIZING ANTIBODIES TO ADAMTS13

- Neutralizing antibodies to ADAMTS13 with serious outcomes, including death, have been reported in patients treated with ADZYNMA. Neutralizing antibodies may result in decreased or lack of response to recombinant or plasma-derived ADAMTS13 (5.2, 6.2).
- Monitor all patients closely for ADAMTS13 activity and development of ADAMTS13 neutralizing antibodies (5.2).

WARNINGS AND PRECAUTIONS
Immunogenicity: ~~Patients may develop antibodies to rADAMTS13 which could potentially result in a decreased or lack of response to rADAMTS13.~~ Neutralizing antibodies to ADAMTS13 with serious outcomes, including death, have been reported following administration of ADZYNMA in the postmarketing setting (5.2, 6.2). Patients may develop antibodies to host cell proteins which could potentially result in adverse reactions. There are no data on risk in previously untreated patients (subjects naïve to plasma-based products). (5.2)

FULL PRESCRIBING INFORMATION:

BOXED WARNING

WARNING: NEUTRALIZING ANTIBODIES TO ADAMTS13

- Neutralizing antibodies to ADAMTS13 with serious outcomes, including death, have been reported in patients treated with ADZYNMA. Neutralizing antibodies may result in decreased or lack of response to recombinant or plasma-derived ADAMTS13 *[see Warnings and Precautions (5.2), Postmarketing Experience (6.2)].*
- Monitor all patients closely for ADAMTS13 activity and development of ADAMTS13 neutralizing antibodies *[see Warnings and Precautions (5.2)].*

WARNINGS AND PRECAUTIONS

5.2 Immunogenicity
~~There is a potential for immunogenicity with ADZYNMA. Patients may develop neutralizing antibodies to ADAMTS13, which could potentially result in a decreased or lack of response to ADAMTS13.~~ Neutralizing antibodies to ADAMTS13 with serious outcomes, including death, have been reported following administration of ADZYNMA in the postmarketing setting *[see Postmarketing Experience (6.2)].* Neutralizing antibodies were not reported in the cTTP clinical trials. All subjects had been previously exposed to ADAMTS13 through plasma-based products. There are no data on immunogenicity with ADZYNMA in previously untreated patients (subjects naïve to plasma-based products) *[see Clinical Pharmacology (12.6)].*

Monitor all patients for ADAMTS13 activity and for development of ADAMTS13 neutralizing antibodies prior to initiation of ADZYNMA and periodically during the course

of treatment with ADZYNMA. If expected ADAMTS13 activity levels are not attained or if acute TTP exacerbation occurs despite appropriate dose, perform an assay that measures ADAMTS13 neutralizing antibody concentrations. Laboratory tests for monitoring neutralizing antibody levels are not capable of distinguishing between inhibitors directed against recombinant ADAMTS13 (ADZYNMA), the patient's endogenous ADAMTS13, or ADAMTS13 from other plasma sources.

Patients may develop antibodies to host cell proteins which could potentially result in adverse reactions. There are no data on immunogenicity to host cell proteins in previously untreated patients (subjects naïve to plasma-based products).

6 ADVERSE REACTIONS
6.2 Postmarketing Experience
The following adverse reactions have been identified during the post-approval use of ADZYNMA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

Blood and Lymphatic System Disorders: Neutralizing antibodies to ADAMTS13 (with serious outcomes, including death) *[see Warnings and Precautions (5.2)].*

PATIENT PACKAGE INSERT

What else should I know about ADZYNMA and hereditary ADAMTS13 deficiency (cTTP)?

Your body can form inhibitors to ADAMTS13. An inhibitor is part of the body's normal defense system. If you form inhibitors, they may stop ADZYNMA from working properly and may be life-threatening. Serious side effects from inhibitors have been reported, including death. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to ADAMTS13.

In accordance with section 505(o)(4), within 30 calendar days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction or notify FDA that you do not believe a labeling change is warranted and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS). Under section 505(o)(4), if you fail to submit a response within 30 calendar days, you would be in violation of the FDCA that may deem your product to be misbranded under section 502(z) and may subject you to enforcement action, including civil monetary penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Please submit your safety labeling submission to STN BL 125795 (i.e., as a new supplement).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – AMENDMENT

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 assess a serious risk of neutralizing antibodies to ADAMTS13 following administration of ADZYNMA.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following postmarketing studies:

1. Conduct a prospective multicenter interventional trial to assess immunogenicity and clinical loss of efficacy of ADZYNMA in patients with severe Congenital Thrombotic Thrombocytopenic Purpura (cTTP), who are on prophylactic or on-demand treatment. Provide a proposal for such a trial, including suitable trial design, safety monitoring, sample size calculation, and trial milestone dates, for our review, based on post-marketing observations of the new serious safety information. If trial TAK-755-3002 is selected to contribute to this requirement, provide a proposal for our review.

2. A non-interventional study to further Evaluate Real-World Safety, including risks associated with the development of neutralizing antibodies, in patients with Congenital Thrombotic Thrombocytopenic Purpura (cTTP), treated with ADZYNMA. This postmarketing study will include cTTP patients who are treated with commercially available ADZYNMA and enrolled patients will be followed for at least 12 months following initiation of ADZYNMA.

Please provide your acknowledgement of the above required postmarketing studies with your safety labeling supplement.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Cara Pardon, at (240) 994-8449 or by email at cara.pardon@fda.hhs.gov.

Sincerely,

Bindu George, MD
Acting Director
Division of Clinical Evaluation Hematology
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research