ADAMTS13, recombinant-krhn (Adzynma™)

Policy # 00887
Original Effective Date: 09/09/2024
Current Effective Date: 09/09/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider ADAMTS13, recombinant-krhn (Adzynma™)‡ for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ADAMTS13, recombinant-krhn (Adzynma) will be considered when the following criteria are met:

- Initial authorization (6 months):
    - Patient has a diagnosis of congenital thrombotic thrombocytopenic purpura (cTTP); AND
    - Diagnosis has been verified by documentation of BOTH of the following:
        - Genetic testing confirming homozygous or compound heterozygous pathogenic variants in the *ADAMTS13* gene; AND
        - Measured ADAMTS13 activity less than 10% of normal ADAMTS13 activity (< 10 IU/dL) at baseline measured by fluorescent resonance energy transfer-von Willebrand factor 73 (FRETS-VWF73) assay; AND
          (Note: baseline refers to before any treatment was received, such as plasma based therapies or Adzynma.)

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- Patient has not been diagnosed with any other thrombotic thrombocytopenic purpura (TTP)-like disorder (e.g., immune TTP, other primary thrombotic microangiopathies, immune thrombocytopenic purpura (ITP), Evans Syndrome); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient must not have a medical history or presence of a functional ADAMTS13 inhibitor (i.e., patient does not have anti-ADAMTS13 autoantibodies) at screening; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is using the requested drug for on-demand treatment AND meets ALL of the following:
  - Patient has experienced a 50% or greater drop in platelet count, OR platelet count is less than 100,000/ microliter; AND
  - Lactate dehydrogenase elevation (LDH) is more than 2 times baseline OR more than 2 times upper limit of normal (ULN) as defined by laboratory values; AND

  *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Dose for on-demand therapy is 40 IU/kg intravenous (IV) infusion on day 1, 20 IU/kg IV infusion on day 2, and 15 IU/kg IV infusion on day 3 and beyond until 2 days after the acute event is resolved; OR
- Patient is using the requested drug for prophylactic treatment AND meets ALL of the following:
  - Patient must have a history of at least one documented TTP event or currently be receiving prophylactic plasma infusion therapy for cTTP; AND
    (Note: routine use of prophylactic plasma infusion therapy should be discontinued once a therapeutic response has been achieved)
  - Patient presents with platelet count greater than 100,000/ microliter; AND
  - Patient presents with LDH less than 2 times the ULN as defined by laboratory values; AND

  *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

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- Dose for prophylactic therapy is 40 IU/kg IV infusion once every other week OR every week depending upon prior dosing regimen or clinical response.

Note: Acute TTP events are defined by a drop in platelet count (≥ 50% of baseline or a platelet count < 100,000/microliter) and an elevation of LDH (> 2 times baseline or > 2 times upper limit of normal [ULN]), and sub-acute TTP events are defined by a thrombocytopenia event or a microangiopathic hemolytic anemia event and organ-specific signs and symptoms (e.g., renal dysfunction events, neurological symptoms events, fever, fatigue/lethargy, and/or abdominal pain).

- Continuation:
  - Patient has received an initial authorization for Adzynma; AND
  - Patient has experienced a positive clinical response while on therapy, as evidenced by documentation of ONE of the following:
    - Utilizing requested drug for on-demand treatment AND platelet count increases to at least 150,000/microliter OR increases to 25% from baseline platelet counts; OR
    - Utilizing requested drug for prophylactic treatment AND decreased number of TTP events; AND

    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Dose for prophylactic therapy is 40 IU/kg once every other week or every week depending upon on prior dosing regimen/clinical response, OR dose for on-demand therapy is 40 IU/kg on day 1, 20 IU/kg on day 2, and 15 IU/kg on day 3 and beyond until 2 days after the acute event is resolved.

Note: Acute TTP events are defined by a drop in platelet count (≥ 50% of baseline or a platelet count < 100,000/microliter) and an elevation of LDH (> 2 times baseline or > 2 times upper limit of normal [ULN]), and sub-acute TTP events are defined by a thrombocytopenia event or a microangiopathic hemolytic anemia event and organ-specific signs and symptoms (e.g., renal dysfunction events, neurological symptoms events, fever, fatigue/lethargy, and/or abdominal pain).

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of ADAMTS13, recombinant-krhn (Adzynma) when any of the following criteria are NOT met to be **not medically necessary.****

- For Initial requests:
  - Patient has not been diagnosed with any other thrombotic thrombocytopenic purpura (TTP)-like disorder
  - Patient must not have a medical history or presence of a functional ADAMTS13 inhibitor (i.e., patient does not have anti-ADAMTS13 autoantibodies) at screening
  - Patient is using the requested drug for on-demand treatment AND meets ALL of the following:
    - Patient has experienced a 50% or greater drop in platelet count, OR platelet count is less than 100,000/ microliter
    - Lactate dehydrogenase elevation (LDH) is more than 2 times baseline or more than 2 times ULN as defined by laboratory values
  - Patient is using the requested drug for prophylactic treatment AND meets ALL of the following:
    - Patient must have a history of at least one documented TTP event or currently be receiving prophylactic plasma infusion therapy for cTTP
    - Patient presents with platelet count greater than 100,000/ microliter
    - Patient presents with LDH less than 2 times the ULN as defined by laboratory values
- For Continuation requests:
  - Patient has experienced a positive clinical response while on therapy, as evidenced by documentation of ONE of the following:
    - Utilizing requested drug for on-demand treatment AND platelet count increase to at least 150,000/microliter OR increase to 25% from baseline platelet counts
    - Utilizing requested drug for prophylactic treatment AND decreased number of TTP events

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of ADAMTS13, recombinant-krhn (Adzynma) when the patient selection criteria are not met (EXCEPT those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Adzynma is a human recombinant form of endogenous ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin type 1 motif, member 13) indicated for prophylactic or on demand enzyme replacement therapy in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP), an ultra-rare blood clotting disorder associated with a deficiency of ADAMTS13. ADAMTS13 is responsible for breaking down clotting protein von Willebrand factor (VWF) into smaller sized multimers, thereby preventing formation of ultralarge VWF multimers and subsequent platelet aggregation. Thrombotic thrombocytopenia purpura (TTP) can either be inherited, as in cTTP (also called hereditary TTP, familial TTP, and Upshaw-Schulman syndrome), or acquired, as with immune mediated TTP (iTTP). In cTTP, ADAMTS13 deficiency appears to be caused by biallelic mutations in the *ADAMTS13* gene; however, iTTP is caused by development of ADAMTS13 autoantibodies. Individuals with cTTP would not have ADAMTS13 autoantibodies but only those individuals with iTTP develop the autoantibodies. Congenital TTP is thought to affect fewer than 1000 people in the United States with symptoms typically developing in infancy or early childhood. However, some individuals may be asymptomatic into adulthood with symptoms not appearing until pregnancy. Individuals may present with mild and nonspecific symptoms such as lethargy, headache, loss of concentration, and abdominal discomfort. Microvascular thrombosis with end-organ damage, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA) can also occur. Acute, severe exacerbations are uncommon but if left untreated, cTTP can be fatal. Diagnosis is based on an ADAMTS13 activity level below 10% and confirmed by genetic testing. Prior to the approval of Adzynma, cTTP management included the use of prophylactic plasma-based therapy to reduce clotting and bleeding risks by replacing absent or low levels of the ADAMTS13 enzyme. Therapeutic plasma exchange (TPE) is usually reserved for severe episodes or for situations with ongoing triggers, such as pregnancy. Adzynma is available in single-dose vials containing nominally 500 or 1,500 IU per vial. Prophylactic therapy

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with Adzynma is dosed 40 IU/kg once every other week; the dosing frequency may be adjusted to 40 IU/kg once weekly based on prior dosing regimen or clinical response. On-demand treatment is dosed 40 IU/kg on treatment day 1, then 20 IU/kg on treatment day 2, followed by 15 IU/kg once daily until two days after the acute event is resolved. The administration dose and volume should be calculated based on the patient's body weight using the actual potency (not the nominal potency) as printed on the vial. All doses should be administered intravenously by a health care professional.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

ADAMTS13, recombinant-krhn (Adzynma) was approved in November 2023 for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

Adzynma was approved with Priority Review, Fast Track, and Orphan Drug designations. A Rare Pediatric Disease Priority Review Voucher was also granted.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The safety and efficacy of Adzynma was evaluated in a prospective, randomized, controlled, open-label, multicenter, two-period crossover study, followed by a single arm continuation period, evaluating prophylactic and on-demand ERT with Adzynma compared to plasma-based therapies in patients with cTTP. In the prophylactic treatment cohort, 46 patients with cTTP were randomized to receive 6 months of treatment with either Adzynma 40 IU/kg or plasma-based therapies (Period 1) and then crossed over to receive the other treatment for 6 months (Period 2). Thirty-five patients entered the 6-month single arm continuation arm (Period 3). No patients receiving Adzynma had an acute TTP event throughout the study, including Period 3. The median duration of exposure to Adzynma was 14 months (patients 12 and older), 4 months (patients 6 to <12 years of age), and 1 month (patients < 6 years of age). The efficacy of prophylactic treatment with Adzynma was

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demonstrated based on the incidence of acute and subacute TTP events (defined per protocol) and TTP manifestations, as well as the incidence of supplemental doses prompted by subacute TTP events over a 6-month time period. An acute TTP event responding to Adzynma was defined as a resolved TTP event when platelet count was ≥ 150,000/μL or platelet count was within 25% of baseline, whichever occurs first, and LDH ≤ 1.5 times baseline or ≤ 1.5 times the ULN, without requiring the use of another ADAMTS13-containing agent. Sub-acute events were defined as a thrombocytopenia event or a MAHA event, and organ-specific signs and symptoms, including but not limited to renal dysfunction events, neurological symptoms events, fever, fatigue/lethargy, and/or abdominal pain. One acute TTP event occurred in a patient receiving plasma-based therapies (i.e. fresh frozen plasma [FFP]) prophylactically during Period 1. No subacute TTP events were reported in patients receiving Adzynma during Periods 1 and 2. In Period 3, two patients receiving Adzynma prophylaxis had two subacute events, of which one was treated with four supplemental doses (two of FFP and two of Adzynma). Four patients receiving plasma-based therapies had a total of five subacute TTP events in Periods 1 and 2. A total of seven supplemental doses, two of FVIII-VWF concentrate, two of FFP, and four of Adzynma were given to three of these patients. The efficacy of Adzynma for the on-demand portion of the study was evaluated based on the proportion of acute TTP events responding to Adzynma in both the prophylactic and the on-demand cohorts throughout the study. The on-demand cohort included five adult patients with a total of six acute TTP events. Of these five patients, two patients were randomized to receive on-demand treatment with Adzynma, and three patients were randomized to receive plasma-based therapies. All six acute TTP events resolved after treatment with either Adzynma or plasma-based therapies. The most common adverse reactions reported with Adzynma were headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting.

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9. Policy History

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08/01/2024 Medical Policy Committee review
08/14/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 08/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No code
HCPCS	J7171
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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