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## Subject: ADAMTS13, recombinant-krhn (Adzynma) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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### DESCRIPTION:

Thrombotic thrombocytopenia purpura (TTP) is an ultra-rare, life-threatening hematologic disease. TTP is thought to be associated with a deficiency in the ADAMTS13 enzyme, which is responsible for breaking down clotting protein von Willebrand factor (VWF). TTP can either be inherited [i.e., congenital TTP (cTTP), Upshaw-Schulman Syndrome] or acquired [immune-mediated TTP (aTTP or iTTP)]. The cause of the deficiency of ADAMTS13 helps distinguish the sub-types. For example, in cTTP the deficiency of ADAMTS13 is caused by mutations of the ADAMTS13 gene, and in iTTP it is caused by ADAMTS13 autoantibodies. The estimated annual prevalence of TTP is 10 cases per 1 million individuals, with less than 1000 people in the United States with cTTP. Clinical presentation typically occurs in infancy or early childhood but may develop in adulthood and/or during pregnancy. Signs and symptoms of cTTP include severe bleeding episodes, strokes, and damage to vital organs. Diagnosis is based on an ADAMTS13 activity level below 10% and confirmed via genetic testing. cTTP can be fatal if not treated. Typical treatment involves prophylactic plasma-based therapy to reduce the risk of clotting and/or bleeding by replenishing the low ADAMTS13 enzyme.

On November 9, 2023, the FDA approved ADAMTS13, recombinant-krhn (Adzynma) for prophylactic or on-demand enzyme replacement therapy (ERT) in adult and pediatric patients with cTTP. ADAMTS13, recombinant-krhn (Adzynma) is a plasma zinc metalloprotease that regulates the activity of VWF by cleaving large and ultra-large VWF multimers to smaller units and thereby reducing the platelet-binding properties of VWF and its propensity to form microthrombi.

The safety and efficacy of ADAMTS13, recombinant-krhn (Adzynma) was evaluated in a prospective, randomized, controlled, open-label, multicenter, crossover study evaluating prophylactic and on-demand ERT with Adzynma compared to plasma-based therapies in patients with cTTP. The clinical trial encompassed a two-period crossover design followed by a single arm continuation period. In the

prophylactic treatment cohort, 46 patients with cTTP were randomized to receive 6 months of treatment with either Adzyna or plasma-based therapies (Period 1) and then crossed over to receive the other treatment for 6 months (Period 2). A total of 35 patients entered the Period 3 continuation. In the prophylactic cohort, the median age was 32.5 years (range: 3 – 58 years), and the mean weight was 67.6 kg. Among the participants, 65.2% were Caucasian and 80.4% were not Hispanic or Latino. The cohort was 58.7% female. No patients receiving Adzyna had an acute TTP event throughout the study, including Period 3. One acute TTP event occurred in a patient receiving plasma-based therapy [i.e., fresh frozen plasma (FFP)] prophylactically during Period 1. No subacute TTP events were reported in patients receiving Adzyna during Periods 1 and 2. In Period 3, two patients receiving Adzyna prophylaxis had two subacute events, of which one was treated with four supplemental doses, two of FFP and two of Adzyna. 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 Adzyna were given to three of these patients. For the on-demand portion of the study, five adult patients ( $\geq 18$  years of age) enrolled and had a total of six acute TTP events. Of these five patients, two patients were randomized to receive on-demand treatment with Adzyna, and three patients were randomized to receive plasma-based therapies. All six acute TTP events resolved after treatment with either Adzyna or plasma-based therapies. The most common adverse reactions reported with ADAMTS13, recombinant-krhn (Adzyna) were headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting.

## **POSITION STATEMENT:**

Initiation of ADAMTS13, recombinant-krhn (Adzyna) **meets the definition of medical necessity** when **ALL** of the specific criteria are met:

1. Diagnosis of congenital thrombotic thrombocytopenic purpura (cTTP) confirmed by molecular genetic testing showing mutation in the ADAMTS13 gene - laboratory or medical record documentation must be submitted
2. Member has not been diagnosed with any other TTP-like disorder (e.g., acquired TTP, immune TTP, other primary thrombotic microangiopathies, immune thrombocytopenia-ITP, Evans Syndrome)
3. ADAMTS13 activity test demonstrates less than 10% of normal activity (Note: Activity may exceed 10% if currently receiving prophylactic plasma infusion therapy) - laboratory or medical record documentation must be submitted
4. Prescribed by a hematologist or specialist in rare genetic diseases
5. One of the following (“a” or “b”):
  - a. Treatment will be used as prophylactic therapy for a member with a history of at least one TTP event\* or receiving prophylactic plasma infusion therapy (Note: routine use of prophylactic plasma infusion therapy should be discontinued once a therapeutic response has been achieved)
  - b. Treatment will be used as on-demand therapy and the member is at risk of a disease exacerbation
6. Dose does not exceed the following (“a” or “b”):

- a. Prophylactic therapy: 40 IU/kg body weight every other week or every week based on prior prophylactic dosing regimen/clinical response
- b. On-demand: 40 IU/kg body weight on Day 1, 20 IU/kg body weight on Day 2, and 15 IU/kg body weight on Day 3 and beyond until two days after the acute event is resolved

**Approval duration:** 6 months

Continuation of ADAMTS13, recombinant-krhn (Adzynma) **meets the definition of medical necessity** when **ALL** of the specific criteria are met:

1. An authorization or reauthorization for ADAMTS13, recombinant-krhn (Adzynma) has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), **OR** the member has previously met **ALL** indication-specific criteria.
2. Member has experienced a clinical meaningful response by one of the following (“a” or “b”): - laboratory or medical record documentation must be submitted
  - a. Documentation of using prophylactic treatment and decreased number of TTP events\*
  - b. Documentation of using on-demand treatment and platelet counts increase to at least 150,000/microliter or increases to 25% from baseline platelet counts
3. Prescribed by a hematologist or specialist in rare genetic diseases
4. Dose does not exceed the following (“a” or “b”):
  - a. Prophylactic therapy: 40 IU/kg body weight every other week or every week based on prior prophylactic dosing regimen/clinical response
  - b. On-demand: 40 IU/kg body weight on Day 1, 20 IU/kg body weight on Day 2, and 15 IU/kg body weight on Day 3 and beyond until two days after the acute event is resolved

**Approval duration:** 1 year

**\*Note:** Acute TTP events are defined by a drop in platelet count ( $\geq 50\%$  of baseline or a platelet count  $< 100,000/\text{microliter}$ ) and an elevation of lactate dehydrogenase (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).

## **DOSAGE/ADMINISTRATION:**

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER’S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

### **FDA-approved**

- ADAMTS13, recombinant-krhn (Adzynma) is indicated for prophylactic or on-demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).
- It is administered intravenous (IV) at an infusion rate of 2 to 4 mL per minute.

- The prophylactic dose is 40 IU/kg body weight administered once every other week; however, the dosing frequency may be adjusted to once weekly based on prior prophylactic dosing regimens or clinical response.
- The on-demand dose is 40 IU/kg body weight on Day 1, 20 IU/kg body weight on Day 2, and 15 IU/kg body weight on Day 3 and beyond until two days after the acute event is resolved.
- Store ADAMTS13, recombinant-krhn (Adzynma) in the original box to protect from light at a refrigerated temperature of 2°C to 8°C (36°F to 46°F) for up to 36 months from the date of manufacture until the expiration date on the vial label and carton. ADAMTS13, recombinant-krhn (Adzynma) may be stored at room temperature not to exceed 30°C/86°F for a period up to 6 months. After storage at room temperature, do not return to the refrigerator. However, do not freeze the product.
- The reconstituted product must be used immediately or within 3 hours after reconstitution when stored at room temperature. Do not use if the solution in the syringe is cloudy or contains particles. Additionally, discard any unused reconstituted product after 3 hours.

### Dose Adjustments

- None

### Drug Availability

- ADAMTS13, recombinant-krhn (Adzynma) is a lyophilized powder in single-dose vials containing nominally 500 or 1500 International Units (IU) per vial and comes with 5 mL of Sterile Water for Injection.
- After reconstitution, the 500 IU and the 1500 IU vials result in a nominal potency of 100 IU/mL and 300 IU/mL, respectively.

## PRECAUTIONS:

### Boxed Warning

- None

### Contraindications

- Previous severe hypersensitivity reaction to ADAMTS13, recombinant-krhn (Adzynma) or any of the excipients.

### Precautions/Warnings

- **Hypersensitivity reactions:** Hypersensitivity reactions may occur with ADAMTS13, recombinant-krhn (Adzynma). If hypersensitivity symptoms occur, discontinue therapy and administer appropriate emergency treatment.
- **Immunogenicity:** Patients may develop antibodies to ADAMTS13, recombinant-krhn (Adzynma), which could potentially result in a decreased or lack of response to therapy. 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).

## BILLING/CODING INFORMATION:

### HCPCS Coding

J7171	Injection, adamts13, recombinant-krhn, 10 IU
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### ICD-10 Diagnosis Codes That Support Medical Necessity

D69.42	Congenital and hereditary thrombocytopenia purpura
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## REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

## DEFINITIONS:

None

## RELATED GUIDELINES:

None

## OTHER:

None

## REFERENCES:

1. Adzynma (ADAMTS13, recombinant-krhn) [package insert]. Takeda Pharmaceuticals U.S.A., Inc., Lexington (MA): November 2023.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL [www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com) Accessed 2/1/24.
3. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL <http://www.dynamed.com>. Accessed 2/1/24.
4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 2/1/24.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/14/24.

## GUIDELINE UPDATE INFORMATION:

03/15/24	New Medical Coverage Guideline – ADAMTS13, recombinant-krhn (Adzynma) IV infusion for prophylactic or on-demand therapy in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).
04/01/24	Revision: Addition of HCPCS code C9167.
05/01/24	Revision: Revised description for code C9167 per CMS update.
07/01/24	Revision: Added HCPCS code J7171 and deleted codes C9167 and J3590.