Plasminogen, Human-tvmh (Ryplazim)

Number: 0976

POLICY

Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Note: Requires Precertification.

Precertification of plasminogen, human tvmh (Ryplazim) is required of all Aetna participating providers and members in applicable plan designs. For precertification of Ryplazim, call (866) 752-7021 (commercial), (866) 503-0857 (Medicare), or fax (866) 267-3277.

I. Criteria for Initial Approval

Aetna considers plasminogen, human tvmh (Ryplazim) medically necessary for the treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when *all* of the following criteria are met:

A. Member has a baseline plasminogen activity level of 45% or less at baseline; *and*

B. Member has a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 (e.g., ligneous conjunctivitis, ligneous gingivitis or gingival overgrowth, vision abnormalities, respiratory distress and/or obstruction, abnormal wound healing).

Aetna considers all other indications as experimental and investigational.

POLICY HISTORY
Effective: 09/10/2021
Next Review: 01/01/2022

Definitions

Additional Information
Clinical Policy Bulletin Notes

II. Continuation of Therapy

Aetna considers continuation of plasminogen, human tvmh (Ryplazim) therapy medically necessary for members with plasminogen deficiency type 1 (hypoplasminogenemia) who are experiencing benefit from therapy as evidenced by disease stability or disease improvement (e.g., improvement in lesion number and/or size, absence of new lesion development, improvement in respiratory function, increased quality of life).

Dosage and Administration

Plasminogen, human-tvmh is available as Ryplazim, which is supplied in a single-dose 50-mL vial containing 68.8 mg of plasminogen as a lyophilized powder for reconstitution with 12.5 mL of Sterile Water for Injection, USP. After reconstitution, each vial will contain 5.5 mg/mL of plasminogen. For intravenous infusion.

The recommended dosage of Ryplazim is 6.6 mg/kg body weight administered intravenously every 2 to 4 days.

Source: Prometic Bioproduction, 2021

BACKGROUND

U.S. Food and Drug Administration (FDA)-Approved Indications

- Ryplazim is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Plasminogen, human-tvmh, is available as Ryplazim (Prometic Bioproduction, Inc.). Treatment with Ryplazim temporarily increases plasminogen levels in the blood.

Ryplazim is contraindicated in patients with known hypersensitivity to plasminogen, or other components of Ryplazim. The label carries warnings and precautions for the following:

- Bleeding: administration may lead to bleeding at lesion sites or

worsen active bleeding.

- Tissue sloughing: respiratory distress due to tissue sloughing may occur in patients with mucosal lesions in the tracheobronchial tree following Ryplazim administration.
- Transmission of infectious agents: Ryplazim is made from human blood and therefore carries a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent.
- Hypersensitivity reactions, including anaphylaxis, may occur.
- Neutralizing antibodies (inhibitors) may develop, although were not observed in clinical trials. If clinical efficacy is not maintained (e.g., development of new or recurrent lesions),then determine plasminogen activity levels in plasma.
- Laboratory abnormalities: Patients receiving Ryplazim may have elevated blood levels of D-dimer. D-dimer levels will lack interpretability in patients being screened for venous thromboembolism (VTE).

The most frequent (incidence 10% or more) adverse reactions in clinical trials were abdominal pain, bloating, nausea, fatigue, extremity pain, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain.

Plasminogen Deficiency Type 1

Plasminogen deficiency type 1, also referred to as hypoplasminogenemia, is a rare genetic disorder characterized by decreased plasminogen levels that causes formation of fibrin-rich, ligneous ("wood-like") pseudomembranous lesions on mucous membranes that can impair normal tissue and organ function. Overall severity of the disorder can vary greatly from one person to another depending where the lesions, or growths, occur. The most common symptom is ligneous conjunctivitis, which can lead to blindness. However, the condition can affect other areas of the body which can lead to serious complications (e.g., obstruction of the airways). Plasminogen deficiency type 1 is caused by mutations in the *PLG* gene, which is inherited in an autosomal recessive pattern. *PLG* mutations can decrease the amount of plasminogen that is produced, alter its function, or both. When the mutations affect plasminogen levels as well as the activity of the protein, plasminogen deficiency type 1 results. There is currently no screening test available; molecular genetic testing can only confirm a diagnosis. Diagnosis

therefore generally relies on clinical symptoms, family medical history, and confirmatory testing. The growths usually recur if they are removed. Replacement therapy increases the plasma level of plasminogen enabling a temporary correction of the plasminogen deficiency and reduction or resolution of extravascular fibrinous lesions (NIH, 2016; NORD, 2016; Prometic Bioproduction, 2021).

On June 4, 2021, the U.S. Food and Drug Administration (FDA) approved Ryplazim (plasminogen, human-tvmh) for the treatment of patients with plasminogen deficiency type 1. FDA approval was based on one single-arm, open-label (unblinded) clinical trial that evaluated the efficacy and safety of Ryplazim in patients with plasminogen deficiency type 1. The clinical trial included a total of 15 patients who had a baseline plasminogen activity level between less than 5% and 45% of normal, and biallelic mutations in the plasminogen (*PLG*) gene. The age range was 4 to 42 years old, including 6 pediatric patients age 4 to 16 years, and 9 adults. All patients received Ryplazim at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks to achieve at least an increase of individual trough plasminogen activity by an absolute 10% above baseline and to treat the clinical manifestations of the disease. Efficacy was established on the basis of overall rate of clinical success at 48 weeks. Overall rate of clinical success is defined as 50% of patients with visible or other measurable non-visible lesions achieving at least 50% improvement in lesion number/size, or functionality impact from baseline. Spirometry was the only test of organ function used and one patient had abnormal spirometry at baseline. This patient had a history of ligneous airway disease with a severe obstructiveventilatory defect (FEV1: 46.7% of predicted normal) at baseline prior to treatment that corrected to normal (FEV1: 89.3% of predicted normal) after 12 weeks of treatment. All patients with any lesion at baseline had at least 50% improvement in the number/size of their lesions (FDA, 2021; Prometic Bioproduction, 2021).

The outcome from the trial on patients with external lesions found that 25 of the 32 (78%) external lesions [with sites mainly located in the eyes (ligneous conjunctivitis), nose, gums (ligneous gingivitis), ligneous lesions of the hands and feet] were resolved by the end of Week 48. There were no recurrent or new external lesions in any patient through Week 48. The outcome from the trial on patients with internal lesions found that 9 of the 12 (75%) assessed internal lesions were resolved by Week 48. The lesion sites were mainly located in the cervix, bronchus, colon, vagina

and uterus. No recurrent or new lesions were found on imaging in any patient through Week 48 (Prometic Bioproduction, 2021).

In summary, the effectiveness of Ryplazim was demonstrated by at least 50% improvement of the patient's lesions in all 11 patients who had lesions at baseline, and absence of recurrent or new lesions in any of the 15 patients through the 48 weeks of treatment.

CPT Codes/ HCPCS Codes/ICD-10 Codes
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+"

Code	Code Description
Other CPT codes related to the CPB:	
96365 – 96368	Intravenous infusion administration
HCPCS codes covered if selection criteria are met:	
Human-tvmh (Ryplazim) - No specific code	
ICD-10 codes covered if selection criteria are met:	
E88.02	Plasminogen deficiency

The above policy is based on the following references:

1. Celkan T. Plasminogen deficiency. J Thromb Thrombolysis. January, 2017; 43(1):132-138.
2. National Institutes of Health (NIH). Type 1 plasminogen deficiency. Genetic and Rare Diseases Information Center (GARD). Bethesda, MD: NIH; updated June 2016.
3. National Organization for Rare Disorders (NORD). Congenital plasminogen deficiency. NORD Rare Disease Database. Danbury, CT: NORD; updated May 2016.
4. Prometic Bioproduction, Inc. Ryplazim - plasminogen injection, powder, lyophilized, for solution. Laval, Quebec, Canada: Prometic Bioproduction; revised June 2021.
5. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018;131(12):1301-1310.
6. U.S. Food and Drug Administration (FDA). FDA approves first treatment for patients with plasminogen deficiency, a rare genetic disorder. Press Release. Silver Spring, MD: FDA; June 4, 2021.

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to Aetna Clinical Policy Bulletin Number: 0976 Plasminogen, Human-tvmh (Ryplazim)

There are no amendments for Medicaid.

new 09/10/2021

PROVIDER BULLETIN
PROVIDER INFORMATION

BlueCross BlueShield Minnesota

February 1, 2021

New Medical, Medical Drug and Behavioral Health Policy Management Updates—Effective April 5, 2021

Blue Cross and Blue Shield of Minnesota and Blue Plus (Blue Cross) will be expanding utilization management requirements, including prior authorization (PA) requirements.

As stewards of healthcare expenditures for our subscribers, we are charged with ensuring they receive the highest quality, evidence-based care. This is accomplished through expanded development of medical policies and through management of these policies to include the PA process. The primary purpose of the PA process is to ensure that evidence-based care is provided to our subscribers, driving quality, safety, and affordability.

The following prior authorization changes will be effective April 5, 2021:

Policy #	Policy Title/ Service	New Policy	Prior Authorization Requirement	Line(s) of Business
II-173	Accepted Indications for Medical Drugs Which Are Not Addressed by a Specific Medical Policy • Plasminogen (Ryplazim™)*	No	New	Commercial
L33394	Coverage for Drugs & Biologics for Label & Off-Label Uses: • Plasminogen (Ryplazim™)*	No	New	Medicare Advantage

* PA will be required upon FDA approval.

Products Impacted

The information in this bulletin applies **only** to subscribers who have coverage through Commercial and Medicare Advantage lines of business.

Submitting a PA Request when Applicable

- **Providers may submit PA requests for any treatment in the above table starting March 29, 2021.**
- Providers must check applicable Blue Cross policy and **attach all required clinical documentation** with the PA request. PA requests will be reviewed when patient-specific, relevant medical documentation has been submitted supporting the medical necessity of the service**.** Failure to submit required information may result in review delays or a denial of the request due to insufficient information to support medical necessity. If a provider does not obtain the required PA before rendering services, Blue Cross will deny claims as provider liability for lack of prior authorization.
- PA approval will be based on the Blue Cross policy criteria. To review Blue Cross criteria:

    - Go to providers.bluecrossmn.com
    - Under Tools & Resources, select "Medical Policy", and read/accept the Blue Cross Medical Policy Statement
    - Select the "+" (plus) sign next to Medical and Behavioral Health Policies, then select "Blue Cross Blue Shield of Minnesota Medical Policies" to access policy criteria.
- Current and future PA requirements can be found using the *Is Authorization Required* tool in the Availity® portal prior to submitting a PA request. Prior Authorization Lists are also updated to reflect additional PA requirements on the effective date of the management change and includes applicable codes. To access the pdf Prior Authorization Lists for all lines of business:
    - Go to providers.bluecrossmn.com
    - Under Tools & Resources, select "Medical Policy", and read/accept the Blue Cross Medical Policy Statement
    - Select the "+" (plus) sign next to "Utilization Management" to access the Prior Authorization Lists.
- If a provider does not obtain the required PA before rendering services, Blue Cross will deny claims as provider liability for lack of prior authorization. The requirement applies to subscribers starting therapy and to those already being treated with a therapy noted above.

Prior Authorization Requests

- Participating providers must submit PA requests online via our free Availity® provider portal.
- For medical drugs, PA's can also be submitted using a NCPDP standard XML file feed to Blue Cross through CenterX, via an integrated Electronic Medical Record (EMR) system. To learn how to do this, providers should contact their EMR vendor for assistance.
- Out of state, non-contracted providers can submit a PA request to Blue Cross by either using the electronic processes above, the fax form located under the Forms & Publications section on the Blue Cross website, or their own PA form.

Note: An approved PA does not guarantee coverage under a subscriber's benefit plan. Subscriber benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies.

Reminder Regarding Medical Policy Updates & Changes:

Medical Policy changes are communicated in the Upcoming Medical Policy Notifications section of the Blue Cross Medical and Behavioral Health Policy website. The Upcoming Policies section lists new, revised, or inactivated policies approved by the Blue Cross Medical and Behavioral Health Policy Committee and are effective at minimum 45 days from the date they were posted. To access the website:

- Go to providers.bluecrossmn.com
- Under Tools & Resources, select "Medical Policy", and read/accept the Blue Cross Medical Policy Statement
- Select the "+" (plus) sign next to "Medical and Behavioral Health Policies" to see the Upcoming Medical Policy Notifications section

Questions?

If you have questions, please contact provider services at (**651**) **662-5200** or **1-800-262-0820**.