Original Effective Date: 01/26/2022
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Last P&T Approval/Version: 07/30/2025
Next Review Due By: 07/2026
Policy Number: C22238-A

Ryplazim (human plasminogen)

PRODUCTS AFFECTED

Ryplazim (human plasminogen)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Plasminogen deficiency type 1 (hypoplasminogenemia)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PLASMINOGEN DEFICIENCY TYPE 1:
   1. Documented diagnosis of plasminogen deficiency type 1 (hypoplasminogenemia) AND
   2. Documentation of member plasminogen activity and antigen levels less than 45% OR Genetic testing that reveals biallelic pathogenic variants in *PLG* gene [DOCUMENTATION

REQUIRED]
AND

3. Documentation of member having 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) OR member is scheduled for an invasive procedure that could cause or contribute to development of lesions due to local trauma.
   AND
4. Documentation of member's treatment plan with dosing and interval for administration

CONTINUATION OF THERAPY:

A. PLASMINOGEN DEFICIENCY TYPE 1:

1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
2. Documentation of positive clinical response as demonstrated by no new lesions, or recurring lesions have improved, or trough plasminogen levels have been maintained during follow-up visits
   AND
3. Documentation of member's treatment plan with dosing and interval for administration

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified hematologist, geneticist, or specialist with experience treating hypoplasminogenemia [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

No restriction

QUANTITY:

6.6 mg/kg every 2 to 4 days
Limited to one month per dispense based on member's treatment plan

PLACE OF ADMINISTRATION:

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Intravenous

DRUG CLASS:

Plasma Proteins

FDA-APPROVED USES:

Indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Congenital plasminogen deficiency type I, also known as plasminogen deficiency (PLGD) or hypoplasminogenemia, is an ultra-rare, genetic, autosomal recessive, multisystem disease in which individuals develop fibrinous pseudomembranes on the mucous membranes of their body (e.g., respiratory, gastrointestinal, and genitourinary tracts; oropharynx; middle ear; skin; and central nervous system).

Typically, plasminogen is broken down into plasmin, which then has multiple functions throughout the body including breaking down fibrin. Since individuals with PLGD lack plasminogen, fibrin accumulates and causes inflammation and woody lesions throughout the body's mucous membranes; it is currently unknown why fibrin accumulates in mucous membranes and not in the blood vessels. The manifestations of PLGD are highly individualized, but the mucous membranes that line the mouth and the inside of the eyelid (i.e., conjunctiva) are generally most affected. The lesions may be painful and can cause severe and potentially life- threatening complications:

- Gum lesions may lead to gingivitis and tooth loss
- Eye, or conjunctiva, lesions may cause tearing and scarring of the cornea, leading to vision loss
- Middle ear lesions can lead to hearing loss
- Respiratory tract lesions can obstruct the airway
- Some children develop occlusive hydrocephalus, so shunt placement may be required

The prevalence of congenital plasminogen deficiency is estimated to be 1.6 per 1 million people in the general population. It is estimated that only 500 people in the United States and 12,000 people worldwide have symptomatic plasminogen deficiency.

There is currently no screening test available for PLGD; molecular genetic testing can only confirm a diagnosis. Diagnosis therefore generally relies on clinical symptoms, family medical history, and confirmatory testing. PLGD is highly individualized, so while some infants and children may show early manifestations, others may not have symptoms until adulthood. There is currently no standardized treatment for individuals with PLGD due to the rarity of the disease. Many reported therapies have only anecdotal evidence to support efficacy or were only used in a single person.
Therapies that have been tried in PLGD include corticosteroids, immunosuppressants (e.g., cyclosporine), antivirals, and heparin. The lesions can be surgically removed but usually grow back. Replacing plasminogen has been the only treatment modality in PLGD shown to improve symptoms and prevent recurrence.

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

obstructive ventilatory 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.
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.

Ryplazim was well tolerated, with no deaths or serious adverse events observed in its clinical trials. The most commonly reported adverse effects in Ryplazim Trial 2 included headache (43%), nasopharyngitis (36%), abdominal pain (29%), nausea (29%), diarrhea (21%), rhinorrhea (21%), and cough (21%).
Several patients experienced adverse events or laboratory abnormalities that were expected due to the activity of plasminogen, which included epistaxis, hematuria, dysmenorrhea, blood in the urine, and elevated D-dimer levels.
Three patients in Ryplazim Trial 2 developed anti-plasminogen antibodies following treatment with Ryplazim; however, trough plasminogen activity levels suggested that these antibodies were not neutralizing antibodies (i.e., inhibitors) to plasminogen. Patients using Ryplazim should be monitored for a loss of clinical effect (new or recurrent lesions), and regular trough plasminogen activity levels should be obtained.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Ryplazim (human plasminogen) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Ryplazim (human plasminogen) include: patients with known hypersensitivity to plasminogen, or other components of Ryplazim.

OTHER SPECIAL CONSIDERATIONS:
Ryplazim 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.

Following reconstitution, each vial will contain 5.5 mg/mL of plasminogen.
1. Calculate the total infusion volume of Ryplazim based on the final plasminogen concentration of 5.5 mg/mL: Infusion volume (mL) = body weight (kg) × 1.2
2. The patient may require additional vials of Ryplazim using the formula in step 1. Round up the estimated number of vials using this formula: Number of vials = infusion volume (mL) × 0.08
To determine dosing frequency, the patient must have a baseline plasminogen activity level. Patients receiving fresh frozen plasma must have a 7-day washout period prior to obtaining this baseline level.

- Start Ryplazim using a dosing frequency of every 3 days.
- Then, obtain a trough plasminogen level approximately 72 hours after the first dose and before the second dose (e.g., if the first dose is given at 8:00 AM on Monday, the trough should be taken at 8:00 AM on Thursday).
  - Plasminogen activity level <10% above baseline: change frequency to every 2 days
  - Plasminogen activity level between 10% and 20% above baseline: maintain dosing at every 3 days
  - Plasminogen activity level >20% above baseline: change dosing to every 4 days
- Maintain this same dosing frequency for 12 weeks while treating active lesions.
  - If lesions resolve after 12 weeks of treatment, continue using Ryplazim at the same dosing frequency and monitor for new lesions every 12 weeks.
  - If lesions have not resolved after 12 weeks of treatment or if new lesions appear, increase dosing frequency in 1-day increments every 4 to 8 weeks (up to a maximum dosing interval of every 2 days), according to the package insert, while continuing to assess lesion resolution. A trough plasminogen activity level should also be checked.

- If the trough plasminogen activity level is ≥10% above baseline trough level, consider other treatment options such as surgical removal of the lesion(s) in addition to plasminogen therapy.
- If the trough plasminogen activity level is <10% above baseline trough level, obtain a second trough plasminogen activity level to confirm. A confirmed low plasminogen activity level in combination with no clinical efficacy may indicate the possibility of neutralizing antibodies. Consider discontinuing Ryplazim.

Ryplazim is administered intravenously through a syringe disc filter. If a patient and/or caregiver receives detailed instructions (see Ryplazim package insert) and training from a healthcare professional, they may be able to safely administer Ryplazim independently. This may be advantageous, given the drug must be administered every 2 to 4 days indefinitely.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J2998	Injection, plasminogen, human-tvmh, 1 mg

AVAILABLE DOSAGE FORMS:
Ryplazim SOLR 68.8MG single dose vial

REFERENCES

1. Ryplazim (plasminogen human-tvmh) lyophilized powder for reconstitution, for intravenous use [prescribing information]. Laval, Quebec, Canada: Prometic Bioproduction Inc; January 2024.
2. Celkan T. Plasminogen deficiency. J Thromb Thrombolysis. January, 2017; 43(1):132-138.
3. National Institutes of Health (NIH). Type 1 plasminogen deficiency. Genetic and Rare Diseases Information Center (GARD). Bethesda, MD: NIH; updated June 2016.
4. National Organization for Rare Disorders (NORD). Congenital plasminogen deficiency. NORD Rare Disease Database. Danbury, CT: NORD; updated May 2016.
5. Prometic Bioproduction, Inc. Ryplazim - plasminogen injection, powder, lyophilized, for solution. Laval, Quebec, Canada: Prometic Bioproduction; revised June 2021.
6. 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.
7. 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.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Duration of Approval References	Q3 2025

REVISION- Notable revisions: Required Medical Information References	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Age Restrictions Other Special Considerations Available Dosage Forms References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file