Clinical Policy: Plasminogen, Human-tvmh (Ryplazim)

Reference Number: LA.PHAR.513
Effective Date:
Last Review Date: 05.01.23
Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Please note: This policy is for medical benefit

Description
Plasminogen (Ryplazim®) is a plasma-derived human plasminogen.

FDA Approved Indication(s)
Ryplazim is indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections® that Ryplazim is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Plasminogen Deficiency Type 1 (must meet all)**:**

1. Diagnosis of symptomatic congenital plasminogen deficiency (C-PLGD) as evidenced by documentation of two of the following (a - c):
   a. Presence of a *PLG* mutation;
   b. Plasminogen activity level ≤ 45%;
   c. Signs or symptoms consistent with C-PLGD (*see Appendix D*);
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 11 months;
4. Dose does not exceed 6.6 mg/kg every second, third, or fourth day (*based upon individual pharmacokinetics*).

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND

criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: LA.PMN.53 for Medicaid.

II. Continued Therapy

A. Plasminogen Deficiency Type 1 (must meet all)**:**

1. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in C-PLGD-associated signs or symptoms (e.g., improvement in the size of visible lesions, imaging of nonvisible lesions, or spirometry if pulmonary involvement (*see Appendix D*));
3. If request is for a dose increase, new dose does not exceed 6.6 mg/kg every second, third, or fourth day (*based upon individual pharmacokinetics*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: LA.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – LA.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
C-PLGD: congenital plasminogen deficiency
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to plasminogen, or other components of Ryplazim
- Boxed warning(s): none reported

Appendix D: Clinical Signs and Symptoms of Congenital Plasminogen Deficiency

C-PLGD (also known as type 1 plasminogen deficiency or hypoplasminoginemia) is a rare autosomal-recessive disorder of the fibrinolytic system. The primary manifestation is development of abnormal extravascular accumulation or growth of fibrin-rich, woody (ligneous) pseudomembranous lesions on mucous membranes throughout the body. Wound healing also may be impaired. The disease appears to be most severe in infants and children. Examples of lesion locations and associated complications (not all inclusive):

- Conjunctival lesions "ligneous conjunctivitis" - most common lesion (may result in visual impairment or blindness)
- Tracheobronchial or renal lesions (may result in respiratory or renal failure)
- Lesions in the cerebral ventricular system (may result in congenital occlusive hydrocephalus)
- Lesions in the ears, nasopharynx, and oral cavity (may result in hearing loss, ligneous tonsillitis or ligneous gingivitis with tooth loss)
- Lesions in the genitourinary tract (may result in dysmenorrhea, abnormal menses, dyspareunia or infertility)

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Shapiro, Amy D. et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020 Mar; 105(3):554-561.

Appendix E: Ryplazim Pivotal Trial

- In a pivotal phase 2/3 clinical trial for the treatment of C-PLGD, 15 patients with C-PLGD were enrolled, including six pediatric patients, for 48 weeks of therapy with Ryplazim.
- All patients treated with Ryplazim achieved the targeted increase from baseline in their individual trough plasminogen activity levels through 12 weeks of therapy.
- In addition, all patients who had active visible lesions when enrolled in the trial had complete healing of their measurable lesions within 48 weeks of initiating therapy.
- Adverse events reported in the clinical study were characterized as mild, with no patient deaths, serious adverse events or adverse events that caused study discontinuation.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
C-PLGD	6.6 mg/kg body weight given every 2 to 4 days (*based upon individual pharmacokinetics*)	6.6 mg/kg

VI. Product Availability

Single-dose vial: 68.8 mg in 50 mL vial (5.5 mg/mL of plasminogen after reconstitution)

VII. References

1. Ryplazim Prescribing Information. Prometic Bioproductions Inc: Laval, Quebec, Canada; November 2021. Available at: https://www.fda.gov/media/149806/download. Accessed August 1, 2022.

2. Product Pipeline: Plasminogen Deficiency. Liminal BioSciences, Inc. Available at: https://liminalbiosciences.com/pipeline/plasminogen/plasminogen-deficiency-clinical-trials/. Accessed October 1, 2020.
3. ClinicalTrials.gov. A study of Prometic plasminogen IV infusion in subjects with hypoplasminogenemia. Available at: https://clinicaltrials.gov/ct2/show/NCT02690714. Accessed October 1, 2020.
4. Shapiro, Amy D. et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020 Mar; 105(3):554-561.
5. Shapiro, Amy D. et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22; 131(12):1301-1310.
6. Mehta R, Shapiro AD. Plasminogen deficiency. Haemophilia. 2008; 14, 1261–1268. DOI: 10.1111/j.1365-2516.2008.01825.x.
7. Schuster V, Hugle B, Tefs K. Plasminogen deficiency. J Thromb Haemost 2007; 5:2315–22.
8. Tefs K, Gueorguieva M, Klammt J, et al. Molecular and clinical spectrum of type I plasminogen deficiency: a series of 50 patients. Blood, 1 November 2006; 108(9):3021-3026.
9. Type 1 plasminogen deficiency. Genetic and Rare Diseases Information Center. National Institutes of Health. Available at https://rarediseases.info.nih.gov/diseases/4380/type-1-plasminogen-deficiency. Accessed August 1, 2022.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2998	Injection, plasminogen, human-tvmh, 1 mg

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Policy created	05.01.23	

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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