# Clinical Policy: Plasminogen, Human-tvmh (Ryplazim)

Reference Number: ERX.SPA.418
Effective Date: 06.04.21
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

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

**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.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 all of the following (a, b, and 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 ≥ 2 years;
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**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. If member has received at least 3 months of Ryplazim treatment, increased trough plasminogen activity by at least 10% from baseline;
3. 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*));
4. 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**
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**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 policy – ERX.PA.01 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.

1. *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.*
2. *A study of Prometic plasminogen IV infusion in subjects with hypoplasminogenemia. Trial record 2 of 2 for: 2002C011G. ClinicalTrials.gov Identifier: NCT02690714. Available at: https://clinicaltrials.gov/ct2/show/NCT02690714?term=2002C011G&draw=2&rank=2. Accessed October 1, 2020.*

## 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; June 2021. Available at: https://www.fda.gov/media/149806/download. Accessed July 6, 2021.
2. Product Pipeline: Plasminogen Deficiency. Liminal BioSciences, Inc. Available at: https://liminalbiosciences.com/pipeline/plasminogen/plasminogen-deficiency-clinical-trials/. Accessed October 1, 2020.
3. Shapiro, Amy D. et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020 Mar; 105(3):554-561.
4. 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.
5. Mehta R, Shapiro AD. Plasminogen deficiency. Haemophilia. 2008; 14, 1261–1268. DOI: 10.1111/j.1365-2516.2008.01825.x.
6. Schuster V, Hugle B, Tefs K. Plasminogen deficiency. J Thromb Haemost 2007; 5:2315–22.
7. 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.
8. A treatment protocol for expanded access administration of Prometic plasminogen due to closure of clinical trial. Trial record 1 of 2 for: 2002C011G. ClinicalTrials.gov Identifier: NCT03642691. Available at: https://clinicaltrials.gov/ct2/show/NCT03642691?term=2002C011G&draw=2&rank=1. Accessed October 1, 2020.
9. A study of Prometic plasminogen IV infusion in subjects with hypoplasminogenemia. Trial record 2 of 2 for: 2002C011G. ClinicalTrials.gov Identifier: NCT02690714. Available at: https://clinicaltrials.gov/ct2/show/NCT02690714?term=2002C011G&draw=2&rank=2. Accessed October 1, 2020.
10. 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 October 6, 2020.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created pre-emptively | 10.01.20 | 11.20 |
| 4Q 2021 annual review: RT4: drug is now FDA-approved; criteria updated per FDA labeling; modified continuation of therapy to require increased trough plasminogen activity; modified examples of positive response to remove qualification of one year on treatment; references reviewed and updated. | 07.06.21 | 11.21 |

**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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.