Clinical Policy: Plasminogen, Human-tvmh (Ryplazim)

Reference Number: CP.PHAR.513
Effective Date: 06.04.21
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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.

It is the policy of health plans affiliated with Centene Corporation® 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:
Commercial – 6 months or to the member's renewal date, whichever is longer
HIM/Medicaid – 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 one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

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: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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:
Commercial – 6 months or to the member's renewal date, whichever is longer
HIM/Medicaid – 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 one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
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: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.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 hypoplasminogenemia) 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 with any lesion at baseline achieved the targeted increase (at least 50% improvement in the number/size of their 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 IV every 2 to 4 days. The total infusion volume to be administered is determined by the formula: Infusion volume (mL) = body weight (kg) x 1.2	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; January 2024. Available at: https://www.ryplazim.com/pdf/kedrion-ryplazim-prescribing-information.pdf. Accessed August 8, 2025.
2. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen, human-tvmh for the treatment of children and adults with plasminogen deficiency type 1. Haemophilia. 2023;29(6):1556-1564.
3. Shapiro, Amy D. et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020 Mar; 105(3):554-561.
4. Shapiro AD, Menegatti M, Palla R, 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.
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. 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 8, 2025.

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	P&T Approval Date
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 to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	07.06.21	11.21
Per prescribing information, modified minimum age from at least 2 years or older to 11 months or older; modified diagnostic requirements from all (a, b, and c) to two of three; removed requirement for increased trough plasminogen activity on continued therapy; HCPCS code updated.	01.10.22	02.22
Added HCPCS code [J2998].	06.30.22	
4Q 2022 annual review: no significant changes; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	08.02.22	11.22
4Q 2023 annual review: no significant changes; references reviewed and updated.	07.10.23	11.23
4Q 2024 annual review: revised Commercial approval durations to "6 months or to the member's renewal date, whichever is longer;" references reviewed and updated.	07.19.24	11.24
4Q 2025 annual review: revised initial approval duration for Medicaid and HIM to 12 months; references reviewed and updated.	07.15.25	11.25

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. The Health Plan 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. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. 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. The Health Plan 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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.