Ryplazim® (plasminogen, human-tvmh) (Intravenous)

Effective Date: 04/01/2022
Dates Reviewed: 03/10/2022, 03/02/2023, 12/07/2023, 01/10/2024, 05/21/2025, 03/17/2026
Scope: Medicaid, Commercial, Medicare

I. Length of Authorization

Coverage will be provided initially for 12 weeks.

- In members with complete response, coverage will be renewed annually thereafter.
- In members with less than complete response, coverage will be renewed for an additional 12 weeks to optimize frequency of administration.

II. Dosing Limits

A. Max Units (per dose and over time) [HCPCS Unit]:

- 757 billable units (757 mg) every 2 days

III. Summary of Evidence

Ryplazim (plasminogen, human-tvmh) was approved for the treatment of plasminogen deficiency (PLGD) type 1 (hypoplasminogenemia), a disorder that can impair tissue and organ function. Approval of Ryplazim was based on a solitary single-arm, open-label, phase 2/3 study in which 14 patients completed 48 weeks of therapy. A single dose of Ryplazim (6.6mg/kg) was given at Week 0 over a 10-30min IV infusion. The same dose of Ryplazim was given every 2 to 4 days during Weeks 1-12. During treatment Weeks 12-48 patients also received the same dose (6.6mg/kg) every 2-4 days, but investigators had the option to modify the dosing schedule. Due to the small sample size no formal statistical analysis was performed, but the primary and secondary endpoints were defined as being met. The common adverse effects for Ryplazim are headache, nasopharyngitis, abdominal pain, nausea, diarrhea, rhinorrhea, and cough.

IV. Initial Approval Criteria

Coverage is provided in the following conditions:

- Member is at least 11 months of age; **AND**
- Prescribed by or in consultation with a hematologist; **AND**
- Member blood pressure is controlled prior to initiation of treatment**; AND**
- Member has healing of lesions or wounds suspected as a source of a recent bleeding event prior to initiating therapy**; AND**
- Member has had baseline plasminogen activity measured prior to therapy and plasminogen activity level is ≤ 45% *(Note: If member is receiving plasminogen supplementation with fresh frozen plasma, allow for a 7-day washout period before obtaining baseline plasminogen activity level)*; **AND**

- Ryplazim is dosed according to the US Food and Drug Administration labeled dosing for PLGD type 1 (see Dosage/Administration table below); AND
- Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Universal Criteria

- Members with bleeding diatheses or on concomitant therapy with anticoagulants, antiplatelet drugs, or other agents which may interfere with normal coagulation will be monitored during and for 4 hours after infusion of Ryplazim; **AND**

Plasminogen Deficiency Type 1 (Hypoplasminogenemia) † Φ [1]

- Member has a history of visible or non-visible lesions (e.g., confirmed by computed tomography, magnetic resonance imaging, ultrasound, etc.)

Note: *All members must initiate therapy at a frequency of every three days.*

† FDA Approved Indication(s); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

V. Renewal Criteria

Coverage can be renewed based on the following criteria:

- Member continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section IV; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe bleeding, respiratory distress due to tissue sloughing, hypersensitivity reactions, including anaphylaxis, etc.; **AND**
    - Member has demonstrated a beneficial response to therapy (i.e., resolution of lesions); **OR**
    - Member's lesions have not resolved after an initial 12 weeks of therapy OR there are new or recurrent lesions; **AND**
        - Member may increase dosage frequency, as outlined below, in one day increments every 4-8 weeks up to the max dosing frequency (i.e., every two days); **AND**
        - Re-assess the trough plasminogen activity level if, after 12 additional weeks of dose optimization, no clinical effect has been noted; **AND**
            - If the trough plasminogen activity level is <10% above the baseline trough level, repeat trough. If low plasminogen is confirmed AND no clinical effect has been demonstrated, consider treatment discontinuation

VI. Dosage/Administration [1]

Indication	Dose
Type 1 Hypo-plasminogenemia	The recommended dosage of Ryplazim is 6.6 mg/kg of body weight administered intravenously every 2 to 4 days. Initiate dosing at a frequency of every three days, then adjust as below. <u>Determination of Dosing Frequency</u> • Obtain a baseline plasminogen activity level (allow for a 7-day washout period if the patient has been receiving fresh frozen plasma); **AND** • Obtain a trough plasminogen activity level approximately 72 hours following the initial dose and prior to the second dose; **AND** – If the plasminogen activity level is <10%***** above baseline, change dosing frequency to every 2 days – If the plasminogen activity level is ≥10 and ≤20%***** above baseline, maintain dosing frequency at every 3 days – If the plasminogen activity level is >20%***** above baseline, change dosing frequency to every 4 days • Maintain dosing frequency as determined above for 12 weeks while treating active lesions; **AND** – If lesions have resolved by week 12, continue at same dosing frequency and monitor for new or recurrent lesions every 12 weeks – If lesions have not resolved by week 12, or there are new or recurrent lesions, increase the dosing frequency in one-day increments every 4-8 weeks up to every 2 day dosing. If desired clinical change does not occur by 12 weeks, check trough plasminogen activity level; **AND** o If the plasminogen activity level is ≥10%***** above the baseline trough level, consider other treatment options (e.g., surgical removal) in addition to plasminogen treatment o If the plasminogen activity level is <10%***** above the baseline trough level, obtain a second trough level to confirm. If low trough level is confirmed, consider discontinuing therapy if no clinical efficacy has been demonstrated
*****Plasminogen activity (%) as absolute change	

VII. Billing Code/Availability Information

<u>HCPCS code</u>:

- J2998 – Injection, plasminogen, human-tvmh, 1 mg; 1 billable unit = 1 mg

<u>NDC:</u>

- Ryplazim 68.8 mg single-dose vial: 70573-0099-xx

VIII. References

1. Ryplazim [package insert]. Laval, Quebec, CA; Prometric Bioproduction, Inc.; September 2025. Accessed March 2026.
2. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22;131(12):1301-1310. doi: 10.1182/blood-2017-09-806729. Epub 2018 Jan 10.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
E88.02	Plasminogen deficiency

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale: Ryplazim was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Ryplazim according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.