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Policy Number: 064.000
Title: Coverage Determination Policy for Ryplazim (Plasminogen, Human-Tvmh)

Regions:	☒ **Texas**	☐ **Florida**	☐ **Indiana**	☐ **New Jersey**	☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Coverage Policy Number: 064.000

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Ryplazim (plasminogen, human-tvmh) is proven and medically necessary for the treatment of **Plasminogen Deficiency Type 1 (hypoplasminogenemia)** when **ALL** of the following criteria are met:

A. Diagnosis of hypoplasminogenemia as measured by plasminogen activity level ≤ 45% of laboratory standard

B. Presence of clinical signs and symptoms of the disease (e.g., ligneous conjunctivitis, gingivitis, tonsillitis, abnormal wound healing, etc.)

C. Prescribed by or in consultation with a hematologist

D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

E. Initial authorization will be for no more than 6 months

Renewal/Continuation of Therapy Requests

Continuation of therapy requests for Ryplazim for the treatment of **Hypoplasminogenemia** will be approved if **ALL** of the following criteria are met:

A. Patient has previously received treatment with Ryplazim therapy

B. Patient has experienced a positive clinical response to Ryplazim therapy (e.g., improved (reduction) in lesion number/size, improvement in wound-healing, plasminogen activity trough level has increased by at least 10 percentage points from baseline; etc.)

C. Prescribed by or in consultation with a hematologist

D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

E. Reauthorization will be for no more than 12 months

Note: Ryplazim is unproven and not medically necessary for the treatment of idiopathic pulmonary fibrosis.

FDA Approved Dose and Indication

FDA Approved Indication	Approved Dosing
Plasminogen deficiency type 1 – (Hypoplasminogenemia)	6.6 mg/kg IV infusion every 2 to 4 days (titrate according to response; see below for determination of dosing frequency* for informational purposes) Initial dosing frequency: (Obtain a baseline plasminogen activity level; if patient is receiving fresh frozen plasma, allow for a 7-day washout period before obtaining levels). Initiate dosing at a frequency of every three days

*Determination of dosing frequency on day 3: Obtain a trough plasminogen activity level about 72 hours after the initial dose and prior to the second dose (same time of day as initial dosing)

- If the plasminogen activity level is less than 10% above baseline, increase frequency to every 2 days
- If plasminogen activity level is 10% to 20% above baseline, maintain frequency at every 3 days
- If plasminogen activity level is more than 20% above baseline, decrease frequency to every 4 days

Maintain this dosing frequency for 12 weeks while treating active lesions

Determination of dosing frequency at week 12:

- If lesions do not resolve by 12 weeks or there are new or recurrent lesions, increase dosing frequency in 1-day increments every 4 to 8 weeks up to Q2D while reassessing clinical improvement until lesion resolution or until lesions stabilize without further worsening. If desired clinical improvement does not occur by 12 weeks, check trough plasminogen activity level.
  - If the trough plasminogen activity level is 10% or more above baseline trough level, consider other treatment options (eg, surgical removal of lesion in addition to plasminogen treatment)
  - If trough plasminogen activity level is less than 10% above baseline trough level, obtain a second level to confirm; if confirmed in combination with no clinical efficacy, consider discontinuing plasminogen treatment due to possibility of neutralizing antibodies
- If lesions resolve by 12 weeks, continue at same dosing frequency and monitor for new or recurrent lesions every 12 weeks

General Background

Plasminogen is a naturally occurring protein synthesized by the liver. Plasminogen is converted to plasmin, which then leads to lysis of fibrin clots in the blood and/or on cell surfaces (wound healing, angiogenesis, tissue remodeling, etc.).

Plasminogen deficiency type 1, or hypoplasminogenemia, is a rare autosomal-recessive disorder of the fibrinolytic system. Deficiency of plasminogen levels cause abnormal extravascular accumulation or growth of fibrin-rich ligneous pseudomembranous lesions on mucous membranes throughout the body. Consequently, the most common clinical manifestation of plasminogen deficiency type 1 is ligneous conjunctivitis (LC), characterized by inflamed, woody growth on the conjunctival membranes – which, if left untreated, may result in visual impairment or blindness. Replacement therapy may increase the plasma level of plasminogen, thereby allowing a temporary correction of the deficiency and reduction of extravascular fibrinous lesions.

Clinical Evidence

The efficacy of plasminogen, human-tvmh in pediatric and adult patients with plasminogen deficiency type 1 was evaluated in RYPLAZIM trial 2, a single-arm, open-label clinical trial (n = 15). Enrolled patients, aged 4 to 42 years, had a baseline plasminogen activity level between < 5% and 45% of normal, and biallelic mutations in the plasminogen (PLG) gene. All patients received plasminogen, human-tvmh at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks, with a primary endpoint of achieving at least an increase of individual trough plasminogen activity by an absolute 10% above baseline. Secondary endpoint was establishment of overall rate of clinical success at 48 weeks, defined by patients with visible [sites mainly located in the eyes, nose, gums, hands and feet] or measurable non-visible lesions [cervix, bronchus, colon, vagina and uterus] achieving ≥ 50% improvement in lesion number/size, or functionality impact from baseline. Authors found that 78% of external lesions and 75% of internal lesions were resolved by week 48, with no recurrent or new external or internal lesions in any patient through week 48 (NCT02690714).

HCPCS Code

HCPCS Code	J2998: plasminogen, human-tvmh, 1 mg
Available Dosage Form	Intravenous Powder for Solution: 68.8 MG
Route of Administration	Intravenous

Acronyms

Ligneous conjunctivitis = LC

Plasminogen gene = PLG

References

1. Ryplazim (plasminogen, human-tvmh) intravenous powder for solution, [prescribing information]. Laval, Quebec, Canada: ProMetic BioTherapeutics, Inc. November 2021.
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 Jan 10.
3. Tefs K, Gueorguieva M, Klammt J, et al. Molecular and clinical spectrum of type I plasminogen deficiency: A series of 50 patients. Blood. 2006 Nov 1;108(9):3021-6.
4. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. J Thromb Haemost. 2007 Dec;5(12):2315-22
5. Ryplazim In: MerativeTM Micromedex® DRUGDEX® (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: 9/5/2023)