Drug Coverage Policy

Effective Date.....05/01/2024
Coverage Policy Number.....IP0382
Policy Title.....Ryplazim

Hematology – Ryplazim

- Ryplazim® (plasminogen, human-tvmh intravenous infusion – Prometic/Kedrion)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Medical Necessity Criteria

Ryplazim is considered medically necessary when the following criteria are met:

1. **Plasminogen Deficiency Type 1 (Hypoplasminogenemia).** Individual meets **ALL** of the following criteria:
    A. Diagnosis of plasminogen deficiency type 1 confirmed by documentation of **BOTH** of the following:
        i. Biallelic pathogenic variants in the PLG gene
        ii. Baseline plasminogen activity level less than or equal to 45% of normal based on the reference range for the reporting laboratory
    B. History of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency

C. Medication is prescribed by, or in consultation with, a hematologist

Dosing. The dose is 6.6 mg/kg body weight intravenously, not more frequently than once every other day.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of plasminogen, human-tvmh (Ryplazim) is considered medically necessary for plasminogen deficiency type 1 when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 3 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9090	Injection, plasminogen, human-tvmh, 1 mg (Code deleted 06/30/2022)
J2998	Injection, plasminogen, human-tvmh, 1 mg

Background

OVERVIEW
Ryplazim, a plasma-derived human plasminogen, is indicated for the treatment of **plasminogen deficiency type 1 (hypoplasminogenemia)**.[1]

Disease Overview
Congenital plasminogen deficiency is an ultra-rare, autosomal recessive disease affecting approximately 500 patients in the US (estimated prevalence of 1.6 per million individuals).[2] Female

predominance has been reported. The median age of first clinical manifestations has been reported as approximately 10 months in one case series.[3] Type 1 deficiency is considered "true" plasminogen deficiency and results in decreased plasminogen antigen and activity levels. Type 2 deficiency is referred to as dysplasminogenemia; plasminogen antigen levels are normal, but functional activity is reduced. Type 2 deficiency is asymptomatic and not clinically relevant. By contrast, type 1 deficiency may present with multisystem disease characterized by fibrin-rich ("woody") pseudomembranes on mucous membranes.[2] Treatment of congenital plasminogen deficiency should be coordinated by a hematologist who is knowledgeable about the disorder.[4]

Clinical Efficacy
Clinical efficacy of Ryplazim was evaluated in one Phase II/III pivotal study in patients with plasminogen deficiency type 1 (n = 15).[1,5] All patients had a baseline plasminogen activity level between < 5% and 45% of normal, as well as biallelic mutations in the *PLG* (plasminogen) gene.[1] The primary clinical efficacy endpoint was overall clinical success. Overall clinical success was defined as 50% of patients with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Patients were not required to have active lesions at baseline; however, they were required to have a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency. Among the 15 patients in the study, a total of 32 external lesions and 12 internal lesions were evaluated. The majority of lesions were resolved by Week 48; no patients experienced new or recurrent lesions.

Dosing Information
Ryplazim dosing frequency is adjusted based on trough plasminogen activity level; the most frequent recommended dosing interval is once every other day. It is recommended to continue dosing for 12 weeks while treating active lesions and then assess for clinical response. If lesions do not resolve by 12 weeks, or if there are new or recurrent lesions, dosing frequency can be escalated (to a maximum of every other day) while assessing clinical improvement until lesion resolution or until the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, an additional trough plasminogen activity level should be obtained. If the trough level is ≥ 10% (absolute change in plasminogen activity) above baseline, surgical removal of the lesions should be considered in addition to plasminogen treatment. If the trough level is < 10% baseline (in combination with no clinical efficacy), consider discontinuing plasminogen treatment due to the possibility of neutralizing antibodies.

References

1. Ryplazim® intravenous infusion [prescribing information]. Laval, Quebec, Canada and Fort Lee, NY: Prometic; November 2021.
2. Shapiro AD, Menegatti M, Palla R, et al. An international registry of patients with plasminogen deficiency (HISTORY). *Haematologica*. 2020;105(3):554-561.
3. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. *J Thromb Haemost*. 2007;5(12):2315-2322.
4. Congenital Plasminogen Deficiency. National Organization for Rare Disorders. Updated October 29, 2021. Available at: https://rarediseases.org/rare-diseases/congenital-plasminogen-deficiency/. Accessed on December 30, 2023.
5. Shapiro AD, Naker 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.

Revision Details

Type of Revision	Summary of Changes	Date

Annual Revision	No criteria changes	05/01/2024

The policy effective date is in force until updated or retired.