PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Ryplazim Prior Authorization Policy
- Ryplazim® (plasminogen, human-tvmh intravenous infusion – Prometic/Kedrion)

REVIEW DATE: 01/03/2024

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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ryplazim. All approvals are provided for the duration noted below. In cases where the approval duration is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ryplazim as well as the monitoring required for adverse events and long-term efficacy, approval requires Ryplazim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ryplazim is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Plasminogen Deficiency Type 1 (Hypoplasminogenemia).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
     - **i.** Patient has a diagnosis of plasminogen deficiency type 1 confirmed by both of the following:
       - **a)** Biallelic mutations in the *PLG* gene; AND
       - **b)** Baseline plasminogen activity level (prior to initiating Ryplazim) ≤ 45% of normal based on the reference range for the reporting laboratory; AND
     - **ii.** Patient has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency; AND
     - **iii.** Ryplazim is prescribed by or in consultation with a hematologist.
   - **B)** Patient is Currently Receiving Ryplazim. Approve for 1 year if the patient meets the following (i and ii):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient has had a clinical response to Ryplazim, as determined by the prescriber; OR
         Note: Examples of clinical response include resolution of active lesions, stabilization of current lesions, and prevention of new or recurrent lesions.
       - **b)** Patient has a trough plasminogen activity level ≥ 10% (absolute change in plasminogen activity) above the baseline trough level (prior to initiating Ryplazim); AND
     - **ii.** Ryplazim is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ryplazim is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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 (). *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.