

plasminogen, human-tvmh (Ryplazim[®])

Medicare Advantage Medical Policy #MNG-036

Original Effective Date: 01/01/2025

Current Effective Date: 01/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of plasminogen, human-tvmh (Ryplazim[®])[‡] for the treatment of plasminogen deficiency type 1 to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for plasminogen, human-tvmh (Ryplazim) will be considered when the following criteria are met:

- Initial (12 weeks)
 - Patient has a diagnosis of plasminogen deficiency type 1 (hypoplasminogenemia) confirmed by BOTH of the following:
 - Baseline plasminogen activity level is $\leq 45\%$ of normal; AND
 - Patient has a documented history of lesions and symptoms consistent with congenital plasminogen deficiency; AND
 - Dose will not exceed 6.6 mg/kg body weight every 2 days
- Continuation (1 year)
 - Patient has received an initial authorization for Ryplazim from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
 - Patient meets ONE of the following:
 - Patient has had a clinical response to Ryplazim as determined by the prescriber (e.g., resolution of active lesions, stabilization of current lesions, and prevention of new or recurrent lesions); OR
 - Patient's trough plasminogen activity level is $\geq 10\%$ (absolute change in plasminogen activity) above the baseline trough level (prior to initiating Ryplazim); AND
 - Ryplazim dose will not exceed 6.6 mg/kg body weight every 2 days.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the continued use of plasminogen, human-tvmh (Ryplazim) when the patient has not responded to therapy within 12 weeks or does not have a trough plasminogen activity level $\geq 10\%$ above baseline to be **not medically necessary**.**

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of plasminogen, human-tvmh when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational**.*

Background/Overview

Ryplazim is a plasma-derived human plasminogen that is indicated for the treatment of patients with the rare condition, plasminogen deficiency type 1. It works by increasing the level of plasminogen in the blood of patients with this deficiency in order to allow the fibrinous lesions to heal. It should be dosed intravenously as 6.6 mg/kg every 2 to 4 days and the frequency of administration should be determined based on monitoring of plasminogen activity level compared to baseline. If the desired clinical change is not achieved after 12 weeks of treatment, the plasminogen activity level should be checked to determine the cause. If the trough plasminogen activity level is $\geq 10\%$ above baseline, other treatment options should be considered, in addition to Ryplazim treatment. If the trough plasminogen activity level is confirmed to be $< 10\%$ above the baseline level, consideration should be given to discontinuing Ryplazim due to the possibility of neutralizing antibodies. It should be noted that the normal plasminogen level is highly variable and depends on age, sex, and external factors (such as tobacco smoking). All patients included in the pivotal trial for Ryplazim had a baseline plasminogen activity level $\leq 45\%$.

Congenital plasminogen deficiency is an ultra-rare, autosomal recessive disease affecting approximately 500 patients in the United States with a median age of first clinical manifestation being reported as approximately 10 months. 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. In contrast, type 1 deficiency may present with multisystem disease characterized by fibrin-rich (“woody”) pseudomembranes on mucous membranes. Ligneous conjunctivitis is the most common manifestation, which can lead to loss of vision if untreated. Additionally, 30% of patients with plasminogen deficiency type 1 present with ligneous gingivitis which can cause periodontal destruction and tooth loss. Other sites include respiratory tract, ears, female genitourinary tract, and kidneys. Lesions are often inflamed and painful, and organ function may be compromised. Lesions in the kidneys, respiratory tract, or cerebral ventricles may be life threatening. There are no other treatments FDA-approved for this condition. Surgical removal of lesions often results in accelerated lesion regrowth. Fresh frozen plasma has been used, but its use is limited by the low volume of plasminogen, risk of volume overload, and the time required for administration.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Ryplazim is approved for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Ryplazim in pediatric and adult patients with plasminogen deficiency type 1 was evaluated in a single-arm, open-label, clinical trial. A total of 15 patients with plasminogen deficiency type 1 were enrolled. All patients had a baseline plasminogen activity level between <5% and 45% of normal, and biallelic mutations in the plasminogen (PLG) gene. The age range of these patients was 4 to 42 years. All patients received Ryplazim at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks to achieve at least an increase of individual trough plasminogen activity by an absolute 10% above baseline and to treat the clinical manifestations of the disease.

Efficacy was established on the basis of overall rate of clinical success at 48 weeks which was defined as 50% of patients with visible or other measurable non-visible lesions achieving at least 50% improvement in lesion number/size, or functionality impact from baseline. All patients with any lesion at baseline had at least 50% improvement in the number/size of their lesions. Of the 32 external lesions, 25 were resolved by the end of Week 48. There were no recurrent or new external lesions in any patient through Week 48. Of the 12 assessed internal lesions, 9 were resolved by Week 48. No recurrent or new internal lesions were found in imaging in any patient through Week 48.

References

1. Ryplazim [package insert]. Prometic Biotherapeutics, Inc. Fort Lee, NJ. Updated November 2021.
2. Ryplazim Drug Evaluation. Express Scripts. Updated January 2022.

Policy History

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10/15/2024 UM Committee review

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Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No code
HCPCS	J2998
ICD-10 Diagnosis	E88.02, D68.8

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

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diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: <https://www.cms.gov/medicare-coverage-database/search.aspx>. You may wish to review the Guide to the MCD Search here: <https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx>.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.