Ryplazim (plasminogen, human-tvmh)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Ryplazim (plasminogen, human-tvmh) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Ryplazim is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

A. Initial Requests: Medical records (e.g., chart notes, lab reports) documenting a baseline plasminogen activity level and a history of lesions and symptoms consistent with diagnosis.
B. Continuation Requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

Criteria for Initial Approval

Plasminogen deficiency type 1 (hypoplasminogenemia)

Authorization of 12 months may be granted for treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when all of the following criteria are met:

A. Member has a baseline plasminogen activity level of 45% or less.

B. Member has a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 (e.g., ligneous conjunctivitis, ligneous gingivitis or gingival overgrowth, vision abnormalities, respiratory distress and/or obstruction, abnormal wound healing).

Continuation of Therapy
Authorization of 12 months may be granted for members with an indication listed in the Criteria for Initial Approval section who are experiencing benefit from therapy as evidenced by disease stability or disease improvement (e.g., improvement in lesion number and/or size, absence of new lesion development, improvement in respiratory function, increased quality of life).

Dosing and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

CLINICAL RATIONALE

Background
Plasminogen deficiency is an ultra-rare genetic disease caused by mutations in plasminogen (PLG), the gene that codes for the production of plasminogen. Plasminogen is activated to plasmin by either tissue-type plasminogen activator or urokinase-type plasminogen activator and serves as the pivotal enzyme in the fibrinolytic pathway involved in both intravascular and extravascular lysis of fibrin and plays a role in wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis. When PLG mutations cause a decrease in the level and activity of plasminogen in the blood, patients develop type 1 plasminogen deficiency (i.e., hypoplasminogenemia) which is characterized by abnormal extravascular accumulation or growth of fibrin-rich, woody (i.e., ligneous) pseudomembranous lesions on mucus membranes throughout the body. Type II plasminogen deficiency (i.e., dysplasminogenemia) occurs when PLG mutations cause a normal level but decreased activity of plasminogen, and these patients often do not have any symptoms. In patients with plasminogen deficiency, ligneous conjunctivitis (LC) is the most common clinical manifestation and is characterized by inflamed, woody growths on the conjunctival membranes. If left untreated, LC can result in visual impairment or blindness. Plasminogen deficiency may also affect the central nervous system (e.g., congenital occlusive hydrocephalus), as well as the ears, nasopharynx, oral cavity (e.g., ligneous gingivitis or tonsillitis), and respiratory, gastrointestinal (GI), and genitourinary tracts. The prevalence of congenital plasminogen deficiency is estimated to be 1.6 per 1 million people in the general population. It is estimated that only 500 people in the United States and up to 12,000 people worldwide have symptomatic plasminogen deficiency. Ryplazim (plasminogen, human-tvmh) is a highly purified Glu-plasminogen derived from human plasma and is the first agent approved by the FDA for the treatment of patients with plasminogen deficiency type 1. Treatment with Ryplazim increases the plasma level of plasminogen, enabling a temporary correction of the plasminogen deficiency and reduction or resolution of the lesions.

Efficacy
The safety and efficacy of Ryplazim (plasminogen, human-tvmh) were evaluated in an unpublished, multinational, single-arm, phase II/III, open-label study in adult and pediatric patients with a documented history of lesions and symptoms consistent with plasminogen deficiency, with plasminogen activity ≤ 45% of normal and with biallelic mutations in the PLG gene (N = 15). Patients enrolled in the trial ranged from 4 years of age to 42 years of age (6 pediatric patients and 9 adult patients), 11 patients were female, and all patients were White. Eleven patients, including 3 pediatric patients, had lesions (32 external lesions and 12 internal lesions), at baseline. All patients received Ryplazim (plasminogen, human-tvmh) 6.6 mg/kg administered every 2 days to every 4 days for 48 weeks to achieve an individual trough plasminogen activity by an absolute 10% above baseline and to treat the clinical manifestations of the disease. The primary efficacy endpoint was overall clinical success at 48 weeks, 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 or size of their lesions. There were no recurrent or new internal lesions (i.e., cervix, bronchus, colon, vagina, and uterus) or external lesions (i.e., eyes, nose, gums, hands, and feet) in any patient through week 48, and 78% of external lesions and 75% of internal lesions were resolved by the end of week 48. One patient had a history of ligneous airway disease with a severe obstructive ventilatory defect (forced expiratory volume in one second [FEV1] = 46.7% of predicted normal) at baseline prior to treatment that corrected to normal (FEV1 = 89.3% of predicted normal) after 12 weeks of treatment. No formal statistical analyses were performed on study outcomes due to the small sample size and known high disease variability. Additional data from Expanded Access and Compassionate Use support the phase II/III efficacy results.

Safety

No patients who received Ryplazim (plasminogen, human-tvmh) died during the clinical trial. One serious adverse event of possible worsening of GI hemorrhage secondary to gastric ulcers was reported. No patients discontinued study participation or Ryplazim (plasminogen, human-tvmh) treatment due to the occurrence of an adverse event. The most frequent adverse events (incidence ≥ 10%) were abdominal pain, gastric dilatation, nausea, fatigue, pain in extremity, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain. Ryplazim (plasminogen, human-tvmh) carries warnings for bleeding, tissue sloughing, and transmission of infectious agents due to it being derived from human plasma.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- C9090 – Injection, plasminogen, human-tvmh, 1 mg (cancelled 7/1/2022)
- J2998 – Injection, plasminogen, human-tvmh, 1 mg (effective 7/1/2022)

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*Some content reprinted from CVSHealth

POLICY HISTORY

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