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Subject: Plasminogen, Human-tmvh (Ryplazim®) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Plasminogen, human-tmvh (Ryplazim) is a purified, plasma-derived human plasminogen that was approved by the U.S. Food and Drug Administration (FDA) in June 2021 for "the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)". Ryplazim was previously granted orphan drug designation by the FDA for the treatment of hypoplasminogenemia in 2013. Ryplazim is the first FDA-approved treatment for patients with hypoplasminogenemia, an ultra-rare autosomal recessive disorder that leads to the development of ligneous (wood-like) pseudomembranes on mucosa. Plasminogen deficiency is caused by mutations in the *PLG* gene on chromosome 6 responsible for making plasminogen. Affected patients are either homozygous for a specific mutation or compound heterozygous with each gene having different mutations. The mutations can decrease the amount of plasminogen that is produced, its function, or both, resulting in two types of plasminogen deficiency: type 1 and type 2. In type 2 (aka, dysplasminogenemia), patients make enough plasminogen, but it does not work normally (plasminogen antigen is normal, but activity is low); patients are asymptomatic. In type 1 (aka, hypoplasminogenemia), patients do not make enough plasminogen (plasminogen antigen and activity are both low); patients often have symptoms. The K19E mutation appears to be the most common mutation among type 1 patients. The reduction in functional plasminogen results in less plasmin to break down fibrin, leading to a buildup of fibrin. The excess fibrin and the resulting inflammation of the tissue results in the characteristic inflamed woody growths.

Plasminogen deficiency type 1 is a systemic disease most commonly involving the eyes, but also can affect the gingiva, central nervous system, skin, respiratory tract, female genital tract, gastrointestinal system, and genitourinary system to varying degrees. Eye lesions, called ligneous conjunctivitis, appear as thick, whitish, hard woody growths inside the upper and/or lower eyelids and can cause chronic tearing, photophobia, pain and corneal abrasions with vision loss. Gum lesions, called ligneous

periodontitis, may result in loss of gums and eventually teeth. Growths in the respiratory tract can lead to serious complications including recurrent pneumonia and obstruction of the airways. Some affected children also have congenital occlusive hydrocephalus. Tissue infection, trauma, or injury often lead to new or worsening lesion development. Lesions often re-grow quickly after they have been removed. Patients should minimize any surgical procedures, including surgical membrane removal, unless lesions become life threatening. The exact incidence or prevalence of the disorder is unknown, but one estimate places the incidence at 1.6 people per 1,000,000 in the general population. Slightly more females have been identified than males. Interestingly, research has not shown a relationship between plasminogen deficiency and the development of blood clots. Also noteworthy is that a relationship has not been established between plasminogen activity levels and development of clinical symptoms. This makes it difficult to predict each person's clinical course (i.e., if and when a person might develop symptoms, how long those symptoms might last, and if they will recur). Diagnosis is based upon identification of characteristic symptoms and lab testing of plasminogen antigen and activity. Plasminogen activity is measured using a chromogenic assay with typical normal range of 70 to 130%; while antigenic testing is commonly performed via immunologic assays with a reported normal range of 6 to 25 mg/dL. Molecular genetic testing for alterations in the *PLG* gene can confirm a diagnosis. Before the approval of Ryplazim treatment option were limited. Fresh frozen plasma (FFP) has been used with some success; however, FFP has a low concentration of plasminogen and requires repeat infusion that can result in allergic reactions and volume overload.

The safety and efficacy of Ryplazim leading to FDA approval was established in a single-arm, open-label trial of 15 patients with plasminogen deficiency type 1. 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 was 4 to 42 years, including 6 pediatric patients age 4 to 16 years, and 9 adults. Eleven patients were female. All patients were white. The average baseline plasminogen activity level was 21.1%. 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. At week 12 the average plasminogen activity trough level was 51%. Efficacy was established on the basis of "overall rate of clinical success" at 48 weeks. Overall rate of clinical success 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. Spirometry was the only test of organ function used and one patient had abnormal spirometry at baseline. This patient had a history of ligneous airway disease with a severe obstructive ventilatory defect (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. All patients with any lesion at baseline had at least 50% improvement in the number/size of their lesions. Among the patients with external lesion, 25 of the 32 (78%) external lesions (with sites mainly located in the eyes, nose, gums, and ligneous lesions of the hands and feet) were resolved by the end of week 48. There were no recurrent or new external lesions in any patient through week 48. Among the patients with internal lesions, 9 of the 12 (75%) assessed internal lesions were resolved by Week 48. The lesion sites were mainly located in the cervix, bronchus, colon, vagina, and uterus. No recurrent or new lesions were found on imaging in any patient through Week 48. Three patients (20%) developed anti-plasminogen antibodies following treatment. Comparison of pharmacokinetic parameters and/or trough activity levels for those positive samples with the parameters assessed either at baseline or for negative samples suggest these antibodies are not neutralizing antibodies (inhibitors) to plasminogen.

POSITION STATEMENT:

Initiation of plasminogen, human (Ryplazim) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. Member has a diagnosis of plasminogen deficiency type 1 (aka, hypoplasminogenemia) as confirmed by **BOTH** of the following ("a" and "b"):
    a. Biallelic mutations in the plasminogen (PLG) gene – *documentation confirming homozygous or compound heterozygous pathogenic mutations in the PLG gene must be submitted*
    b. Baseline plasminogen activity level less than 45% of normal – *laboratory documentation of a baseline plasminogen activity level (within 6 months of initiating Ryplazim therapy) must be submitted*
2. Member has symptomatic disease resulting from the presence of ligneous pseudomembranous lesions on mucosal surfaces [lesion sites may include, but are not limited to, the eyes, gingiva, central nervous system, skin, respiratory tract, female genital tract, gastrointestinal system, and genitourinary system], **AND** the lesions are causing significant functional impairment, pain, and/or decreased quality of life – *documentation from the medical record citing the presence of lesions and its impact on the member must be submitted*
3. Ryplazim is being prescribed by, or in consultation, with a specialist with experience in the management of plasminogen deficiency (for example, a medical geneticist)
4. Dosage of Ryplazim does not exceed 6.6 mg/kg body weight (rounded up to the next whole vial size) every 2 days

Approval duration: 6 months

Continuation of plasminogen, human (Ryplazim) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. An authorization or reauthorization for Ryplazim has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of plasminogen deficiency type 1 (if another health plan, documentation of a health plan-paid claim for Ryplazim during the 90 days immediately before the authorization request must be submitted); **OR** the member has previously met **ALL** indication-specific criteria
2. Member has demonstrated a beneficial response to therapy as evidence by resolution, reduction, and/or stabilization of lesions – *medical record documentation citing the impact of treatment on the member lesions must be submitted*
3. Ryplazim is being prescribed by, or in consultation, with a specialist with experience in the management of plasminogen deficiency (for example a medical geneticist)
4. Dosage of Ryplazim does not exceed 6.6 mg/kg body weight (rounded up to the next whole vial size) every 2 days

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

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FDA-approved

- Indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)
- The recommended dosage is 6.6 mg/kg body weight administered IV through a syringe disc filter every 2 to 4 days
    - Obtain a baseline plasminogen activity level. If the patient is receiving plasminogen supplementation with fresh frozen plasma, allow for a 7-day washout period before obtaining baseline plasminogen activity level.
    - Initiate dosing at a frequency of every three days
    - Obtain a trough plasminogen activity level approximately 72 hours following the initial dose and prior to the second dose (same time of day as initial dosing)
        - If the plasminogen activity level is <10% above the baseline plasminogen level, change dosing frequency to every 2 days
        - If the plasminogen activity level is ≥10 and ≤20% above baseline, maintain dosing frequency at every 3 days
        - If the plasminogen activity level is >20% above baseline, change dosing frequency to every 4 days
    - Maintain dosing frequency as determined above for 12 weeks while treating active lesions
        - If lesions do not resolve by 12 weeks, or there are new or recurrent lesions, increase dosing frequency in one-day increments every 4 to 8 weeks up to every 2-day dosing while reassessing clinical improvement until lesion resolution or until the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, check trough plasminogen activity level.
            - If the trough plasminogen activity level is ≥10% above the baseline trough level, consider other treatment options, such as surgical removal of the lesion in addition to plasminogen treatment
            - If the trough plasminogen activity level is <10% above the baseline trough level, obtain a second trough plasminogen activity level to confirm. If low plasminogen activity level is confirmed in combination with no clinical efficacy, consider discontinuing plasminogen treatment due to the 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.
- The total infusion volume and number of vials needed are calculate using the following formulas which is based on a final plasminogen concentration of 5.5 mg/mL. The total dose should be infused slowly over 10 to 30 minutes (approximately 5 mL/min).
    - Infusion volume (mL) = body weight (kg) × 1.2

- Number of vials = Infusion volume (mL) × 0.08

- Refer to the product labeling for preparation, reconstitution, and administration instructions.

Dose Adjustments

- Hepatic Impairment - Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed
- Renal Impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- Single-dose, 50 mL vial containing 68.8 mg of plasminogen (human) as a lyophilized powder for reconstitution with 12.5 mL of sterile water for injection (SWFI) [5.5 mg/mL after reconstitution]
- Store at temperatures of 2°C to 25°C (36°F to 77°F) in its original carton until ready to use. Do not freeze.
- Once reconstituted, Ryplazim must be administered within 3 hours. Do not refrigerate after reconstitution.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Patients with known hypersensitivity to plasminogen, or other components of Ryplazim

Precautions/Warnings

- **Bleeding**: Patients with plasminogen deficiency type 1 may bleed from active mucosal disease-related lesions during therapy. Depending on the lesion sites, this may manifest as gastrointestinal (GI) bleeding, hemoptysis, epistaxis, vaginal bleeding, or hematuria. Ryplazim administration may lead to bleeding at lesion sites or worsen active bleeding. Discontinue Ryplazim if serious bleeding occurs. Monitor patients during and for 4 hours after infusion when administering Ryplazim to patients with bleeding diatheses and patients taking anticoagulants, antiplatelet drugs, and other agents which may interfere with normal coagulation.
- **Tissue Sloughing**: Respiratory distress due to tissue sloughing may occur in patients with mucosal lesions in the tracheobronchial tree following Ryplazim administration. Please monitor appropriately.
- **Transmission of Infectious Agents**: Ryplazim is made from human blood and therefore carries a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent.
- **Hypersensitivity Reactions**: Hypersensitivity reactions, including anaphylaxis, may occur with Ryplazim. If symptoms occur, discontinuer and administer appropriate treatment.

- **Neutralizing Antibodies:** Neutralizing antibodies (inhibitors) may develop, although were not observed in clinical trials. If clinical efficacy is not maintained (e.g., development of new or recurrent lesions), then determine plasminogen activity levels in plasma.
- **Laboratory Abnormalities**: Patients receiving Ryplazim may have elevated blood levels of D-dimer. D-dimer levels will lack interpretability in patients being screened for venous thromboembolism (VTE).

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J2998	Plasminogen, human-tvmh 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E88.02	Plasminogen deficiency

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/11/21.

GUIDELINE UPDATE INFORMATION:

09/15/21	New Medical Coverage Guideline.
04/01/22	Revision: Added HCPCS code C9090.
07/01/22	Revision: Added HCPCS code J2998 and deleted codes C9090 and J3590.