Policy Title:	**Ryplazim (plasminogen, human-tvmh)** (Intravenous)		
		Department:	PHA
Effective Date:	04/01/2022		
Review Date:	03/10/2022, 03/02/2023, 12/07/2023, 01/10/2024		

Purpose: To support safe, effective, and appropriate use of Ryplazim (plasminogen, human-tvmh).

Scope: Medicaid, Commercial, Medicare-Medicaid Plan (MMP)

Policy Statement:

Ryplazim (plasminogen, human-tvmh) is covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process.

Procedure:

Coverage of will be reviewed prospectively via the prior authorization process based on criteria below.

Documentation:

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

A. Initial requests: documentation of baseline plasminogen activity level and chart notes documenting number and severity of lesions
B. Continuation of therapy requests: documentation of plasminogen activity level 72 hours after first dose and chart notes documenting clinical response, and additional plasminogen activity level, if applicable

Summary of Evidence:

Ryplazim (plasminogen, human-tvmh) was approved for the treatment of plasminogen deficiency (PLGD) type 1 (hypoplasminogenemia), a disorder that can impair tissue and organ function. Approval of Ryplazim was based on a solitary single-arm, open-label, phase 2/3 study in which 14 patients completed 48 weeks of therapy. A single dose of Ryplazim (6.6mg/kg) was given at Week 0 over a 10-30min IV infusion. The same dose of Ryplazim was given every 2 to 4 days during Weeks 1-12. During treatment Weeks 12-48 patients also received the same dose (6.6mg/kg) every 2-4 days, but investigators had the option to modify the dosing schedule. Due to the small sample size no formal statistical analysis was performed, but the primary and secondary endpoints were defined as being met. The common adverse effects for Ryplazim are headache, nasopharyngitis, abdominal pain, nausea, diarrhea, rhinorrhea, and cough. Due to the increase in plasminogen activity epistaxis, hematuria, dysmenorrhea, and elevated D dimer were also observed. The warnings associated with Ryplazim are worsened bleeding at lesion sites, tissue sloughing, viral transmission (similar to that seen in IVIG), neutralizing antibodies, and laboratory abnormalities.

Initial Criteria:

1. Patient has documented diagnosis of plasminogen deficiency (PLGD) type I;
    a. Diagnosis is evidenced by the following:
        i. Plasminogen activity level ≤45%
        ii. Documented history of lesions (external and/or internal) and symptoms consistent with a diagnosis of congenital PLGD (the severity of disease will be highly individualized and may even vary between members of the same family);
        AND
2. Documented vaccination history to Hepatitis A virus (HAV) and Hepatitis B virus (HBV), or patient has received their first vaccine dose and is scheduled to receive the second vaccine dose; AND
3. Prescribed by or in consultation with a hematologist; AND
4. Patient is at least 11 months of age; AND
5. Ryplazim is dosed according to the US Food and Drug Administration labeled dosing for PLGD type 1 (see Dosage/Administration table below); AND
6. MMP members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Continuation of Therapy Criteria:

- Patient continues to meet all initial criteria and is tolerating therapy with Ryplazim; AND
- Documentation of a positive clinical response to therapy as evidenced by resolution of lesions and no new or reoccurring lesions have occurred; AND
- Ryplazim is dosed according to the US Food and Drug Administration labeled dosing for PLGD type 1 (see Dosage/Administration table below)

Coverage durations:

- Initial coverage: 12 weeks
- Continuation of therapy coverage: 6 months

Per §§ 42 CFR 422.101, this clinical medical policy only applies to INTEGRITY in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

Policy Rationale:
Ryplazim was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Ryplazim according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local

Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

Dosage/Administration:

Indication	**Dose**	**Maximum dose (1 billable unit = 1 mg)**
PLGD type 1	6.6mg/kg every 2-4 days Ryplazim is dosed based on trough levels and clinical response: a. Baseline plasminogen trough level obtained and Ryplazim is initially dosed at 6.6mg/kg every 3 days b. Trough level is ordered at 72 hours after 1st dose (prior to second dose): i. If trough plasminogen activity level increases from baseline at 72 hours <10%, increase frequency to every 2 days, ii. If trough plasminogen activity level increases from baseline at 72 hours ≥10% but ≤20%, maintain frequency of every 3 days, iii. If trough plasminogen activity level increases from baseline at 72 hours >20%, decrease frequency to every 4 days; c. At 12 weeks: i. If lesions still present or new/reoccurrence, increase dosing frequency in 1 day increments every 4-8 weeks up to every 2 days until lesions resolve or stabilize ii. If lesions resolve, continue same dosing frequency. iii. If desired clinical response does not occur in 12 weeks, check trough plasminogen activity level a. If trough plasminogen level <10% above the baseline trough level at 12 weeks, confirm plasminogen trough level and if confirmed, consider discontinuation. b. If trough plasminogen level ≥10% above the baseline trough level at 12 weeks, consider surgical removal of lesions.	757 mg (11vials) every 2 days

Investigational use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes:
Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT codes are:

HCPCS/CPT Code	Description
J2998	Injection, plasminogen, human-tvmh, 1mg

References:

1. Ryplazim (plasminogen, human-tvmh) [prescribing information]. Prometric Biotherapeutics Inc. Laval, Quebec, Canada; June 2023. Accesssed November 2023.