Clinical Criteria

Subject:	Ryplazim (plasminogen, human-tvmh)		
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Overview

This document addresses the use of Ryplazim (plasminogen, human-tvmh), an intravenously administered human plasma-derived plasminogen product that is FDA approved for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Plasminogen deficiency (PLGD) type 1, or hypoplasminogenemia, is an ultra-rare genetic disorder caused by alterations in the PLG gene resulting in reduced plasminogen levels. Individuals with PLGD type 2 have normal plasminogen levels with reduced activity, and often have no symptoms. Hypoplasminogenemia may be diagnosed by molecular genetic testing which is available only at specialized laboratories. It is often identified through characteristic symptoms, family and patient history, and lab tests measuring the activity of plasminogen. Reduced plasminogen activity results in excess fibrin which builds up in mucous membranes to form thick growths or lesions. These occur most often in the conjunctiva (ligneous conjunctivitis), but may be present in mouth, nose, ear, gastrointestinal tract, respiratory tract, and genitourinary track, causing significant morbidity. Though plasminogen plays a role in clot formation and breakdown, evidence does not suggest an increased risk for thrombosis in individuals with PLGD type 1. Prior to the approval of Ryplazim, treatment options were limited to surgery and non-specific therapies showing inconsistent success.

Ryplazim was studied in a small single-arm phase 2/3 study which enrolled individuals with a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 and a plasminogen activity level ≤45%. Ryplazim treatment for 12 weeks showed an improvement in plasminogen activity levels and an improvement in the number/size of lesions or organ function. It is administered as an intravenous infusion every 2 to 4 days. Plasminogen activity and active lesions should be assessed at baseline and monitored throughout treatment to guide dosing frequency. If the desired clinical change does not occur by 12 weeks, plasminogen activity is checked. Other treatment options, such as surgery, may be added to plasminogen treatment if plasminogen activity is ≥10% above initial baseline level. If low plasminogen activity level (<10% [absolute change] above baseline trough level) is confirmed in combination with no clinical efficacy, consider discontinuing treatment due to possibility of neutralizing antibodies.

Similar to other products derived from human plasma, such as IV immunoglobulin products, Ryplazim carries a remote risk of transmitting infectious agents or viruses. However, risk is mitigated based on donor screening and manufacturing processes. Ryplazim also has a warning for tissue sloughing which may occur at mucosal lesions as plasminogen activity is restored. Based on its mechanism of action patients should also be monitored for bleeding, neutralizing antibody formation, and laboratory abnormalities such as elevated levels of D-dimer.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ryplazim (plasminogen, human-tvmh)

Initial requests for Ryplazim (plasminogen, human-tvmh) may be approved if the following criteria are met:

I. Individual has a diagnosis of plasminogen deficiency type 1 (hypoplasminogenemia); **AND**
II. Documentation is provided that ~~T~~the diagnosis has been confirmed by the following (Shapiro 2018):
    a. Individual has a plasminogen activity level ≤ 45%; **AND**
    b. Individual has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency.

Continuation requests for Ryplazim (plasminogen, human-tvmh) may be approved if the following criteria are met:

I. Documentation is provided that ~~T~~there is confirmation of clinically significant response to therapy as evidenced by the following:
   A. Resolution or improvement of baseline lesions (if present) with no new or recurrent lesions; **OR**
   B. Individual had achieved or maintained trough plasminogen activity level ≥10% above initial baseline level.

Requests for Ryplazim (plasminogen, human-tvmh) may not be approved for the following:

~~I. All indications not included above; **OR**~~
I. Individual with plasminogen deficiency type 2; **OR**
II. When the above criteria are not met and for all other indications.

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Initial Approval Duration: 12 weeks
Continuation Approval Duration: 1 year

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J2998	J2998-Injection, plasminogen, human-tvmh, 1 mg
ICD-10 Diagnosis	
E88.02	Plasminogen deficiency
D68.8	Other specified coagulation defects

Document History

Revised: 08/19/2022
Document History:
- 08/19/2022 – Annual Review: Wording and formatting updates. Administrative update to add documentation. Coding Reviewed: Added ICD-10-CM D68.8.
- 08/20/2021 – Annual Review: Add new criteria clinical criteria for Ryplazim. Coding Reviewed: Added HCPCS J3490, J3590. All diagnoses pend. Added HCPCS C9090. Effective 7/1/2022 Added HCPCS J2998. Added ICD-10-CM E88.20. Removed HPCS C9090, J3490, J3590. Removed all diagnosis pend.

References

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 7, 2022.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
5. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22;131(12):1301-1310. doi: 10.1182/blood-2017-09-806729.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.