Ryplazim (plasminogen, human-tvmh) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
10/1/2023	10/1/2022

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Ryplazim® (plasminogen, human-tvmh) Lyophilized powder for reconstitution, for intravenous use	• Treatment of patients with plasminogen deficiency type I (hypoplasminogenemia)		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Plasminogen deficiency	Plasminogen deficiency (PLGD) is an autosomal recessive, multisystem disorder classified as either Type I PLGD (also called hypoplasminogenemia) or Type II (also called dysplasminogenemia). In Type I PLGD both plasminogen protein levels and functional activity are both reduced. Type II PLGD is a dysfunctional deficiency where plasminogen protein levels may be normal, but activity is reduced. Type II appears to be more common than Type I. These distinctions have major clinical implications, with type I disease patients are symptomatic and Type II patients are asymptomatic. Severe hypoplasminogenemia is associated with compromised extracellular fibrin clearance during wound healing, leading to pseudomembranous (ligneous) lesions on affected mucous membranes (eye, middle ear, mouth, pharynx, duodenum, upper and lower respiratory tract, and female genital tract).(2,3) The most commonly recognized manifestations of PLGD are lesions on the conjunctiva of the eye, called ligneous conjunctivitis. These lesions can cause significant morbidity, and pseudomembranes affecting the respiratory system and central nervous system can cause fatal complications. Diagnosis is often delayed for months, or even years or decades, as the condition is extremely rare and the spectrum of presenting findings is broad.(3)

	The PLG gene encodes plasminogen. The gene has structural similarity to apolipoprotein(a) and an internal sequence that encodes angiostatin, a suppressor of metastasis. Disease severity can differ in individuals with the same genotype, even within families.(3) Plasminogen is the precursor to plasmin, a serine protease that cleaves fibrin and other proteins to restore blood vessel patency and maintain the extracellular matrix following establishment of hemostasis. Plasmin contributes to wound healing, regulation of the inflammatory response, and tissue remodeling. It degrades fibrin and other matrix glycoproteins, activates matrix metalloproteinases (MMPs), and stimulates release of the transforming growth factor (TGF)-beta. Plasminogen is primarily produced by the liver, although other tissues contribute to synthesis. Other tissues besides the liver that produce plasminogen include the brain, kidney, heart, lungs, intestines, uterus, spleen, and thymus.(3) Like many of the clotting proteins, plasminogen levels can vary among individuals, and clinical findings are rarely significant unless deficiency is severe. The amount of plasminogen needed to prevent symptoms of PLGD may vary by individual. Due to disease rarity, it is challenging to determine a cutoff above which symptoms will not occur.(3) Laboratory testing involves measurement of plasminogen levels (both activity and antigen). The typical normal range of plasminogen activity is approximately 70 to 130%. Activity level less than 40% is consistent with deficiency although an absolute cutoff has not been established, and some individuals with clinical manifestations of disease may have higher levels. The normal range of plasminogen antigen levels is approximately 6 to 25 mg/dL, Discordance between activity and antigen levels suggests Type II PLGD.(3) Without plasminogen replacement, many individuals survive to adulthood with chronic complications. However, lesions can progress to cause blindness, loss of hearing, complications of hydrocephalus, and/or bronchial obstruction, which can be fatal.(3) Various therapies have been tried to treat individuals with Type I PLGD. Surgical removal of the growths may be beneficial initially, but the growths usually recur if the patient is not treated with some form of plasminogen. Medications including high-dose intravenous corticosteroid treatment, heparin, cyclosporine, azathioprine, hyaluronidase, and alpha-chymotrypsin. These therapies have shown no or only limited benefit, or have been reported to be beneficial in only single cases.(4) Fresh frozen plasma (FFP) has also been used as a treatment for plasminogen deficiency. FFP has been administered as an IV infusion when multiple body systems are affected or as eye drops and eye injections for ligneous conjunctivitis. When administered intravenously, fluid overload may become a concern. In addition, some people develop reactions to FFP, usually to some other protein component of the

	plasma that may make infusions difficult. Treatment with plasminogen concentrate is a better treatment option.(4) There are 2 main forms of native plasminogen, one with glutamic acid at it N terminus (Glu-plasminogen) and one with lysine at its N terminus (Lys-plasminogen). Glu-plasminogen has a half-life of 2 to 2.5 days and Lys-plaminogen has a half-life of 0.8 days. Glu-plasminogen is the predominant (greater than 95%) form of circulating native plasminogen. Upon binding to a fibrin clot, Glu-plasminogen is cleaved and converted into the more readily activated Lys-plasminogen.(5) The concentration of plasminogen in human plasma is approximately 200 mg/L.(6)
Efficacy(1)	Ryplazim is a Glu-plasminogen (greater than 95% purity). The efficacy of Ryplazim in pediatric and adult patients with plasminogen deficiency Type I was evaluated in a single-arm, open-label clinical trial (RYPLAZIM Trial 2) in 15 patients. 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. Overall rate of clinical success is 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.
Safety(1)	Ryplazim is contraindicated in patients with known hypersensitivity to plasminogen, or other components of Ryplazim.

REFERENCES

Number	Reference
1	Ryplazim Prescribing Information. Prometic Bioproduction Inc. June 2021.
2	Schuster V, Hügle B, Tefs K. Plasminogen deficiency. J Thromb Haemost. 2007 Dec;5(12):2315-22. doi: 10.1111/j.1538-7836.2007.02776.x. Epub 2007 Sep 26. PMID: 17900274.
3	Shapiro AD. UpToDate Plasminogen deficiency. Literature review current through January 2023. Topic last updated February 2023.
4	National Organization of Rare Diseases (NORD). Rare Disease Database. Congenital Plasminogen Deficiency. Accessed at Congenital Plasminogen Deficiency - NORD (National Organization for Rare Disorders) (rarediseases.org).
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;131(12):1301-1310. doi:10.1182/blood-2017-09-806729
6	Cederhom-Williams SA. Concentration of plasminogen and antiplasmin in plasma and serum. J Clin Pathol 1981;34:979-981.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Ryplazim	plasminogen, human-tvmh for iv soln	68.8 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Ryplazim	Plasminogen, Human-tvmh For IV Soln	68.8 MG					Dependent on patient weight and number of doses		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Ryplazim	plasminogen, human-tvmh for iv soln	68.8 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	CRITERIA FOR APPROVAL **Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of plasminogen deficiency Type I (hypoplasminogenemia) **AND** 2. The patient has symptomatic internal or external lesions consistent with plasminogen deficiency Type I (i.e., ligneous conjunctivitis, ligneous gingivitis, and/or pseudomembranous lesions on mucus membranes [middle ear, respiratory tract gastrointestinal tract]) **AND**

Module	Clinical Criteria for Approval
	3. The patient's baseline (before treatment with the requested agent) plasminogen activity has been assessed **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., ophthalmologist, specialist from a hemophilia and thrombosis treatment center) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies please see Quantity Limit criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. ONE of the following: A. The patient has had at least a 10% increase in plasminogen activity from baseline (before treatment with the requested agent) **OR** B. The patient has had a 50% improvement in symptomatic internal or external lesion numbers or size from baseline (before treatment with the requested agent) **OR** C. The prescriber has provided information supporting the continued use of the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., ophthalmologist, specialist from a hemophilia and thrombosis treatment center) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies please see Quantity Limit criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: A. The requested dose is within the FDA labeled dosing (i.e., 6.6 mg/kg) **AND** B. The requested quantity (number of doses) is appropriate based on intended use **OR** 2. The prescriber has provided clinical reasoning for exceeding the defined program quantity limit (dose and/or number of doses) (medical records required) **Length of Approval:** 12 months

