

New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	Ryplazim™ (plasminogen, human-tvmh) [Prometic Biotherapeutics, Inc.]
Dosage Formulations:	Single dose vial containing 68.8 mg of plasminogen (human) (5.5 mg/mL after reconstitution with 12.5 mL of sterile water for injection).
FDA Approval Date: FDB File Date:	FDA: June 4, 2021 FDB: December 5, 2021
Indication:	For the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)
Mechanism of Action:	Treatment with Ryplazim temporarily increases plasminogen levels in blood.
Dose/ Administration:	<ul style="list-style-type: none"> • The recommended dosage of Ryplazim is 6.6 mg/kg administered intravenously every 2 to 4 days (Q2D to Q4D). • To calculate the total infusion volume of Ryplazim, the following formula is provided: <ul style="list-style-type: none"> ○ Infusion volume (mL) = body weight (kg) x 1.2 • To calculate the number of vials used per infusion, the following formula is provided: <ul style="list-style-type: none"> ○ Number of vials = Infusion volume (mL) x 0.08 • Determination of dosing frequency: <ul style="list-style-type: none"> ○ 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 plasminogen activity level. ○ Initiate Ryplazim dosing at a frequency of every three days (Q3D). ○ Obtain a trough plasminogen activity level approximately 72 hours following the initial dose of Ryplazim and prior to the second dose. <ul style="list-style-type: none"> ▪ If plasminogen activity level is < 10% above the baseline plasminogen level, change dosing to every two days ▪ If plasminogen activity level is ≥ 10 and ≤ 20% above baseline, maintain dosing frequency at Q3D. ▪ If the plasminogen activity level is > 20% above baseline, change dosing frequency to Q4D. • Maintenance Dosing: maintain dosing frequency as determined above for 12 weeks while treating active lesions. <ul style="list-style-type: none"> ○ If lesions do not resolve by 12 weeks, or there are new or recurrent lesions, increase dosing frequency in one-day increments every 4-8 weeks up to Q2D dosing while reassessing clinical improvement until lesion resolution or until 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 therapy options. ○ 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 indefinitely at same dosing frequency and monitor for new or recurrent lesions every 12 weeks.
Disease State Clinical Highlights:	<ul style="list-style-type: none"> • Plasminogen deficiency type 1 is an inherited autosomal recessive disease associated with inflamed growths on the mucous membranes, the moist tissues that line body openings such as the eye, mouth, nasopharynx, trachea, and female genital tract. • Individuals with hypoplasminogenemia have a pathogenic variant in the <i>PLG</i> gene, which encodes the enzyme plasminogen. Plasminogen is broken down to plasmin, which has multiple functions throughout the body, including breaking down fibrin. Since

	<p>individuals with plasminogen deficiency type 1 lack plasminogen, fibrin accumulates and causes inflammation and growths throughout the body's mucous membranes.</p> <ul style="list-style-type: none"> • The most common clinical finding is ligneous conjunctivitis, a condition marked by formation of pseudomembranes on the inside of the eyelid that progresses to white, yellow-white, or red thick masses with a wood-like consistency. This can lead to vision loss. • Growths that occur in the gastrointestinal (GI) tract can cause ulcers, and growths in the trachea can lead to breathing problems. Hydrocephalus may be present at birth in a small number of individuals. • Prevalence is estimated to be 1.6 per 1 million people. There are roughly 500 people in the United States with symptomatic hypoplasminogenemia. • Plasminogen activity level is used to assess patients with hypoplasminogenemia. The reference range for plasminogen activity level is 75-140%. Plasminogen activity below 75% may represent a congenital deficiency state. Generally, lower plasminogen activity levels correlate to more severe symptoms. • Currently, no treatment for plasminogen deficiency type 1 has been established. Some cases of ligneous conjunctivitis have been successfully treated using a combination of surgery and plasminogen eye drops. Recurrence of growths after surgery is common.
<p>Drug Clinical Highlights:</p>	<ul style="list-style-type: none"> • First FDA-approved treatment option for plasminogen deficiency type 1. The FDA previously granted Ryplazim both Orphan Drug and Rare Disease designations. • Made from purified human plasma, Ryplazim works to increase the level of plasminogen in the blood. • Ryplazim is administered intravenously through a syringe disc filter. If a patient and/or caregiver receives detailed instructions and training from a healthcare professional, they may be able to safely administer Ryplazim independently. • Warnings and Precautions: <ul style="list-style-type: none"> ○ Bleeding <ul style="list-style-type: none"> ▪ Administration may cause or worsen active bleeding at lesion sites. Discontinue Ryplazim if serious bleeding occurs. Patients with a tendency to bleed or bruise easily or those taking anticoagulants or antiplatelet drugs should be monitored during and for at least 4 hours after the infusion. ○ Tissue Sloughing <ul style="list-style-type: none"> ▪ Tissue sloughing at mucosal sites may occur after initiation of treatment with Ryplazim. Monitor patient with lesions in the tracheobronchial tree during and after infusion as respiratory distress may occur. ○ Transmission of Infectious Agents <ul style="list-style-type: none"> ▪ Because Ryplazim is derived from human plasma, it carries a risk of transmitting infectious diseases. Based on effective donor screening and product manufacturing processes, Ryplazim carries a remote risk of disease transmission. ○ Hypersensitivity Reactions ○ Neutralizing Antibodies <ul style="list-style-type: none"> ▪ Formation of neutralizing antibodies to plasminogen following the administration of Ryplazim has not been reported to date. Monitor patients for the loss of clinical efficacy as manifested by the development of new or recurrent lesions while on adequately dosed Ryplazim. ○ Laboratory Abnormalities <ul style="list-style-type: none"> ▪ Patients receiving Ryplazim may have elevated levels of D-dimer in blood. Interpret D-dimer levels with caution in patients being screened for venous thromboembolism (VTE), as elevated levels may be associated with the physiological activity of Ryplazim and not indicative of VTE. • Safety and efficacy were evaluated in pediatric and adult patients in a single-arm, open-label clinical trial (RYPLAZIM Trial 2: NCT02690714) <ul style="list-style-type: none"> ○ A total of 15 patients with plasminogen deficiency type 1 were enrolled. Patients were 4 to 42 years of age, including 6 pediatric patients aged 4 to 16 years.

- All patients had a baseline plasminogen activity level between < 5% and 45% of normal. All patients were confirmed to have biallelic pathogenic variants in the *plasminogen (PLG)* gene.
- Primary Endpoints:
 - 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.
 - Number and percentage of patients who achieved target trough plasminogen activity levels, defined as an increase of individual plasminogen activity trough level by at least an absolute 10% above baseline, for at least 3 measurements in 12 weeks. Primary endpoint success was defined as at least 80% of evaluable patients achieving target trough plasminogen activity levels.
- Spirometry was the only test of organ function used, and one patient had abnormal spirometry at baseline. This patient had a history of ligenous airway disease with a severe obstructive ventilator 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 with Ryplazim.
- All patients with any lesion at baseline had at least 50% improvement in the number/size of their lesions. There were no recurrent or new external or internal lesions found in any patient.

Lesion Site	Total Lesions	Resolved (%)
External	32	25 (78%)
Internal	12	9 (75%)

- All patients achieved target trough plasminogen activity levels during initial 12-week treatment period.
- Adverse Events
 - No serious adverse events were observed in the clinical trials.
 - Adverse events with an incidence of at least 10% in the two clinical trials and treatment protocols are listed below:

Adverse Reactions	Number of Patients (%) (N=19)
Abdominal pain	3 (16%)
Gastric dilation (bloating)	3 (16%)
Nausea	3 (16%)
Fatigue	3 (16%)
Pain in extremity	3 (16%)
Hemorrhage	3 (16%)
Constipation	2 (11%)
Dry mouth	2 (11%)
Headache	2 (11%)
Dizziness	2 (11%)
Arthralgia	2 (11%)
Back pain	2 (11%)

Price Per Unit (WAC):

- \$2,064.00 per vial
- Cost estimate for 70 kg participant:
 - Infusion volume (mL) = 70 kg x 1.2 = 84 mL
 - Number of vials = Infusion volume (84 mL) x 0.08 = 6.72, rounded up to 7 vials
 - 7 vials x \$2,064.00 = \$14,448.00 per infusion
 - Cost per infusion x 183 = \$2,643,984.00 (yearly cost for Q2D dosing)
 - Cost per infusion x 122 = \$1,762,656.00 (yearly cost for Q3D dosing)
 - Cost per infusion x 92 = \$1,329,216.00 (yearly cost for Q4D dosing)

Therapeutic Alternatives:

- Ryplazim is the first product to be FDA-approved for the treatment of plasminogen deficiency type 1.
- Currently, there are no standardized treatment protocols or guidelines for affected individuals. Surgical removal of growths may be beneficial initially, however recurrence

	<p>is very common. Therapies including corticosteroids, immunosuppressants (cyclosporine), blood thinners (heparin), plasma infusion, and antivirals have been used to treat hypoplasminogenemia but offer only anecdotal evidence to support efficacy.</p> <ul style="list-style-type: none"> Plasminogen replacement is the only therapy shown to improve symptoms and prevent recurrence.
<p>Prior Authorization Approval Criteria:</p>	<p>Must meet the following criteria:</p> <p><u>Initial Therapy:</u></p> <ul style="list-style-type: none"> Prescribed by or in consultation with a hematologist or other specialist in the treated disease state AND Documented diagnosis of plasminogen deficiency type 1 (E88.02), including: <ul style="list-style-type: none"> Baseline plasminogen activity level $\leq 45\%$ AND Documented history of lesions (external and/or internal) and symptoms consistent with a diagnosis of plasminogen deficiency type 1, including documentation of number and size of lesions at baseline (if external) AND Genetic testing to confirm diagnosis AND Participant is not currently pregnant AND Documented vaccination history or immunity to hepatitis A (HAV) and hepatitis B (HBV), or patient has received their first vaccine dose and is scheduled to receive their second vaccine dose AND Initial therapy approved for 3 months <p><u>Continuation of Therapy:</u></p> <ul style="list-style-type: none"> Documented benefit from therapy: <ul style="list-style-type: none"> Decrease in size or number of lesions from baseline Trough plasminogen activity levels maintained during follow-up visits Continued approval for 12 months <p>Additional Provider Diagnostic/Monitoring Criteria, if desired:</p> <ul style="list-style-type: none"> Reassess clinical efficacy every 12 weeks. Prior to initiation of treatment with Ryplazim, confirm healing of lesions or wounds suspected as a source of a recent bleeding event.
<p>Implication to State Medicaid Program:</p>	<ul style="list-style-type: none"> LOE: N/A Only 1 or 2 patients would be expected to require Ryplazim therapy in a 1 million-member health plan. Ryplazim will be available through a limited distribution network of specialty pharmacies. Monitor for development of long-acting formulations, competitor products.

References:

- RYPLAZIM (plasminogen) [package insert]. Laval, Quebec, Canada: Prometic Bioproduction Inc.; June 2021.
- IPD Analytics. New Drug Review: Ryplazim (plasminogen, human tmh). June 2021.
- 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. Epub 2018 Jan 10.
- NIH, Genetic and Rare Diseases Information Center. Type 1 Plasminogen Deficiency. Updated June 13, 2016. Accessed June 16, 2021. [Type 1 plasminogen deficiency | Genetic and Rare Diseases Information Center \(GARD\) – an NCATS Program \(nih.gov\)](https://rarediseases.info.nih.gov/diseases/10222/type-1-plasminogen-deficiency)
- Mehta R, Shapiro AD. Plasminogen Deficiency. *The Official Journal of the World Federation of Hemophilia*. <https://doi.org/10.1111/j.1365-2516.2008.01825.x>. October 2008.
- Schuster V, Hugle B, Tefs K. Plasminogen Deficiency. *Journal of Thrombosis and Haemostasis*. <https://doi.org/10.1111/j.1538-7836.2007.02776.x>. September 2007.
- Mayo Clinic Laboratories. “Plasminogen Activity, Plasma.” [PSGN - Clinical: Plasminogen Activity, Plasma \(mayocliniclabs.com\)](https://www.mayocliniclabs.com). Accessed June 18, 2021.