RYPLAZIM® DIAGNOSTIC CHECKLIST

Ryplazim® plasminogen, human-tvmh

	Assessment	Findings suggestive of Plasminogen Deficiency Type 1 (PLGD-1)	Comments
☐	Patient history/ clinical evaluation	• Pseudomembranous lesions[1] • Impaired wound healing[1]	• PLGD-1 is the most common cause of ligneous conjunctivitis (LC).[1] • LC is the most common symptom in PLGD-1, followed by ligneous gingivitis.[1] • Other symptom sites include the ears, nose, respiratory tract, gastrointestinal tract, urinary tract, and female reproductive tract.[1]
☐	Family medical history	• Confirmed diagnosis in a first-degree relative	• The possibility of increased incidence of thrombotic disease among heterozygous (ie, asymptomatic) family members is still being explored.[2,3]
☐	Plasminogen activity functional assays[4] • Chromogenic assay • Clot lysis time	• Activity level ≤45%[5]	• Functional assays should be performed before antigen level assays (see below), with normal results ruling out PLGD.[4,5]
☐	Plasminogen antigen assays[4] • ELISA assay • Immunoelectrophoresis • Laser nephelometry • Radioimmunoassay	• Antigen concentration <150 mg/L	• Antigen assays in combination with activity assays distinguish PLGD-1 from PLGD-2. For example[1]:
☐	Molecular genetic test (optional)	• Mutations in *PLG* gene	• The K19E mutation affects 34% of patients with PLGD-1, but other mutations associated with PLGD-1 are still being discovered, with variable effects on severity or progression of clinical course.[6,7]
☐	Lesion biopsy (optional)	• Eroded epithelium with fibrin-rich deposits[1] • Granulation tissue[1]	• Plasminogen may be undetectable in membrane tissue.[1]

	Activity	Antigen
PLGD-1	Low	Low
PLGD-2	Low	Normal

INDICATIONS AND USAGE

RYPLAZIM (plasminogen, human-tvmh) is a plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS:

RYPLAZIM is contraindicated in patients with known hypersensitivity to plasminogen or other components of RYPLAZIM.

WARNINGS AND PRECAUTIONS:

- Bleeding: RYPLAZIM administration may lead to bleeding at active mucosal disease-related lesion sites or worsen active bleeding not related to disease lesions. 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, or other agents which may interfere with normal coagulation.

Please see additional Important Safety Information on back and accompanying Full Prescribing Information.

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Ryplazim®
plasminogen, human-tvmh

References:

1. Schuster V, Seregard S. Ligneous conjunctivitis. *Surv Ophthalmol.* 2003;48(4):369-388.
2. Martin-Fernandez L, Marco P, Corrales I, et al. The unravelling of the genetic architecture of plasminogen deficiency and its relation to thrombotic disease. *Sci Rep.* 2016;6:39255.
3. Plasminogen deficiency. Indiana Hemophilia & Thrombosis Center. Accessed May 2, 2024. https://www.ihtc.org/plasminogen-deficiency
4. Plasminogen (PLG). DiaPharma. Accessed May 2, 2024. https://diapharma.com/plasminogen-plg
5. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. *J Thromb Haemost.* 2007;5(12):2315-2322.
6. Tefs K, Gueorguieva M, Klammt J, et al. Molecular and clinical spectrum of type I plasminogen deficiency: a series of 50 patients. *Blood.* 2006;108(9):3021-3026.
7. Shapiro AD, Menegatti M, Palla R, et al. An international registry of patients with plasminogen deficiency (HISTORY). *Haematologica.* 2020;105(3):554-561.

IMPORTANT SAFETY INFORMATION, cont.

WARNINGS AND PRECAUTIONS, cont.

- 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 plasma 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, discontinue RYPLAZIM and administer appropriate treatment.
- Neutralizing Antibodies: Neutralizing antibodies (inhibitors) may develop, although they were not observed in clinical trials. If clinical efficacy is not maintained (e.g., development of new or recurrent lesions), determine plasminogen activity trough 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).

ADVERSE REACTIONS:

The most frequent (incidence ≥ 10%) adverse reactions in clinical trials were abdominal pain, bloating, nausea, fatigue, extremity pain, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain.

To report SUSPECTED ADVERSE REACTIONS, contact KEDRION at 1-855-427-6378 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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