

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RYPLAZIM® safely and effectively. See full prescribing information for RYPLAZIM.

**RYPLAZIM® (plasminogen, human-tvmh)**  
lyophilized powder for reconstitution, for intravenous use  
Initial U.S. Approval: xxxx

### INDICATIONS AND USAGE

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

### DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

The recommended dosage of RYPLAZIM is 6.6 mg/kg body weight given every 2 to 4 days. (2.1)

### DOSAGE FORMS AND STRENGTHS

RYPLAZIM is available in a single-dose 50-mL vial containing 68.8 mg of plasminogen as a lyophilized powder for reconstitution with 12.5 mL of Sterile Water for Injection, USP (SWFI). After reconstitution, each vial will contain 5.5 mg/mL of plasminogen. (3)

### CONTRAINDICATIONS

RYPLAZIM is contraindicated in patients with known hypersensitivity to plasminogen, or other components of RYPLAZIM. (4) (11)

### WARNINGS AND PRECAUTIONS

- Bleeding: RYPLAZIM administration may lead to bleeding at lesion sites or worsen active bleeding. 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, and other agents which may interfere with normal coagulation. (5.1)

- 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. (5.2)
- Transmission of Infectious Agents: RYPLAZIM is made from human blood 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. (5.3)
- Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, may occur with RYPLAZIM. If symptoms occur, discontinue RYPLAZIM and administer appropriate treatment. (5.4)
- Neutralizing Antibodies: Neutralizing antibodies (inhibitors) may develop, although were not observed in clinical trials. If clinical efficacy is not maintained (e.g., development of new or recurrent lesions), then determine plasminogen activity levels in plasma. (5.5)
- 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). (5.6)

### ADVERSE REACTIONS

The most frequent (incidence  $\geq 10\%$ ) adverse reactions in clinical trials were abdominal pain, bloating, nausea, fatigue, extremity pain, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Prometic at +1(800) 735-4086 and [prometicsmb@continuumindia.com](mailto:prometicsmb@continuumindia.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

### 2 DOSAGE AND ADMINISTRATION

**For intravenous use after reconstitution only.**

#### 2.1 Dosage

##### Dose Determination

The recommended dosage of RYPLAZIM is 6.6 mg/kg body weight administered intravenously every 2 to 4 days (Q2D to Q4D).

Calculate the total infusion volume of RYPLAZIM using Formula (1), which is based on a final plasminogen concentration of 5.5 mg/mL. Administer the exact infusion volume determined using Formula (1) to the patient.

$$\text{Formula (1):} \quad \text{Infusion volume (mL)} = \text{body weight (kg)} \times 1.2$$

May require more than one reconstituted vial of RYPLAZIM to obtain the infusion volume calculated using Formula (1). Round up the estimated number of vials using Formula (2).

$$\text{Formula (2):} \quad \text{Number of vials} = \text{Infusion volume (mL)} \times 0.08$$

##### Determination of Dosing Frequency

1. 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 baseline plasminogen activity level.
2. Initiate RYPLAZIM dosing at a frequency of every three days (Q3D).
3. Obtain a trough plasminogen activity level approximately 72 hours following the initial dose of RYPLAZIM and prior to the second dose (same time of day as initial dosing)
  - a. If the plasminogen activity level is  $< 10\%$  \* above the baseline plasminogen level, change dosing frequency to Q2D;
  - b. If the plasminogen activity level is  $\geq 10$  and  $\leq 20\%$  \* above baseline, maintain dosing frequency at Q3D;
  - c. If the plasminogen activity level is  $> 20\%$  \* above baseline, change dosing frequency to Q4D.
4. Maintain dosing frequency as determined above for 12 weeks while treating active lesions
  - a. 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 the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, check trough plasminogen activity level.
    - 1) If the trough plasminogen activity level is  $\geq 10\%$  \* above the baseline trough level, consider other treatment options, such as surgical removal of the lesion in addition to plasminogen treatment.
    - 2) 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 [see *Neutralizing Antibodies (5.5)*].

- b. If lesions resolve by 12 weeks, continue at same dosing frequency and monitor for new or recurrent lesions every 12 weeks.  
\* Absolute change in plasminogen activity (%)

## 2.2 Preparation and Reconstitution

Prepare RYPLAZIM within 3 hours of administration. Gather the following additional supplies before performing reconstitution and administration:

- One 20-mL syringe per vial of RYPLAZIM for product reconstitution
- 18- to 22-gauge needles for reconstitution and administration
- Sterile Water for Injection, USP (SWFI) (10-mL, 20-mL or 50-mL vials)
- One syringe disc filter per infusion (Baxter Supor® 5micron Syringe Filter or equivalent)
- One (or more) administration syringe(s) (20-mL, 30-mL or 60-mL)
- Alcohol wipes
- Antiseptic surface wipes
- Medical tape
- Butterfly needle or sterile infusion set
- 10 mL normal saline
- Sterile gauze pad
- Bandage

### Reconstitution of RYPLAZIM

Determine the number of RYPLAZIM vials needed using Formula (2) [see *Dosage and Administration (2.1)*]. Check the expiration date of each vial of RYPLAZIM. Discard any expired vials. Allow RYPLAZIM vials to equilibrate to room temperature before reconstitution (at least 15 minutes if stored at 5 °C). Do not refrigerate after reconstitution.

Work on a clean surface and wash hands before performing the following procedures.

1. Remove the caps from the RYPLAZIM vials and Sterile Water for Injection, USP (SWFI) vials to expose the central portion of the rubber stoppers.
2. Sterilize the surface of the rubber stoppers with alcohol wipes and allow to dry. Do not blow on it.
3. Using a 20-mL sterile syringe with a sterile 18- to 22-gauge needle, withdraw 12.5 mL of SWFI for each vial of RYPLAZIM.

Note: If using 10-mL vials of SWFI, each vial of RYPLAZIM requires two 10-mL vials of SWFI. Withdraw 9.0 mL of SWFI from the first 10-mL vial. Discard the first needle, attach a new 18- to 22-gauge sterile needle and withdraw 3.5 mL SWFI from the second 10-mL vial to equal 12.5 mL. Discard the used SWFI vials. Repeat this process for each vial of RYPLAZIM that needs to be reconstituted.

If using a 20-mL or 50-mL vial of SWFI, each vial of RYPLAZIM requires only one vial of SWFI for reconstitution. Discard the used SWFI vials.

4. Using the same needle and syringe gently and slowly add the 12.5 mL of SWFI to the RYPLAZIM vial, directing the syringe down toward the side of the RYPLAZIM vial to prevent foaming. This should resemble a stream along the side of the vial (Figure 1). Discard the used syringe and needle(s).



**Figure 1**

5. Gently swirl the vial by rotating it slowly to ensure that the lyophilized powder dissolves fully (Figure 2). Do not shake the vial. RYPLAZIM should fully dissolve within 10 minutes. Discard the vial if RYPLAZIM is not fully dissolved after 10 minutes.



**Figure 2**

6. Observe the reconstituted vials; the solution should be colorless and clear to slightly opalescent. Discard the vial if discoloration or particulate matter are observed.
7. Repeat Steps 1 to 6 above to reconstitute each additional vial of RYPLAZIM.

Preparation of RYPLAZIM for Administration

Select an administration syringe of appropriate volume based on the infusion volume calculated using Formula (1) [see *Dosage and Administration (2.1)*].

Note: A 30-mL syringe can hold up to 2 vials of reconstituted RYPLAZIM and a 60-mL syringe can hold up to 4 vials of reconstituted RYPLAZIM.

Using the selected administration syringe(s) with 18- to 22-gauge needle(s), slowly withdraw the reconstituted RYPLAZIM from each vial to administer the exact infusion volume calculated using Formula (1) [see *Dosage and Administration (2.1)*].

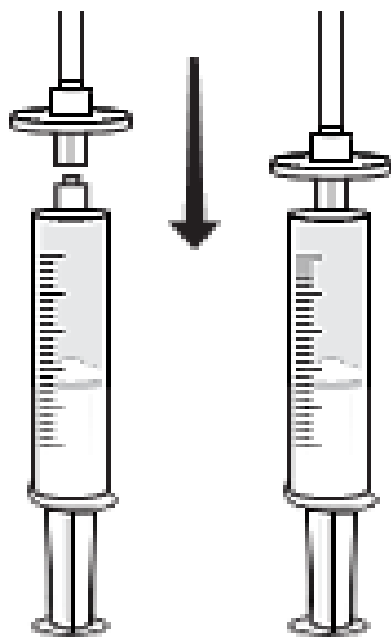
Do not mix RYPLAZIM with other medications.

### 2.3 Administration

For intravenous use only through a syringe disc filter.

Follow the steps below for infusion:

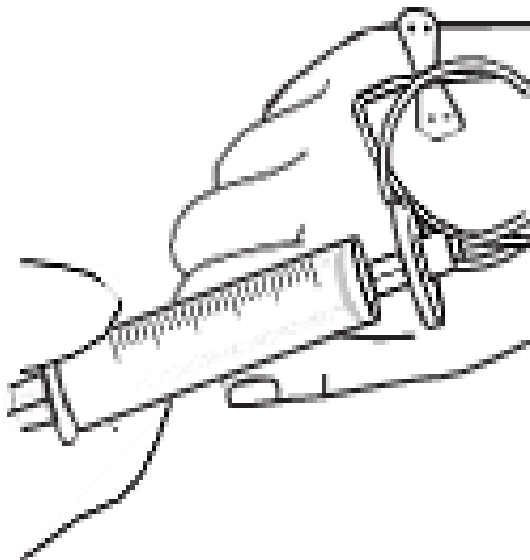
1. One filter is needed per infusion.
2. Only administer RYPLAZIM by infusing it into a vein through a syringe disc filter.
3. Inspect the solution in the syringe. Do not use if discoloration or particulate matter are observed.
4. Administer RYPLAZIM by a separate infusion line. Do not administer RYPLAZIM with other medications.
5. Draw 10 mL of normal saline into a different syringe. Push the plunger down to remove any air bubbles.
6. Attach a syringe disc filter to the pre-filled syringe of normal saline (from previous step) and the infusion tubing with the butterfly needle. (Figure 3)



**Figure 3**

7. Inject the normal saline through the syringe disc filter and butterfly needle tubing to remove any air bubbles.
8. Remove the normal saline syringe. The syringe disc filter must remain attached to the tubing, as it is required for administration of the RYPLAZIM. Discard the normal saline syringe.
9. Attach the administration syringe containing RYPLAZIM to the syringe disc filter that is connected to the butterfly needle tubing.

10. Choose a peripheral vein (e.g., antecubital or dorsum of hand). Clean the injection site with a sterile alcohol wipe and allow to dry. Do not blow on it.
11. Insert the butterfly infusion set needle in the peripheral vein, and tape in place.
12. Infuse the total dose of RYPLAZIM slowly over 10-30 minutes (approximately 5 mL/min). Using a timer (e.g., watch or clock), push the plunger of the syringe approximately 1 mL every 12 seconds. (Figure 4)



**Figure 4**

13. Discard any open vials, unused solution, and administration equipment following administration.

### **3 DOSAGE FORMS AND STRENGTHS**

RYPLAZIM is available in a single-dose 50 mL vial containing 68.8 mg of plasminogen as a lyophilized powder for reconstitution with 12.5 mL of sterile water for injection (SWFI). After reconstitution, each vial will contain 5.5 mg/mL of plasminogen in a colorless and clear to slightly opalescent solution.

### **4 CONTRAINDICATIONS**

RYPLAZIM is contraindicated in patients with known hypersensitivity to plasminogen or other components of RYPLAZIM [See *Hypersensitivity Reactions (5.4)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Bleeding**

Patients with plasminogen deficiency type 1 may bleed from active mucosal disease-related lesions during RYPLAZIM therapy. Depending on the lesion sites, this may manifest as gastrointestinal (GI) bleeding, hemoptysis, epistaxis, vaginal bleeding, or hematuria.

RYPLAZIM may worsen active bleeding not related to disease lesions. One patient with a recent history of GI bleeding due to gastric ulcers experienced GI bleeding two days after receiving the second dose of RYPLAZIM. The patient

received RYPLAZIM through a compassionate use program and the dose was 6.6 mg/kg body weight every 2 days. Endoscopy showed multiple ulcers with one actively bleeding ulcer near the pylorus. Given the mechanism of action of plasminogen in fibrinolysis, it is possible that RYPLAZIM played a role in either prolonging or worsening the active bleeding. RYPLAZIM has not been studied in patients at increased risk for bleeding due to disease or injury.

Prior to initiation of treatment with RYPLAZIM, confirm healing of lesions or wounds suspected as a source of a recent bleeding event. RYPLAZIM may prolong or worsen bleeding in patients with bleeding diatheses or in patients taking anticoagulants and/or antiplatelet drugs and other agents which may interfere with normal coagulation. 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. If a patient develops uncontrolled bleeding (defined as any gastrointestinal bleeding or bleeding from any other site that persists longer than 30 minutes), seek emergency care and discontinue RYPLAZIM immediately.

## **5.2 Tissue Sloughing**

Tissue sloughing at mucosal sites may occur after initiation of treatment with RYPLAZIM as plasminogen activity levels are restored to physiological levels and fibrinolysis occurs. Lesions in the respiratory, gastrointestinal and genitourinary systems may slough following treatment resulting in bleeding or organ obstruction. Patients with tracheobronchial lesions may develop airway obstruction or hemoptysis. Closely monitor patients with either confirmed or suspected airway disease as manifested by cough, wheezing, shortness of breath, or changes in speech (dysphonia). Initiate the treatment with RYPLAZIM in an appropriate clinical setting with personnel trained in airway management and readily-available respiratory support equipment. Monitor at-risk patients in such a setting for a minimum of 4 hours after receiving their first dose of RYPLAZIM.

Patients with gastrointestinal and genitourinary lesions may experience tissue sloughing that causes pain, bleeding, or passage of tissue from affected organ systems. Patients should report persistent abdominal, flank, or pelvic pain to their physicians.

## **5.3 Transmission of Infectious Agents**

Because RYPLAZIM is derived from human plasma, it carries a risk of transmitting infectious agents. Based on effective donor screening and product manufacturing processes, RYPLAZIM carries a remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely low. It is also possible that unknown infectious agents may be present in RYPLAZIM. The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for RYPLAZIM [see *Description (1)*].

Report any infection thought to be possibly transmitted by RYPLAZIM to Prometic at 1-800-735-4086 and [prometicsmb@continuumindia.com](mailto:prometicsmb@continuumindia.com), or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## **5.4 Hypersensitivity Reactions**

Hypersensitivity reactions, including anaphylaxis, may occur with RYPLAZIM [see *Contraindications (4)*]. In case of a hypersensitivity reaction, discontinue RYPLAZIM immediately and treat according to standard medical practice.

## **5.5 Neutralizing Antibodies**

Formation of neutralizing antibodies (inhibitors) to plasminogen following the administration of RYPLAZIM has not been reported to date [See *Immunogenicity (6.2)*]. Monitor patients for the loss of clinical efficacy as manifested by the development of new or recurrent lesions while on RYPLAZIM therapy, and obtain plasminogen activity trough levels to confirm that adequate plasminogen activity levels have been achieved and are being maintained [see *Dosage and Administration (2)*].

## **5.6 Laboratory Abnormalities**

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 (fibrinolysis of ligneous lesions) and not indicative of VTE. Consider other tests to screen for VTE in patients receiving RYPLAZIM, as D-dimer levels will lack interpretability.

## **6 ADVERSE REACTIONS**

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

### **6.1 Clinical Trials Experience**

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data described in this section reflect exposure to RYPLAZIM in two single-arm, open-label clinical trials as well as expanded access and compassionate use programs for a total of 29 patients with plasminogen deficiency type 1 who received at least one dose of RYPLAZIM. Patients were between 11 months and 42 years of age. There were 18 pediatric patients and 11 adult patients. Fifteen patients were female. Twenty-eight patients were Caucasian, and one patient was Asian.

RYPLAZIM Trial 1 enrolled 7 patients (5 female) of whom 2 were pediatric patients (age 13 to 15 years) and 5 were adults. Five patients received two infusions: one 2 mg/kg infusion, and one 6 mg/kg infusion. Two patients received a single 6 mg/kg infusion. There were no adverse reactions in this trial.

RYPLAZIM Trial 2 enrolled 15 patients (11 female) of whom 6 were pediatric patients (age 4 to 16 years) and 9 were adults. Six of the 15 patients participated in RYPLAZIM Trial 1. Treatment duration ranged from 48 to 124 weeks. All patients received RYPLAZIM at a dose of 6.6 mg/kg administered every second, third or fourth day for 48 weeks.

A long-term treatment protocol enrolled 12 patients (8 female) of whom 8 were pediatric patients (age 16 months to 16 years) and 4 were adults. Eight patients in this treatment protocol continued from Trial 2 and 4 patients were from individual expanded access protocols in the US. All 12 patients continue to receive RYPLAZIM at the dose of 6.6 mg/kg every 2 to 4 days.

Fourteen patients (5 female) received RYPLAZIM through expanded access programs. There were 8 pediatric patients (age 11 months to 17 years) and 6 adults. Patients' dosage regimens were adjusted based on clinical response, and the regimens varied between 6.6 mg/kg every 1 to 7 days.

Table 1 shows the most frequent adverse reactions (incidence  $\geq 10\%$ ) observed in the two trials and in the treatment protocols.



**Table 1 Adverse Reactions Reported in  $\geq 10\%$  of Patients with Plasminogen Deficiency Type 1 (N=19\*)**

<b>Adverse Reactions</b>	<b>Number of Patients (%) (N = 19)</b>
Abdominal pain	3 (16%)
Gastric dilatation (bloating/feel bloated)	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%)

\*Age range of patients: 16 months to 42 years.

9 patients who received RYPLAZIM through single-patient expanded access were not included in the total population for the determination of adverse reaction frequency because their safety data were not as rigorously collected as patients in the clinical trials. Also not included is one patient from trial 1 who only received a single dose.

## **6.2 Immunogenicity**

In RYPLAZIM Trial 2, three patients (20%) developed anti-plasminogen antibodies following RYPLAZIM treatment. Comparison of pharmacokinetic (PK) parameters and /or trough activity levels for those positive samples with the parameters assessed either at baseline or for negative samples suggest these antibodies are not neutralizing antibodies (inhibitors) to plasminogen.

The detection of anti-plasminogen antibodies depends on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of antibody positivity in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies to RYPLAZIM with the incidence of antibodies to other products may be misleading.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no clinical trials of RYPLAZIM use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with RYPLAZIM to assess whether it can cause fetal harm when administered to a pregnant woman. In the United States, the background risk of major birth defects is about 3%, and miscarriage occurs in up to 20% of clinically-recognized pregnancies.

### **8.2 Lactation**

#### Risk Summary

Endogenous plasminogen is excreted in human milk; however, there is no information available on the presence of RYPLAZIM in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RYPLAZIM and any potential adverse effects on the breastfed infant from RYPLAZIM or from the underlying maternal condition.

#### 8.4 Pediatric Use

The safety and efficacy of RYPLAZIM has been established in pediatric patients. Use of RYPLAZIM is supported by the two clinical trials, and expanded access and compassionate use programs that included 18 pediatric patients age 11 months to 17 years [see *Clinical Studies (14)*, and *Adverse Reactions (6)*].

#### 8.5 Geriatric Use

The safety and effectiveness of RYPLAZIM have not been established in geriatric patients. Clinical studies of RYPLAZIM for this indication did not include patients age 65 years and over. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## 11 DESCRIPTION

RYPLAZIM is a Glu-plasminogen (> 95% purity) which is the native circulating form of plasminogen in the blood. RYPLAZIM is a sterile, white to off-white, lyophilized preparation of purified, plasma-derived plasminogen (human) to be reconstituted and administered by the intravenous route. Each vial of RYPLAZIM contains 68.8 mg of plasminogen. Following reconstitution with 12.5 mL of sterile water for injection (SWFI), the RYPLAZIM solution contains 5.5 mg/mL plasminogen and the following inactive ingredients: sodium citrate, sodium chloride, glycine, and sucrose. RYPLAZIM contains no preservatives. Biological potency of the plasminogen is determined by a chromogenic assay calibrated with a standard.

All plasma used in the manufacturing of RYPLAZIM is tested using serological assays for hepatitis B virus (HBV) surface antigen and antibodies to human immunodeficiency virus-1/2 (HIV-1/2) and hepatitis C virus (HCV). The plasma is also tested via nucleic acid amplification testing for HBV, HCV, HIV-1, hepatitis A virus (HAV) and human parvovirus B19 virus. Only plasma pools negative for HIV-1, HCV, HBV, and HAV, and containing levels of human parvovirus B19 DNA  $\leq 10^4$  IU/mL are used for the manufacture of RYPLAZIM.

The RYPLAZIM manufacturing process encompasses a series of chromatography adsorbents to purify plasminogen and includes multiple steps and controls to ensure that the purified plasminogen is essentially free of known adventitious agents. First, three orthogonal viral removal/inactivation steps are included: affinity chromatography for removal of enveloped and non-enveloped viruses; solvent/detergent treatment for inactivation of enveloped viruses; and 20 nm nanofiltration for removal of both enveloped and non-enveloped viruses. Two independent studies demonstrated effective viral removal/inactivation afforded by these three steps using validated scaled-down models. The overall virus reduction achieved in these studies for enveloped viruses was  $\geq 11.8$  logs and for non-enveloped viruses was  $\geq 7.1$  logs, as summarized in **Error! Reference source not found.** Second, the plasma used in this process is Human Source Plasma from FDA-approved collection centers; thus, there is minimal risk of contamination that could cause transmissible spongiform encephalopathies. Lastly, the product is tested for microbial and endotoxin levels throughout the process.

**Table 2: Viral Clearance Capacity of the Manufacturing Process**

Process Step	HIV-1	BVDV	PRV	HAV	PPV	Reo-3	EMCV
Affinity chromatography	≥ 5.2	ND*	ND*	3.6	2.6	ND*	3.6
Solvent/Detergent treatment	≥ 6.1	≥ 5.8	≥ 6.5	NA**	NA**	NA**	NA**
Nanofiltration	≥ 5.9	≥ 6.0	≥ 6.5	≥ 7.1	≥ 7.0	≥ 7.1	≥ 7.6
<b>Total LRV</b>	<b>≥ 17.2</b>	<b>≥ 11.8</b>	<b>≥ 13.1</b>	<b>≥ 10.7</b>	<b>≥ 9.7</b>	<b>≥ 7.1</b>	<b>≥ 11.2</b>

\*ND: Not determined; \*\*NA: Not Applicable; LRV: Log reduction value; BVDV = Bovine viral diarrhea virus; EMCV = Encephalomyocarditis virus; HAV = Hepatitis A virus; HIV-1 = Human immunodeficiency virus type 1; PPV = Porcine parvovirus; PRV = Pseudorabies virus; Reo-3 = Reovirus Type 3

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Treatment with RYPLAZIM temporarily increases plasminogen levels in blood.

### 12.2 Pharmacodynamics

Plasminogen deficiency type 1 is characterized by decreased plasminogen levels that causes formation of fibrin-rich, liginous pseudomembranous lesions on mucous membranes that can impair normal tissue and organ function. Replacement therapy increases the plasma level of plasminogen enabling a temporary correction of the plasminogen deficiency and reduction or resolution of extravascular fibrinous lesions.

### 12.3 Pharmacokinetics

The pharmacokinetics of RYPLAZIM were assessed by plasminogen activity (chromogenic assay) in plasma. Plasminogen was measured as both absolute and baseline-adjusted levels.

In RYPLAZIM Trial 2, pharmacokinetic analyses were conducted in 15 patients (9 adults) who completed at least 12 weeks of RYPLAZIM 6.6 mg/kg administered every second, third or fourth day and had sufficient plasma samples. Full pharmacokinetic profiles of plasminogen were measured over 96 hours after the first and Week 12 infusions, and trough levels of plasminogen were measured at baseline and at Weeks 2, 4, 6, 8, 10, and 12.

Mean absolute plasminogen activity in adult and pediatric patients reached physiological levels (70% to 130%) immediately after the first infusion, were sustained for approximately 24 hours, and remained an absolute 10% above baseline 72 hours after dosing. After 12 weeks, mean absolute plasminogen activity in adult and pediatric patients reached physiological levels (70% to 130%) immediately after dosing, were sustained for approximately 24 hours, and continued to maintain an absolute 10% above baseline 96 hours after dosing.

Although some inter-patient variability was observed, PK parameters for baseline-adjusted plasminogen activity levels were generally similar between adult and pediatric patients.

**Table 3: Mean ( $\pm$  Standard Deviation) Pharmacokinetic Parameters of Baseline-Adjusted <sup>a</sup> Plasminogen Activity Levels in Adult and Pediatric Patients After the First Dose and 12 Weeks RYPLAZIM**

PK Parameter	First Dose Adult (N=9)	Week 12 Adult (N=9)	First Dose Pediatric (N=6)	Week 12 Pediatric (N=6)	First Dose Total (N=15)	Week 12 Total (N=15)
AUC <sub>Last</sub> (hr*%)	2860.9 (700.7)	4665.6 (762.1)	3367.6 (852.8)	4641.6 (1393.4)	3063.6 (778.7)	4656.0 (1012.7)
AUC <sub>Inf</sub> (hr*%)	3317.3 (915.7)	5676.0 (1186.6)	4038.5 (1104.2)	5815.5 (1863.5)	3605.8 (1023.9)	5731.8 (1431.7)
CL (mL/h/kg)	1.5 (0.5)	0.9 (0.2)	1.3 (0.4)	0.9 (0.3)	1.4 (0.5)	0.9 (0.3)
C <sub>max</sub> (%)	90.9 (17.5)	127.4 (17.4)	102.0 (31.1)	120.3 (31.6)	95.3 (23.5)	124.6 (23.3)
Half-life (hr)	32.4 (13.1)	38.5 (7.1)	36.3 (10.0)	40.3 (5.0)	34.0 (11.7)	39.2 (6.2)
MRT <sub>Last</sub> (hr)	29.7 (3.7)	33.0 (1.6)	31.8 (2.0)	34.2 (1.5)	30.6 (3.2)	33.5 (1.6)
V <sub>ss</sub> (mL/kg)	62.8 (11.2)	47.2 (5.6)	64.1 (12.9)	52.5 (15.2)	63.3 (11.4)	49.3 (10.4)
T <sub>1/2</sub> (hr)	32.4 (13.1)	38.5 (7.1)	36.3 (10.0)	40.3 (5.0)	34.0 (11.7)	39.2 (6.2)

AUC<sub>Last</sub> = area under the time-concentration curve, from time 0 to the last measured time point; AUC<sub>Inf</sub> = extrapolated area under the time-concentration curve, from time 0 to infinity; CL = clearance; C<sub>max</sub> = peak concentration; MRT<sub>Last</sub> = mean residence time from time 0 to the last measured time point; V<sub>ss</sub> = steady-state volume of distribution; T<sub>1/2</sub> = half-life

<sup>a</sup> Baseline-adjusted plasminogen activity levels were calculated by subtracting the baseline (pre-infusion) value from each subsequent time-point. Note: plasminogen activity levels measured with a chromogenic assay.

**Table 4 : Mean ( $\pm$  Standard Deviation) Plasminogen Activity Trough Levels in Adult and Pediatric Patients Through 12 Weeks of RYPLAZIM dosing.**

Study Population	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
<b>Adult</b> (N = 9)	20.3 (13.7)	44.7 (18.6)	50.8 (17.1)	55.4 (12.0)	50.3 (19.5)	51.1 (15.5)	51.7 (12.3)
<b>Pediatric</b> (N = 6)	22.3 (5.1)	47.7 (7.4)	46.2 (10.5)	47.8 (9.8)	45.2 (14.8)	48.8 (6.4)	50.0 (12 6)
<b>Combined</b> (N = 15)	21.1 (10.8)	45.9 (14.8)	48.9 (14.6)	52.4 (11.5)	48.3 (17.4)	50.2 (12.4)	51.0 (12.0)

Plasminogen activity levels measured with a chromogenic assay. Normal range: 70%-130%, as determined by the laboratory.

Individual plasminogen activity values reported as < 5% were set at 5% for mean calculation.

There was no Week 2 plasminogen activity trough value for one adult patient; however, an unscheduled Week 3 value was obtained and used for mean calculation. Baseline value corresponds to endogenous plasminogen level.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted to evaluate the effect of RYPLAZIM on carcinogenesis, mutagenesis, or impairment of fertility.

### 13.2 Animal Toxicology and/or Pharmacology

No toxicity was observed in healthy rats following intravenous administration of RYPLAZIM at dose levels of 1.2, 7.3, and 21.8 mg/kg/day for 5 consecutive days.

## 14 CLINICAL STUDIES

The efficacy of RYPLAZIM in pediatric and adult patients with plasminogen deficiency type 1 was evaluated in a single-arm, open-label clinical trial (RYPLAZIM Trial 2). A total of 15 patients with plasminogen deficiency type 1

were enrolled. All patients had a baseline plasminogen activity level between <5% and 45% of normal, and biallelic mutations in the *plasminogen (PLG)* gene. The age range of these patients was 4 to 42 years, including 6 pediatric patients age 4 to 16 years, and 9 adults. Eleven patients were female. All patients were White. 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. Spirometry was the only test of organ function used and one patient had abnormal spirometry at baseline. This patient had a history of ligueous airway disease with a severe obstructive ventilatory 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. All patients with any lesion at baseline had at least 50% improvement in the number/size of their lesions.

External Lesions: Twenty-five of the 32 (78%) external lesions [with sites mainly located in the eyes (ligneous conjunctivitis), nose, gums (ligneous gingivitis), ligueous lesions of the hands and feet] were resolved by the end of Week 48. There were no recurrent or new external lesions in any patient through Week 48.

Internal Lesions: Nine of the 12 (75%) assessed internal lesions were resolved by Week 48. The lesion sites were mainly located in the cervix, bronchus, colon, vagina and uterus. No recurrent or new lesions were found on imaging in any patient through Week 48.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

RYPLAZIM is supplied in a single-dose vial [NDC 70573-099-01] containing 68.8 mg of plasminogen (human) (5.5 mg/mL after reconstitution with 12.5 mL of SWFI), one vial per carton [NDC 70573-099-02]. The treating physician will provide reconstitution and administration supplies. RYPLAZIM contains no preservatives.

- Store RYPLAZIM at temperatures of 2°C to 25°C (36°F to 77°F) in its original carton until ready to use. Do not freeze.
- Once reconstituted, RYPLAZIM must be administered within 3 hours. Do not refrigerate after reconstitution.
- Store diluent and syringe disc filters at 20°C to 25°C (68°F to 77°F).
- Do not use RYPLAZIM or diluent after the expiration date on the carton and vial labels.

## 17 PATIENT COUNSELING INFORMATION

- Advise patients and/or caregiver to read the FDA-approved patient labeling (*Patient Information and Instructions for Use*).
- Counsel patients and/or caregiver to discontinue RYPLAZIM and immediately contact their physicians if signs or symptoms of a possible hypersensitivity reaction occur, such as hives, generalized urticaria, angioedema, chest tightness, wheezing, tachycardia, and hypotension [see *Contraindications (4)*, *Warnings and Precautions (5.4)*].
- Inform patients that bleeding from active mucosal disease-related lesions and worsening of active bleeding not related to those lesions during RYPLAZIM therapy may occur. Depending on the lesion sites, this may manifest as gastrointestinal bleeding, hemoptysis, epistaxis, vaginal bleeding, or hematuria. Prior to initiation of treatment with RYPLAZIM, lesions or wounds suspected as the source of recent bleeding events should be confirmed to have healed. RYPLAZIM may prolong or worsen bleeding in patients with bleeding diatheses and/or taking anticoagulants or antiplatelet drugs. If a patient develops serious bleeding, seek emergency care and discontinue RYPLAZIM immediately [see *Warnings and Precautions (5.1)*].
- Inform patients that tissue sloughing at mucosal sites may occur at initiation of RYPLAZIM therapy as lesions resolve. Patients with respiratory lesion are at risk for respiratory compromise and initial treatment with RYPLAZIM should be performed in a clinical setting with close monitoring. Patients with lesions in gastrointestinal and genitourinary systems may experience tissue sloughing that may cause pain, mucosal

bleeding, or passage of tissue referable to those organ systems. Patients should report persistent abdominal, flank or pelvic pain to their physicians if not resolved. [see *Warnings and Precautions (5.2)*].

- Inform patients and/or caregiver that RYPLAZIM is made from human plasma and may contain infectious agents that can cause disease (eg, viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent and, theoretically the CJD agent). Explain that the risk that RYPLAZIM may transmit an infectious agent has been reduced by screening the plasma donors, by testing donated plasma for certain virus infections, and by inactivating or removing certain viruses during manufacturing. Counsel patients and/or caregiver to report any symptoms that concern them. [see *Warnings and Precautions (5.3)*].
- Advise patients and/or caregivers that antibodies may develop during treatment that make RYPLAZIM less effective [see *Warnings and Precautions (5.5)*].
- Advise female patients who are pregnant or may become pregnant that the potential effects of RYPLAZIM on pregnancy and breastfeeding are unknown. They should notify their physicians if they become or intend to become pregnant, or if they plan to breastfeed. [see *Use in Special Populations (8.1) and (8.2)*].
- Self-administration: ensure patient/caregiver has received detailed instructions and training and has shown the ability to safely and independently administer RYPLAZIM.

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