U.S. FOOD & DRUG ADMINISTRATION

Memorandum

DATE: March 5, 2021

TO: Crystal Melendez, RPM, CBER/OTAT/DRPM/RPMBI
Alexey Khrenov, Ph.D., Committee Chair, CBER/OTAT/DPPT/HB
Gavin Imperato M.D., Clinical Reviewer, CBER/ OTAT/DCEPT/CHB

FROM: Kristine T. Khuc, Pharm.D.
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Advertising and Promotional Labeling Branch (APLB)
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THROUGH: Lisa L. Stockbridge, Ph.D.
Branch Chief
APLB/DCM/OCBQ

SUBJECT: RYPLAZIM [plasminogen, human- tvmh]
BLA: 125659/0
Sponsor: Prometic Biotherapeutics

Background

The sponsor submitted:
_x_ New Approval
___ Changes Being Effected (CBE) supplement
___ Prior Approval Supplement (PAS)
___ Major Amendment

Submission contains:
_x_ Prescribing Information (PI)
_x_ Patient Package Insert (PPI)
_x_ Package and/or container labels
___ Other

Submission Date: September 04, 2020

PDUFA Action Date: **June 05, 2021**

APLB Comments/Recommendations

This is the second labeling review for an original Biologics License Application submitted by Prometic Biotherapeutics on August 14, 2017 for RYPLAZIM (plasminogen, human). On April 09, 2018, Prometic Biotherapeutics received a Complete Response letter, which outlined various deficiencies to their application. The applicant submitted their responses and updated labeling on September 04, 2020. APLB reviewed the revised draft PI, PPI, and IFU. The following comments are from a promotional and comprehension perspective.

GENERAL

- Use active voice and command language whenever possible throughout the PI.
- Add the suffix "-tvmh" to your proper name.
- Revise the Initial U.S. Approval date to four-digit year of BLA approval.
- The Revised Date is the month and year of BLA approval, written as MM/YYYY.

HIGHLIGHTS

PRODUCT TITLE

Present the proper name in small case lettering within parentheses. In the second row, present the dosage form then the route of administration of the product. For example,

RYPLAZIM® (plasminogen, human-tvmh)
lyophilized powder for reconstitution, for intravenous use

DOSAGE AND ADMINISTRATION

The administration directive directly beneath this header should stand alone. Place a return before the next sentence in this section.

CONTRAINDICATIONS

This is a required section. Add the contraindication statement from the FPI.

WARNINGS AND PRECAUTIONS

List the risks in this section in decreasing order of severity and public health significance with a concise summary of the risk and how to prevent, monitor, or mitigate the risk. Ensure that any changes made in the FPI are reflected here.

ADVERSE REACTIONS

Avoid using the term "adverse event." Please revise to "adverse reaction." Also, revise the incidence rate of the most commonly reported adverse reactions to a percentage rate to more appropriately capture the observed reaction.

PATIENT COUSELING INFORMATION

Revise the reference to patient counseling information to **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**

FULL PRESCRIBING INFORMATION: CONTENTS

- Under the CLINICAL PHARMACOLOGY section, add the required subsection 12.2 Pharmacodynamics.

- Ensure any changes in the table of contents is consistent with the FULL PRESCRIBING INFORMATION.

FULL PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

In order to avoid confusion, underneath subsection 2.3 Administration, the administration statement should either be deleted or be revised to the exact wording in the directive immediately beneath the header for section 2.

CONTRAINDICATIONS

Add a cross reference to section 11 DESCRIPTION, which contains information regarding the components considered to cause a reaction in patients with a known hypersensitivity.

WARNINGS AND PRECAUTIONS

- This section may need revision as the warnings and precautions listed under this section should be in decreasing order of severity and public health significance.

- Under subsection 5.1, the following statement "Allergic type hypersensitivity reactions have not been observed with RYPLAZIM but are theoretically possible" minimizes the risk that such reaction may occur. We recommend revising to "Hypersensitivity reactions may occur with RYPLAZIM."

- Under subsection 5.2, the statement "No seroconversions for hepatitis B or C (HBV or HBC) or human immunodeficiency virus (HIV) or any other known infectious agents were reported with the use of RYPLAZIM during the clinical trials," minimizes the risk of infectious agents. Also, add required wording for this subsection. For further reference, please refer to *Revised Preventive Measures to Reduce the Possible Risk of*

Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products-Guidance for Industry.

> "Plasma is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely 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 remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin."

- In subsection 5.3, revise the risk information about neutralizing antibodies to RYPLAZIM by including ways to monitor or mitigate this risk if applicable. Delete the company contact information because it directs the user to look elsewhere for more information by openly soliciting discourse with the sponsor.

- Subsection 5.4 describes transient and serious bleeding risk with the product. Consider moving this up towards the beginning of this section versus more theoretical risks. In addition, avoid using vague, undescriptive phrases such as "caution is recommended in such cases." Instead, describe the recommended steps to monitor this risk.

- Subsection 5.5 pertains to tissue sloughing, which is not a theoretical risk. Thus, consider moving this risk up towards the beginning of this section.

- Monitoring plasminogen levels is also mentioned in the neutralizing antibodies subsection, consider combining these two subsections (i.e., 5.3 and 5.6) together for cohesiveness.

ADVERSE REACTIONS

- Please revise the incidence rate of the most frequent adverse reactions to a percentage (e.g., >10%). This statement should be the same as in the **HIGHLIGHTS** section.

- Is bleeding a commonly reported adverse reaction? If so, please include it in the list of the most common adverse reaction rather than making it a cross reference.

- In subsection 6.1, please remove the italics for the required regulatory statement beneath this subsection.

- Avoid using the term "adverse events" in this section. Include only adverse reactions, as defined in 21 CFR §201.57(c)(7).

- Within Table 1, delete the footnote at the bottom defining the term "adverse events."

DRUG INTERACTIONS

This is not a required section. If there are no data to report, this section may be deleted. However, if retaining this section, delete the first sentence and revise the second sentence by detailing the specific steps to take for patients on anticoagulant and antiplatelet drugs.

USE IN SPECIFIC POPULATIONS

- Avoid bolding unless it is required by regulation. Under subsection 8.1 and 8.2, the subsection subheading "Risk Summary" should be underlined rather than bolded.

- Under subsection 8.2, delete the sentence "Because many drugs are excreted in human milk, caution should be used when RYPLAZIM is administered to a nursing woman" because it is considered uninformative to the reader.

- Under the same subsection, include the statement "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 material condition." For further reference regarding conforming to PLLR, please consult the *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*.

DESCRIPTION

In the second paragraph, we recommend deleting the reference to the Code of Federal Regulations and Health Canada Requirements. This type of information does not belong in the PI.

CLINICAL PHARMACOLOGY

- Within subsection 12.1, avoid lengthy descriptions and refrain from including disease pathology information as it does not belong in the PI.

- Subsection 12.2 Pharmacodynamics is a required subsection. Please develop this subsection.

CLINICAL STUDIES

- Avoid using research terminology (i.e., phase 3). Instead, just describe the studies.

- Please ensure that the Clinical Global Impression-Global Improvement Scales scores are appropriate for inclusion in this section. This is a subjective clinical instrument and seems highly promotional when used in this context.

HOW SUPPLIED/STORAGE AND HANDLING

Add latex information.

PATIENT PACKAGE INSERT (PATIENT INFORMATION)

- This document is entitled "Patient Information" not "FDA-APPROVED PATIENT LABELING." Please revise.

- Revise the proper name to include the suffix- tvmh.

- Revise information in this document to be in consumer-friendly language.

- Underneath the header "What is RYPLAZIM?" revise the phrase "injectable medicine to "inject into the vein." Consider deleting the last two sentences under this header as it may be too complex for patient labeling.

- Under "What should I tell my healthcare provider before using RYPLAZIM?' revise the phrase "medicinal products" to "medicine."

- Under the header "How do I take RYPLAZIM?"
  - In the second bullet, revise the phrase "self-administration" to "injecting it yourself."
  - In the third bullet, delete the last phrase "based on your body weight." This extra piece of information is unnecessary to inform the patient when using this product.
  - In the last bullet, revise the sentence to state "Your healthcare provider may order periodic blood tests to check your plasminogen level."

- Revise the header "What are the possible side effects of RYPLAZIM?" to "What are the possible or reasonably likely side effects of RYPLAZIM?"
  - Create a bulleted list of the most common effects to enhance readability.
  - The fourth bullet contains a lot of information and the most important safety information is buried in the paragraph. Consider creating a bulleted list of the signs and symptoms that may occur and what action to take.
  - Lastly, the patient or caregiver will report side effects to the FDA. Please delete Prometic's contact information.

- Under the header "How do I store RYPLAZIM?"
  - Combine similar information about storage to the beginning of the list.
  - Avoid abrreviations. Spell out "WFI."
  - In the third bullet, delete "Discard any leftover RYPLAZIM" as this information does not pertain to storage.

- Delete the header "What else should I know about RYPLAZIM?" In addition, the last two sentences do not need bulleting and can stand alone.

- Add the name, address of the manufacturer, and license number at the end of the document. Also, please date this document.

INSTRUCTIONS FOR USE

- Please list the proper name and suffix alongside the proprietary name.
- Avoid the overuse of bolding, as this decreases readability.
- Avoid abbreviations. Spell out "WFI" the first time it is used.
- Under the header "Gathering Supplies," the first 3 steps contain information not pertaining to gathering supplies. Please delete and move the appropriate steps to the "Preparing RYPLAZIM" section. Start this section with step 4. Combine and group related items or items to be used in conjunction to each other.
- Under the header "Infusing the RYPLAZIM,", the first 4 steps do not necessarily discuss a stepwise approach for the infusion. Delete information that is redundant or that may be combined with other steps to simplify this section. Start this section with examining the administration syringe for signs of discoloration or particulate matter prior to infusion.
- Date this document.

PACKAGE AND CONTAINER LABELS

Add the suffix- tvmh to the proper name on the package and container labels.

If you have any questions regarding this review, please contact Kristine T. Khuc, Consumer Safety Officer at (240) 402-8982.