Memorandum

DATE: March 6, 2018

TO: Alexey Khrenov, Chairperson, CBER/OTAT/DPPT/HB
Pratibha Rana, RPM, CBER/OTAT/DRPM/RPMBII

FROM: Alpita Popat, PharmD, MBA
CBER/OCBQ/DCM/APLB

THROUGH: Lisa L. Stockbridge, Ph.D.
CBER/OCBQ/DCM/APLB

SUBJECT: Labeling Review
RYPLAZIM [Plasminogen (Human)]
BLA 125659/0
Sponsor: Prometic Bio Therapeutics Inc.

Background: The sponsor submitted:

X New Approval
____ Changes Being Effected (CBE) supplement
____ Prior Approval Supplement (PAS) Amendment
____ Major Amendment

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

Submission Date: August 14, 2017

PDUFA Action Date: April 13, 2018

APLB Comments/Recommendations

On August 14, 2017, Prometic Bio Therapeutics, Inc. (Prometic), submitted an original Biologics Licensing Application (BLA) for RYPLAZIM [Plasminogen (Human)]. RYPLAZIM is indicated for replacement therapy in pediatrics and adults with congenital plasminogen deficiency.

On September 8, 2017, APLB recommended that the proposed proprietary name, RYPLAZIM, be found acceptable.

APLB reviewed the proposed labeling and carton/container labels submitted on August 14, 2017. The following comments are from a promotional and comprehension perspective.

GENERAL

- To improve readability, use bulleted lists and tables. Do not use bulleting when there is only one item or concept.
- Use active voice to enhance readability and comprehension.
- Use bolding only when required by regulations or guidance. Overuse of bolding minimizes the importance of all bolded messages.
- Avoid the use of clinical research jargon (e.g., Phase 1, Phase 2, Phase 3, Phase 2/3, primary endpoint, secondary endpoint, pivotal), as it reduces readability and comprehension.

HIGHLIGHTS (HL)

- Present all section headings as bolded and UPPERCASE letters, with the heading in the center of a horizontal line (solid or dashed) that extends across the entire width of the column. Ensure that white space precedes each major heading.
- Ensure that information listed in the **HIGHLIGHTS** is cross-referenced with the section(s) or subsection(s) of the FPI that contains more detailed information.
- The **Product Title** should present the proprietary name in UPPERCASE lettering, the proper name in lower case lettering within parentheses followed by the dosage form. For example:

  RYPLAZIM™ [Plasminogen (Human)] Lyophilized powder for reconstitution for intravenous use

- The **INDICATIONS AND USAGE** section requires a concise statement that includes the indication and limitation of use. The proper name is not required. For example:

  RYPLAZIM™ is plasma-derived human plasminogen indicated for replacement therapy in pediatrics and adults with congenital plasminogen deficiency.

  Delete the three bullets following the indication because they are neither indications nor limitations for the product.

In the accelerated approval statement, please include a reference to the **14 CLINICAL STUDIES** section for a discussion of the available evidence.

- Under **DOSAGE AND ADMINISTRATION**, cross-reference to the **FULL PRESCIBING INFORMATION** (FPI) for detailed information on reconstitution and administration. For example:

  > See full prescribing information for instructions on reconstitution of lyophilized power, and preparation and administration of reconstituted product. (2.2)

- Under **DOSAGE AND ADMINISTRATION**, remove the statement "RYPLAZIM must be prepared and administered by a healthcare professional or by an adequately trained patient or caregiver." Limitation of user requires limited distribution. Practice of medicine statements do not belong in the prescribing information.

- The **CONTRAINDICATIONS** section is a required heading and cannot be omitted. List all contraindications from the FPI. If there are no contraindications, this section must be included with the statement, "None."

- List **WARNINGS AND PRECAUTIONS** in decreasing order of severity with a concise summary of the adverse reaction/risk and recommendations for the prescriber to prevent, monitor for, or mitigate the risk. This should be in the same order as presented in the FPI with cross-reference to the FPI for further details.

- In the **ADVERSE REACTIONS** section, please revise the incidence rate of the most frequent adverse reactions to a percentage (e.g., incidence rate greater than 10%). Since the total number of subjects was small, any adverse reaction reported could signal a significant effect. Using the cutoff frequency as "2", rather than 10% or 14%, minimizes the importance of observed risk.

- Please add Prometic's phone number to report SUSPECTED ADVERSE REACTIONS.

- Remove the line with the "Revised:" date. This is included when supplements change the prescribing information.

TABLE OF CONTENTS (TOC)

Do not include FDA-approved patient labeling as a subsection heading in the TOC.

FULL PRESCRIBING INFORMATION (FPI)

1 INDICATIONS AND USAGE

- For readability and comprehension, revise the indications to a concise statement that includes the indication and limitation of use (see above).

- Delete the three bullets in this section because they do not describe the indication.

2 DOSAGE AND ADMINISTRATION

- Add a space between the use statement and section 2.1.

- Delete the two sentences regarding preparation and administration by a healthcare professional or by an adequately trained patient of caregiver. This product does not have limited distribution, so this type of directive does not belong in the prescribing information. Furthermore, placing this or any other information directly beneath the bolded use information detracts from the use information.

- For consistency and ease in style sheet interoperability, this section should be sub-sectioned into three parts with the following headings:

  2.1 Dose
  2.2 Preparation
  2.3 Administration

- The noncommittal sentence, "The procedures below are provided as general recommendations for the preparation and reconstitution of RYPLAZIM," introduces doubt about the legitimacy of any of the instructions that follow and invites innovations that may lead to medication error. This sentence does not belong in the prescribing information, which encompasses the FDA-approved instructions for safe use of this product. We recommend deleting this sentence. Any doubt about any steps in the preparation or the reconstitution of this product should be resolved prior to approval.

3 DOSAGE FORMS AND STRENGTHS

This section should include only the potency and description of the dosage form. Please delete "with 12.5 ml of WFI" this is not the dosage form of the product nor included in the packaging.

4 CONTRAINIDICATIONS

Consider revising this contraindication. RYPLAZIM doesn't have any inactive ingredients that are not already present in the human body. The only sensitivity would be to plasminogen itself. Theoretical possibilities do not belong in **CONTRAINDICATIONS.**

If there are no contraindications, this section must include the following:

None.

5 WARNINGS AND PRECAUTIONS

- Present risks in this section in decreasing order of severity and public health significance. If **hypersensitivity** reaction is a theoretical possibility, it should not be the first warning or precaution. If it is included at all, the following statement minimizes any risk: "Allergic type hypersensitivity reactions have not been observed with RYPLAZIM but are theoretically possible." So, if this included, please revise the statement to, "Hypersensitivity reactions may occur with RYPLAZIM.", and move it to the bottom of the list.

- Current subsection **5.2 Transmissible Infectious Agents** is templated language. The addition of the statement, "No seroconversions for hepatitis B or C (HBV or HCV) 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 this *required* warning. We recommend the statement below. (*See Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products*)

  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.

- Current subsection **5.3 Neutralizing Antibodies** is soliciting patient discourse with the applicant. This will allow open discussion by the applicant. We recommend revising this subsection to give specific details about monitoring or reporting, rather than openly telling the healthcare provider or caregiver to directly contact the applicant "for consideration of additional testing." Consider combining this information with the rest of monitoring and laboratory tests, under one subsection heading (currently **5.6 Monitoring and Laboratory Tests**).

- If bleeding is considered a risk, this should be moved to the beginning of **5 WARNINGS AND PRECAUTIONS**. The phrase "No cases of serious bleeding have occurred," is vague and minimizes the risk of bleeding. We recommend deleting this phrase. Similarly, the phrase, "caution is recommended in such cases," is vague and should be deleted.

- Tissue sloughing also should be moved up in **5 WARNINGS AND PRECAUTIONS**, as it is more than a theoretical risk.

6 ADVERSE REACTIONS

- In the **ADVERSE REACTIONS** section, please use the incidence rate of the most frequent adverse reactions to a percentage (e.g., incidence rate greater than 10%). This statement should be the same as in the **HIGHLIGHTS** section.

- In subsection **6.1 Clinical Trials Experience**, please remove the italics font for the required regulatory statement beneath the subsection heading and add a space after the statement.

- Avoid using internal company study titles (e.g. RYPLAZIM Trial 1 and Trial 2). Instead, describe the trial using the full title of the study.

- The Phase 1 trial is a preliminary safety study on a few patients (n=7 in this case). The statement that there were no adverse reactions "in this clinical trial" minimizes potential safety risks for plasminogen.

- The list of adverse reactions that were seen in one patient, but were "likely manifestations of the physiological activity of RYPLAZIM accompanying resolution of the lesions," should be separated from the rest of the adverse reaction information. This dense paragraph will not be

read and will serve to minimize the risks noted on other patients receiving RYPLAZIM. We suggest revising this long list to include only adverse reactions (not "events" which were "likely manifestations of the physiological activity of RYPLAZIM accompanying resolution of the lesions"). If these truly are adverse reactions of the product, then their incidence is **7%** and, perhaps, should be considered for a table. If so, a useful table would divide these by body system.

- Incidence reporting should be by whole numbers. These data do not have the significance to express incidence to the tenths or hundredths.

7 DRUG INTERACTIONS

It is not necessary to report the absence of drug interaction trials when there is an obvious mechanistic reason for a drug interaction. Reword this section for readability, stressing the important message and explaining what "use with caution" entails. For example:

Due to its mechanism of action, RYPLAZIM may increase the risk of bleeding. For this reason, patients taking anticoagulants or antiplatelet drugs require increased monitoring.

8 USE IN SPECIFIC POPULATIONS

- In the **8.1 Pregnancy** subsection, the statement, "RYPLAZIM should be given to a pregnant woman only if clearly needed" is not recommended because it is not considered informative. We recommend deleting this statement.

- In the **8.5 Geriatric Use** subsection use the following regulatory statement (21 CFR §201.57(c)(9)(v)):

> Clinical studies of RYPLAZIM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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

This section is densely worded, reducing readability and comprehension. Is recitation of parts of the CFR, as well as Health Canada requirements, necessary for the safe and effective use of plasminogen products?

12 CLINICAL PHARMACOLOGY

This section requires clinically relevant information to the organized beneath the three pre-specified subsections listed below. (*See Draft Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*)

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

14 CLINICAL STUDIES

- Refrain from using terms such as "primary endpoint" or "secondary endpoint" be deleted. Instead, describe only those endpoints that were found to be both statistically and clinically significant or demonstrated a meaningful lack of effect.

- Clinical Global Impression-Global Improvement Scale scores are subjective clinical instruments, which are not often used outside of psychiatric settings. The statement that the scores were "very much improved in all subjects" is promotional and, potentially, not adequately comprehended by the targeted healthcare providers for this product.

- The statement that "*all* subjects achieved the *highest* quality of life scores" [emphasis added] is highly promotional. This type of statement requires substantiation using a validated quality of life instrument(s). Given that a large percentage of patients were pediatric (4 patients, or 29%, under 18 years old), potentially more than one instrument would be needed to evaluate quality of life.

16 HOW SUPPLIED/STORAGE AND HANDLING

Delete the 3rd bullet "Store diluent and syringe disc filters at 20°C to 25°C (68°F to 77°F)" because it is not provided with your product.

PATIENT PACKAGE INSERT (PPI)

"FDA-APPROVED PATIENT LABELING" is a category, not a single type of patient labeling. The first patient labeling piece following the FPI appears to be a PATIENT PACKAGE INSERT (PPI). The PPI must be revised to patient-friendly language, which entails using simple sentences and active voice.

- Under **What is RYPLAZIM**?, please revise the first sentence to read: "RYPLAZIM is a medicine injected into your vein." The term "injectable medicine" is too broad and may lead to medication error if the user does not understand that this requires intravenous administration.

  The overall wording of this section is too high level. Please consider the following:

  > RYPLAZIM is a plasminogen replacement medicine that is injected into your vein. Your healthcare provider is giving you RYPLAZIM because your body does not make enough plasminogen. This problem causes you to have difficulty with blood clots, healing wounds, and forming normal skin in parts of your body.

- The statement, under **Who should not use RYPLAZIM?** does not make sense. The healthcare provider will already have determined whether the patient will get this product. Since this product is not under a Risk Evaluation Mitigation Strategy (REMS), this patient labeling is not a MEDGUIDE and would not require this section. Consider leaving section out completely. If

history with plasminogen is important to report, it can be added to the list in the next section, "**What should I tell my healthcare provider before using RYPLAZIM?**

- Revise "medicinal products" to "medicines" in the second and third bullets under "**What should I tell my healthcare provider before using RYPLAZIM?**

- Revise the first bullet under "**How do I take RYPLAZIM?**" to: RYPLAZIM is injected into your vein.

- Revise the second bullet under "**How do I take RYPLAZIM?**" to: You can get RYPLAZIM at your healthcare provider's office, clinic, or hospital. You can ask your healthcare provider if you can learn to give yourself treatments at home.

- Revise the third bullet under "**How do I take RYPLAZIM?**" to: Your dose of RYPLAZIM is based on your body weight. Follow your healthcare provider's instructions.

- Revise the fourth bullet under "**How do I take RYPLAZIM?**" to: Your healthcare provider will need to test your blood while you are taking RYPLAZIM.

- The section **"What are the possible side effects of RYPLAZIM?"** should be titled "**What are the possible or reasonably likely side effects of RYPLAZIM?"**

- For readability and comprehension, we suggest revising the format in **"What are the possible or reasonably likely side effects of RYPLAZIM?"** For example, bullet the common side effects and remove extra information that the patient can't report or mitigate. It is important to explain why some symptoms need reporting (e.g., allergic reaction). Further, it is unnecessary to repeat information covered in other sections of the PPI. Finally, patients should report adverse reactions to FDA, not the applicant. Consider the following for this section:

  The most common side effects are:

  - Headache
  - Nausea
  - Back Pain
  - Runny nose

  You may have some blood in your urine or have blood or tissue pieces in your bowel movements as plasminogen helps your body heal.

  Tell your healthcare provider or go to the emergency department right away if you have

  - Heavy bleeding.
  - Pain in your back, groin or pelvis, as these may be signs of a blockage.
  - Trouble breathing, wheezing, chest tightness, dizziness, swelling, itching, or rash, as these may be signs of an allergic reaction.

> These are not all the side effects of RYPLAZIM. You can ask your healthcare provider for information that is written for health professionals. Talk to your healthcare provider about any symptoms that concern you.
>
> You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- Under **"How do I store RYPLAZIM?"**, the bullets are not in logical order. The fifth bullet should be the first bullet. Consider making the statement, "Discard any leftover RYPLAZIM." a separate bullet.

- Delete the second bullet under **"How do I store RYPLAZIM?.** This may lead to confusion about what to store in refrigeration and minimizes the second sentence of the first bullet (i.e., "Do not freeze.").

- Under **"How do I store RYPLAZIM?**, spell out "WFI."

- The information currently under **"What else should I know about RYPLAZIM?"** does not belong under that heading. It is the language at the end of a medication guide. If the desire is to keep this language, it should be presented as a paragraph at the end of the PPI:

  > Medicines are sometimes prescribed for purposes other than those listed. Do not use RYPLAZIM for any other condition than that prescribed by your healthcare provider or give your prescription to anyone else.

- The name and address of the manufacturer, as well as the license number, should be presented at the bottom of this PPI, as it may be separated from the rest of the file.

INSTRUCTIONS FOR USE (IFU)

Generally, instructions for use are directed toward the healthcare provider. The following comments take into consideration that these may be used by a trained patient or caregiver.

- It is unnecessary and distracting to have the bolded warning at the top of this IFU. The only time a patient will have access to this product is through a prescription from the healthcare provider, which would only occur if the patient or caregiver were already trained.

- The sentence, "The steps listed below are general guidelines for using RYPLAZIM," is vague and introduces doubt about the legitimacy of any of the instructions that follow. We recommend deleting this sentence. Aside from individual personalization introduced by the healthcare provider, the IFU must be able to stand on its own.

- Delete directives that are repetitious (e.g., work on a clean, flat surface) and put each directive in its order of use.

- Ensure that an abbreviation is spelled out at first use (e.g., WFI).

- It seems that the list does not include all necessary supplies, and some supplies are not necessary.

- It is not clear that all the air bubbles are out of the infusion set prior to infusion (or inserting the infusion needle). Re-examine the steps regarding the saline flush of the filter, infusion tubing, and butterfly.

- Under "Gathering Supplies," the first three steps that have little to do with the gathering of the supplies. Consider starting with the list in Step 4 (perhaps with checkboxes instead of bullets). Group items that will be used together. Current Step 1 can be a short statement following the item "Required number of vials of RYPLAZIM." For example

  - □ Vials of RYPLAZIM (Your healthcare provider has told you how many vials you need to use for each treatment)
  - □ One 18- to 22-gauge needle per vial
  - □ One 20 mL syringe per vial
  - □ One syringe disc filter for every 15 vials needed
  - □ Sterile Water for Injection (WFI)
  - □ Butterfly needle and administration syringe(s) (or sterile infusion set)
  - □ 22-gauge needle
  - □ 10 mL normal saline
  - □ syringe for normal saline

  - □ Alcohol wipes
  - □ Sterile gauze pads
  - □ Medical tape or bandage

- The rest of the information currently under "Gathering Supplies" belongs under "Preparation":

  1. Work on a clean, flat surface.
  2. Make sure RYPLAZIM vials and WFI are at room temperature before preparation.
  3. Check expiration dates. Do not use expired RYPLAZIM or WFI.
  4. Wash hands thoroughly.
  5. Remove caps from the RYPLAZIM and WFI vials, exposing the rubber stoppers.
  6. Clean stoppers with alcohol wipes and allow to air dry. Do not blow on the stoppers. Do not touch rubber stoppers after cleaning them.

     For each of the RYPLAZIM vials:

  7. Using the 20 mL syringe with a 18-22-gauge syringe needle, draw up (b) (4) mL of WFI. Remove air bubbles.
  8. Gently and slowly puncture the RYPLAZIM vial with the WFI syringe needle and slowly add the 12.5 mL of WFI to the RYPLAZIM. Prevent foaming by gently streaming the WFI down the inner side of the RYPLAZIM vial.
  9. Remove the needle.
  10. Gently swirl RYPLAZIM vial to dissolve. Do not shake. (It may take (b) (4) minutes to fully dissolve RYPLAZIM. Discard if product is not fully dissolved after (b) (4) minutes).
  11. Inspect reconstituted RYPLAZIM. It should be colorless and clear to slightly (b) (4) Discard if cloudy or discolored.

After all RYPLAZIM is reconstituted, fill the administration syringe:

12. Using a 22-gauge needle, slowly draw up RYPLAZIM into one or more administration syringes (based on required dose). Do not mix with other medicines.
13. Remove any air bubbles.
14. Remove needle from administration syringe(s).
15. Once prepared, RYPLAZIM must be kept at room temperature and used within (b) (4) hours.

- Under "Infusing the RYPLAZIM," the patient or caregiver is told to infuse the product before cleaning the injection site. This section must be put into a logical order and directives that do not belong under administration should be removed to improve readability. Ensure that the infusion completed using the steps provided is free from air bubbles. For example:

    1. Immediately prior to infusion, re-examine RYPLAZIM to ensure that it does not have discoloration or particles in it. Discard if it is not (b) (4) colorless.
    2. Prepare the disc filter:
        a. Draw 10 mL of normal saline into a syringe and remove air bubbles.
        b. Attach syringe disc filter between the syringe with saline and the infusion tubing.
    3. Locate an injection site.
    4. Clean injection site with a sterile alcohol wipe and allow to dry. Do not blow on it.
    5. Insert butterfly needle of infusion set into vein.
    6. Inject normal saline through syringe disc filter and butterfly needle.
    7. Remove saline syringe.
    8. Attach administration syringe to the disc filter.
    9. Infuse RYPLAZIM slowly over 10-30 minutes (approximately 5 mL/min).
    10. After infusion is complete, remove butterfly needle and press down on infusion site with gauze.
    11. Cover with bandage or medical tape.
    12. Discard needles, syringes, tubing, vials, and filters as medical waste.

CONTAINER and PACKAGE LABEL

- Delete the second proper name, plasminogen, directly beneath the proprietary name. The proper name belongs above the proprietary name. (See 21 CFR §610.62)

- The logo and white space between the proper name and the proprietary name adversely affects the prominence of the proper name. The proper name must appear directly above the proprietary name and should be at least as prominent as the proprietary name. There should not be intervening matter.