Memorandum

DATE: 05/10/17

TO: Ze Peng, Chairperson
CBER/OTAT/DPPT/HB

Thomas Maruna, RPM
CBER/OTAT/DRPM

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

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

SUBJECT: Labeling Review
FIBRYNA [fibrinogen (human)]
BLA 125612/0
Sponsor: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

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)
_____ Patient Package Insert (PPI)
__X__ Package and/or container labels
__X__ Other (IFU)

Submission Date: June 9, 2016

PDUFA Action Date: June 9, 2017

APLB Comments/Recommendations

On June 9, 2016, OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. submitted an original Biologics License Application (BLA) for FIBRYNA® [fibrinogen (human)] indicated for the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

On July 22, 2016, APLB recommended that the proposed proprietary name, FIBRYNA, be found acceptable.

APLB reviewed the proposed labeling (submitted on February 16, 2017), the proposed carton/container labels (submitted on June 9, 2016), and the Medical Officer's review memo (dated April 28, 2017). The following comments are from a promotional and comprehension perspective.

HIGHLIGHTS

- The **HIGHLIGHTS** should not exceed ½ page. Use command language and summary statements throughout, especially in **WARNINGS AND PRECAUTIONS**, which will remedy this concern.

- The proprietary name should be in UPPER-CASE and the rest of the product title should be lower case. For example: FIBRYNA [fibrinogen (human)].

- Bold font within labeling is reserved for regulatory language. Under the heading **DOSAGE AND ADMINISTRATION**, bold font is overused and may lead to loss of readability. We recommend revising the bolded statement beneath this heading to:

  For intravenous use after reconstitution only.

  Please delete the second bolded sentence, which is considered practice of medicine and does not belong in the prescribing information.

- Please define the "components" in the **CONTRAINICATIONS** statement. This statement should be able to stand alone.

- In the **WARNINGS AND PRECAUTIONS** section, the bullet "Thrombotic events have not been reported in patients receiving FIBRYNA," minimizes the potential risk of thrombotic events with this product class. In addition, the statement, "Weigh the benefits of administration versus the risks of thrombosis," is vague, and it adds to the risk minimization with the lack of reported reactions in the clinical trials. If there is concern that the product class carries the risk of thrombosis, revise this warning to state that thrombosis may occur with FIBRYNA. If there is no concern, delete this bullet.

- Please add a cut-off frequency to the common adverse reactions statement in the **ADVERSE REACTIONS** section. We note that this statement is not consistent with the adverse reactions presented in the **6.1 Clinical Trials Experience** subsection. Please revise.

- In the **USE IN SPECIFIC POPULATIONS** section, the Pregnancy statement is no longer used in the **HIGHLIGHTS** in the absence of information. (See *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*) for more information.

CONTENTS

- Ensure that the Table of Contents aligns with the sections and subsections of the **FULL PRESCRIBING INFORMATION**.

- Conforming to the Pregnancy and Lactation Labeling Rule will change the subsection content organization and headings in **USE IN SPECIFIC POPULATIONS** (See *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*). Please update the **CONTENTS** accordingly.

FULL PRESCRIBING INFORMATION

Product Title

- The product name should be the same at the top of the **HIGHLIGHTS** and **FULL PRESCRIBING INFORMATION** sections.

- Ensure that the proper name is the correct for this class of products. For example, is it fibrinogen (human) or human fibrinogen?

- The proprietary name should be in UPPER-CASE and the rest of the product title should be lower case. For example: FIBRYNA [fibrinogen (human)].

- Please refer to product by its name, FIBRYNA [fibrinogen (human)], not the term concentrate. While the proprietary name with the proper name may be used at the beginning of each section, choose to use either the proprietary or the proper name consistently throughout the rest of the text. Usually, the proprietary name is used throughout the text of the PI.

2 DOSAGE AND ADMINISTRATION

- Delete the indication. The indication belongs in **INDICATIONS AND USAGE**.

- Under the heading **DOSAGE AND ADMINISTRATION**, we recommend using the bolded statement:

For intravenous use after reconstitution only.

Please delete the second bolded sentence, which is considered practice of medicine and does not belong in the prescribing information.

- Use active voice and command language wherever possible. For example:

2.1 Dose
Calculate the dose based on the target plasma fibrinogen level to control the type of bleeding, actual measured plasma fibrinogen level, and body weight. Use the following formula:

$$\text{Dose (mg/kg body weight)} = \frac{[\text{Target level (mg/dL)} - \text{measured level (mg/dL)}]}{1.8 \text{ (mg/dL per mg/kg body weight)}}$$

If fibrinogen target is unknown, dose at 70 mg/kg body weight.

4 CONTRAINDICATIONS

List the components that contribute to the contraindication.

5 WARNINGS AND PRECAUTIONS

The bullet "Thrombotic events have not been reported in patients receiving FIBRYNA," minimizes the potential risk of thrombotic events with this product class. In addition, the statement, "Weigh the benefits of administration versus the risks of thrombosis," is vague, and it adds to the risk minimization with the lack of reported reactions in the clinical trials. Revise this bullet to present the class effect, if it exists. For example, "FIBRYNA may cause thrombosis..." If no class effect exists, consider deleting this bullet.

6 ADVERSE REACTIONS

- Include the statement of the most common adverse reactions, with their cutoff frequency, beneath the heading of section **6 ADVERSE REACTIONS** section (before subsection 6.1). For example:

  The most common adverse reactions observed in clinical studies (>5%) were allergic type reactions [*see Warnings and Precautions (5.1)*]

- The statement, "No serious adverse reactions have been reported in clinical studies with FIBRYNA so far" is considered misleading and promotional in tone. We recommend deleting this sentence.

6.1 Clinical Trials Experience

- The regulatory required name for this section is **6.1 Clinical Trials Experience**. Please delete **Clinical Studies Experience**.

- Please provide description of overall clinical trial database from which the adverse reactions have been drawn, including overall exposure (number of patients, dosage, duration), demographics of exposed population, designs of trial, and any critical exclusions from safety database.

- Please provide any immunogenicity data if available for this product.

8 USE IN SPECIFIC POPULATIONS

Revise subsections 8.1, 8.2, 8.3 and 8.4 to conform to the new Pregnancy and Lactation Labeling Rule (PLLR). (See *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*)

13 NONCLINICAL TOXICOLOGY

Delete this section when there are no data.

14 CLINICAL STUDIES

- Pharmacokinetic and pharmacodynamic data belong in the **12 CLINCAL PHARMACOLOGY** section of the FPI.

- We recommend revising this section to limit its contents to a detailed discussion of the clinical studies of efficacy, including study design, endpoints, population, and results (see 21 CFR §201.57(c)(15)). Any discussion of a clinical study that relates to risk must reference the other sections of the labeling where the risk is identified or discussed (see 21 CFR §201.57(c)(15)(ii)).

- There is no need to subsection **14 CLINICAL STUDIES** in the absence of differing indications or clinically significantly different studies.

- The summary of the safety and efficacy studies is promotional in tone. In particular, the following statements are promotional or misleading

    - "minor bleeding event" would require definition/quantification
    - "successful" and "good or excellent efficacy" would require definition/quantification (consider describing the rating scale for these vague terms)
    - "No related serious adverse events or deaths and no cases of thromboembolism, allergic reactions or inhibitors to fibrinogen were reported for any patients during the study," is all promotional language that minimizes the contraindications and the warnings and precautions for this product.

15 REFERENCES

This section should only include references for circumstances where the labeling must summarize, or otherwise rely on, a recommendation by an authoritative scientific body, standardized methodology, scale, or technique, and only include a reference when it is needed for the safe and effective use of FIBRYNA. Do not include any outdated references or reference to unpublished data.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Please use active voice and command language wherever possible.
- Avoid redundancy and group similar concepts together.
- Refrain from including practice of medicine.

INSTRUCTIONS FOR USE

- Please use active voice and command language wherever possible.
- Align instructions with figures.

CONTAINER LABEL

APLB has no comments on the container label.

PACKAGE LABEL

APLB has no comments on the package label.