Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Jonathan Reich, MD Medical Officer, Pharmacovigilance Branch 2 Division of Pharmacovigilance (DPV), OBPV, CBER Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Octapharma USA, Inc.
Product:	Fibryga [(Fibrinogen (Human)]
STN:	BL 125612/99
Indication:	For the treatment of acute bleeding episodes in adults and children with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibryga is not indicated for dysfibrinogenemia.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2022

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The triggers for this pediatric postmarketing safety review include the FDA approvals of:

- June 7, 2017, initial approval (original BLA 125612/0) for the treatment of acute bleeding episodes in adults and adolescents ≥ 12 years of age with congenital fibrinogen deficiency
- December 23, 2020, efficacy supplement approval (sBLA 125612/67) to expand the indication for on-demand treatment of acute bleeding episodes to pediatric patients <12 years of age with congenital fibrinogen deficiency

[Of note, at the time of the 2017 initial approval, the trade name for this product was Fibryna; which was later changed to Fibryga.]

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

Fibryga is a human plasma-derived, sterile, purified, virus-inactivated and nanofiltered fibrinogen concentrate. It is supplied as a lyophilized powder for reconstitution for intravenous injection.

1.3 Regulatory History

- On June 7, 2017, FDA approved Fibryna original BLA 125612/0 for for the treatment of acute bleeding episodes in adults and adolescents ≥ 12 years of age with congenital fibrinogen deficiency
- On December 23, 2020, FDA approved sBLA 125612/67 to expand the indication for on-demand treatment of acute bleeding episodes to pediatric patients <12 years of age with congenital fibrinogen deficiency

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
- FAERS reports for Fibryga received by FDA from June 7, 2017, to April 30, 2022 (PAC review period)
- Manufacturer's Submissions
    - Fibryga U.S. package insert (USPI), updated December 22, 2020
    - Applicant response regarding dose distribution data [response to information request dated May 19, 2022, under BL 125612/99,]

    - Risk Management Plan, Version 1, dated May 3, 2016
    - Periodic safety reports
    - Postmarketing requirement (PMR) study annual status update reports
- FDA Documents
    - BLA 125612/0 Fibryna Approval Letter, dated June 7, 2017
    - BLA 125612/67 Fibryga Approval Letter, dated December 23, 2020
    - BLA 125612/0 Fibryna Pharmacovigilance Plan Review Memorandum
    - BLA 125612/67 Fibryga Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA[1]

There were (b) (4) Fibryga distributed in the U.S. during June 1, 2017, to April 30, 2022 (which aligns with period since initial approval on June 7, 2017). For the period of June 7, 2017 (International birth date (IBD)) to April 30, 2022, there were (b) (4) Fibryga distributed worldwide.

There were (b) (4) Fibryga distributed in the U.S. during December 1, 2020, to April 30, 2022 (this aligns with period since FDA approval of efficacy supplement on December 23, 2020). There were (b) (4) Fibryga distributed worldwide during January 01, 2021, to April 30, 2022.

Octapharma does not have access to any additional information about patient exposure in the pediatric age group (< 18 years) versus adults (> 18 years and older). As described in the USPI, Fibryga dosing, duration of dosing, and frequency of administration should be individualized based on the extent of bleeding, laboratory values, and the clinical condition of the patient.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP) is the Risk Management Plan, version1, dated May 3, 2016, which lists the important identified risks and important potential risks displayed in Table 1.

[1] Distribution data is protected as confidential commercial information and may require redaction from this review.

Table 1: Fibryga safety concerns

Important Identified Risks
• Hypersensitivity reactions, including anaphylactic reactions • Thromboembolic events
Important Potential Risks
• Suspected transmission of infectious agents
Missing Information
• Safety in elderly patients • Safety in pregnant or breast-feeding women • Safety in patients with hepatic impairment

Risk Management Plan, Version 1, dated 03-May-2016

The important identified and potential risks for Fibryga are labeled events in the USPI.

- **Hypersensitivity reactions:** Hypersensitivity reactions may occur with Fibryga and this risk is described under Section 5.1 *Warnings and Precautions* in the USPI.

- **Thrombosis:** The important identified risk of thrombosis is further described in Section 5.2 *Warnings and Precautions* in the USPI. Thrombosis may occur spontaneously in patients with congenital fibrinogen deficiency with or without the use of fibrinogen replacement therapy. Thrombotic events have been reported in patients receiving Fibryga. Treatment with human fibrinogen concentrate has been associated with risk of thrombosis at target fibrinogen levels that were less than 150 mg/dL. The risk of thrombosis may be greater when the target fibrinogen plasma level is 150 mg/dL. The USPI instructs healthcare providers to weigh the benefits of Fibryga administration versus the risks of thrombosis. Patients receiving Fibryga should be monitored for signs and symptoms of thrombosis. In addition to labeling this risk, and routine pharmacovigilance, FDA required the sponsor to conduct a safety postmarketing study to assess a signal of a serious risk of thromboembolic events in children and adults following Fibryga treatment (please see section 5.2 of memo).

- **Suspected transmission of infectious agents:** Fibryga is made from human plasma. Products made from human plasma may contain infectious agents. Transmissible infectious agents are further described under Section 5.3 *Warnings and Precautions* in the USPI.

The identified and potential risks for Fibryga are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. In

addition, there is a safety postmarketing requirement (PMR) study to assess a signal of a serious risk of thromboembolic events in children and adults following Fibryga treatment (please see section 5.2 of memo). There is no Risk Evaluation and Mitigation Strategy (REMS) for Fibryga.

5.2 Postmarketing studies

Fibryga has an ongoing safety-related PMR study under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess a signal of a serious risk of thromboembolic events in children and adults following Fibryga treatment. The sponsor is required to conduct the following study[2]:

- A prospective observational study in children and adults with congenital afibrinogenemia and hypofibrinogenemia treated with Fibryga for at least 10 major bleeding events to further characterize the risk of thromboembolic events following Fibryga treatment.
- Study milestone dates:
    - Final Protocol Submission: January 15, 2021
    - Study Completion Date: December 31, 2027
    - Final Report Submission: June 30, 2028

The current status of this study is ongoing. No new safety concerns have been identified from this study to date. FDA will continue to review annual PMR status update reports and the final study report when available.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Fibryga received during June 7, 2017, to April 30, 2022 (PAC review period). FAERS stores reports of postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

[2] PMR#1 in BL 125612/67 approval letter dated December 23, 2020. Note that this PMR (which includes patients of all ages) replaced the previous PMR in patients ≥12 years of age (PMR#2 described in BL 125612/0 approval letter dated June 7, 2017).

6.2 Results

A query of FAERS for adverse event reports for Fibryga or Fibryna during the PAC review period (June 7, 2017 to April 30, 2022) retrieved 8 serious reports, including 1 U.S. and 7 foreign reports. There was one foreign death report in an adult. There was a single U.S. pediatric serious report.

Table 2: FAERS reports for Fibryga during 6/7/2017 to 4/30/2022 (PAC review period)

Age (years)	Serious non-fatal, US	Serious non-fatal, foreign	Deaths, US	Deaths, foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18	1	0	0	0	0	0	1	0
≥18	0	6	0	1	0	0	0	7
Unknown	0	0	0	0	0	0	0	0
All	1	6	0	1	0	0	1	7

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

6.2.1 Deaths

During June 7, 2017, to April 30, 2022 (PAC review period), there was one foreign death report involving an 80-year-old woman who received Fibryga while she underwent major cardiac surgery (double bypass, replacement of the biological mitral valve, tricuspid annuloplasty, and an attempted repair of the aortic valve) and experienced a complicated clinical course including a post-surgery angiography scan which identified chronic occlusion of the celiac and the superior mesenteric arteries and multiple renal cortical ischemic plaques. She developed perioperative liver failure and died. It was not reported whether the patient had a history of congenital fibrinogen deficiency.

6.2.2 Serious Non-fatal Reports

During June 7, 2017, to April 30, 2022 (PAC review period), there were 7 serious, non-fatal reports; including 1 U.S. and 6 foreign reports. The single U.S. report involved a pediatric patient.

The 7 serious reports are briefly summarized below:

- 9-year-old female with congenital afibrinogenemia received Fibryga and experienced fever (101.4F). No additional information is available.
- 55-year-old man with a hemorrhage received Fibryga, the report is for an ineffective response. The providers document no rise in fibrinogen levels.
- 33-year-old female developed anaphylactic shock and disseminated intravascular coagulopathy receiving 5 medications including an intravenous antibiotic after a C-section done for severe pre-eclampsia. She recovered.

- 53-year-old male developed anaphylactic shock after heart surgery. He received multiple medications and the shock was adjudicated to be possibly due to Fibryga or the five other drugs he received at the same time. He recovered.
- 33-year-old pregnant woman (16 weeks gestation) with history of acute myeloid leukemia was reported to be undergoing "*a therapeutic abortion for maternal preservation*" and experienced a complicated clinical course with estimated 2L blood loss and was administered Fibryga. She went on to a undergo a hemostasis hysterectomy and developed acute respiratory distress syndrome and cardio-respiratory arrest. She recovered a sinus rhythm after multiple concomitant medications.
- 40-year-old male reported low blood pressure. No information is provided.
- 79-year-old female with hypofibrinogenemia who developed low blood pressure and oxygen saturations while receiving therapy for polytrauma. Her condition resolved with stabilization.

Reviewer comments: Review of these events did not identify any new safety concerns and there were no new clusters or unusual trends in the pattern of adverse events. The two anaphylactic shock cases are both in patients who received multiple medications precluding adjudication of causality. Of note, hypersensitivity reactions are also labeled under Section 5.1 Warnings and Precautions in the USPI.

6.2.3 Non-serious Reports

There were no non-serious reports for Fibryga during the PAC reporting period.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Fibryga were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis as of June 27, 2022. Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

A query of Empirica Signal using the Product Name (S) run did not identify any Preferred Terms with a disproportional reporting alert.
Reviewer comments: There are no new safety concerns raised by data mining.

6.4 Periodic safety reports and Postmarketing requirement (PMR) study annual status update reports

The manufacturer's postmarketing periodic safety reports for Fibryga covering the review period were reviewed. The adverse events reported were consistent with those seen in FAERS. The manufacturer's PMR study annual status update reports were

reviewed. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the U.S. National Library of Medicine's PubMed.gov database on June 27, 2022 for peer-reviewed literature, with the search terms "Fibryga" or "Fibryna" and published dates in the proximity of the surveillance period, retrieved 2 articles. Titles and abstracts were reviewed for relevance to safety information for Fibrinogen, and 2 articles relevant to safety were identified and are summarized below. No new safety concerns were identified.

Table 5: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Djambas Khayat, C, et. al., "Efficacy and safety of fibrinogen concentrate for on-demand treatment of bleeding and surgical prophylaxis in paediatric patients with congenital fibrinogen deficiency." Haemophilia, 2021 Mar;27(2):283-292.	14 pediatric patients (median age = 6 years, range 1-10 years) with congenital fibrinogen deficiency received human fibrinogen concentrate (either Fibryga or Octapharma AG) for treatment of bleeding or prophylaxis prior to surgery. There were two reported adverse events, one of which was adjudicated to be serious: portal vein thrombosis. No allergic reactions or deaths were reported.
Solomon, C, et. al., "Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data", Thromb Haemost 2015 Apr;113(4):759-71.	A review of over 650,000 doses of fibrinogen given since the mid-1980s demonstrated the rate of adverse drug reactions was roughly 1:6,000 doses. For specific reactions of concern: Hypersensitivity: 1:32,000 doses Thromboembolic events: 1:23,300 doses Suspected viral transmission: 1:31,000 doses The authors conclude the safety profile for fibrinogen is favorable.

Reviewer Comment: The literature seems consistent that this product has a favorable safety profile.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, PMR annual status update reports, and the published literature for Fibryga does not indicate any new safety concerns. The PAC review was initiated due to:

- June 7, 2017, initial approval (original BLA 125612/0) for the treatment of acute bleeding episodes in adults and adolescents ≥ 12 years of age with congenital fibrinogen deficiency
- December 23, 2020, efficacy supplement approval (sBLA 125612/67) to expand the indication for on-demand treatment of acute bleeding episodes to pediatric patients <12 years of age with congenital fibrinogen deficiency

Overall, there are very few reports for Fibryga in FAERS. There were no pediatric deaths and only a single pediatric non-fatal serious report. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Fibryga and safety postmarketing requirement (PMR) study to assess a signal of a serious risk of thromboembolic events in children and adults following Fibryga treatment.