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)
Through:	Meghna Alimchandani, MD Acting Director, Division of Pharmacovigilance (DPV), OBPV, CBER
From:	Firoozeh Alvandi, MD Medical Officer, Pharmacovigilance Branch 1 (PB1), DPV, OBPV, CBER
Subject:	SEVENFACT Safety and Utilization Review for the Pediatric Advisory Committee
Sponsor:	Laboratoire Francais du Fractionnement et des Biotechnologies Societe Anonyme (LFB S.A.)
Product:	SEVENFACT [coagulation factor VIIa recombinant human-jncw]
STN:	125641/177
Indication:	Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors
Meeting Date:	Pediatric Advisory Committee Meeting, November 13, 2025

Contents

1 INTRODUCTION

1.1 Objective

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present 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 were the

- April 1, 2020, initial approval of SEVENFACT under submission tracking number (STN) 125641/0 for the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors, and
- November 22, 2022, approval of SEVENFACT supplemental BLA (sBLA) under STN 125641/67 to include data from a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) study in the SEVENFACT U.S. prescribing information (USPI). As described in the Sevenfact USPI, section 8.4 Pediatric Use: *The safety and effectiveness of SEVENFACT for the treatment and control of bleeding episodes have not been established in children < 12 years of age. Effectiveness was not demonstrated in a trial of 25 pediatric patients 6 months to < 12 years of age. The safety and effectiveness of SEVENFACT in infants less than 6 months of age have not been evaluated*.

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

1.2 Product Description

SEVENFACT is produced by recombinant DNA technology using genetically engineered rabbits into which the DNA coding sequence for human FVII has been introduced. Human Factor VII is expressed in the rabbit mammary gland and secreted into the milk. During purification and processing, FVII is enzymatically converted to activated Factor VII (FVIIa).

Patients with hemophilia can develop neutralizing antibodies (inhibitors) to exogenous plasma derived or recombinant Factor VIII replacement products, leading to ineffective control of bleeding episodes. In these patients SEVENFACT can be used to treat bleeding episodes.

1.3 Regulatory History

SEVENFACT was approved in the U.S. on April 01, 2020, for treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors. SEVENFACT is not indicated for treatment of congenital factor VII deficiency.

On November 22, 2022, FDA approved a supplement (under STN 125641/67) to the Biologics License Application (BLA) for SEVENFACT which fulfilled the Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) #1 for a study in patients less than 12 years-of-age and updated Section 8.4, Pediatric Use, of the SEVENFACT U.S. Prescribing Information (see Section 5.2, Postmarketing studies). On June 20, 2024, FDA approved a supplement (under STN 125641/128) for a new 2 mg dosage strength of SEVENFACT and a co-packaged 3mL sterile water for injection (WFI) pre-filled glass syringe.

SEVENFACT is approved in the US and Mexico, Europe, United Kingdom, and Great Britain.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for SEVENFACT received during April 01, 2020, to June 30, 2025 (PAC review period)
- Manufacturer's Submissions
    - Pharmacovigilance Plan, dated September 26, 2025
    - SEVENFACT U.S. prescribing information, dated June 2024
    - Applicant response to information request regarding dose distribution data, received August 11, 2025
    - Applicant response to information request regarding dose distribution data, received September 15, 2025
    - Periodic Safety Reports
- FDA Documents
    - SEVENFACT Approval Letter (STN 125461/0), April 01, 2020
    - Division of Pharmacovigilance Review Memorandum (STN 125461/0), September 19, 2017
    - Division of Pharmacovigilance Review Memorandum
    - SEVENFACT Supplement Approval Letter (125641/67), November 22, 2022
    - Advertising and Promotional Labeling Branch (APLB) Review Memorandum (125641/128), April 18, 2024
    - SEVENFACT STN Supplement Approval Letter (125641/128), June 20, 2024
- Publications (see Literature Search in Section 7, Literature Review)

3 SAFETY RELATED LABEL CHANGES IN REVIEW PERIOD

There have been no safety-related label changes for SEVENFACT since licensure.

4 PRODUCT UTILIZATION DATA

LFB S.A. provided distribution data for the PAC review period. The sponsor stated that distribution of SEVENFACT started on December 10, 2020.

For the PAC review period (April 01, 2020, through June 30, 2025), there were distributed in the US, corresponding to an estimated exposure patient-years in the US.

For the period of July 15, 2022[1], through June 30, 2025, there were distributed outside of the US (Europe, Middle East, Latin America), corresponding to an estimated exposure of patient-years outside of the US.

These estimates were provided by the manufacturer for FDA review. The manufacturer estimated patient-years exposure with this formula: quantity (activated) sold (mg) / mg (i.e., the mean daily dose) x 365). Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) for SEVENFACT is dated September 26, 2025. According to the PVP, there are no identified risks for SEVENFACT. Important potential risks for SEVENFACT include allergic/anaphylactoid and anaphylactic reactions, immunogenicity (i.e., antibody development and associated lack of efficacy), thromboembolic events, and drug-drug interactions (such as thrombotic events when used simultaneously with activated prothrombin complex concentrates (aPCCs) and other FVIIa-containing products). The manufacturer plans to monitor these potential risks as part of routine surveillance.

Table 2: SEVENFACT Safety Concerns[2]

Important Identified Risks	None
Important Potential Risks	Allergic/anaphylactoid and anaphylactic reactions Immunogenicity Thromboembolic events Drug-drug interactions

[1] SEVENFACT was only approved in the US in 2020 and 2021. Approval in non-US jurisdictions occurred in 2022.
[2] SEVENFACT Pharmacovigilance Plan, dated July 30, 2020.

Important Identified Risks	None
Important Missing Information	Use in: Elderly population (≥65 years old) Patients with renal impairment Patients with liver impairment Pregnant and lactating women

Hypersensitivity reactions can occur in patients with history of IgE-based hypersensitivity to casein. There were no severe allergic reactions reported in the SEVENFACT clinical trials. The SEVENFACT prescribing information, under Warnings and Precautions, states that "Hypersensitivity reactions, including anaphylaxis, can occur with SEVENFACT". The contraindications include patients with a severe hypersensitivity reaction to SEVENFACT or any of its components and a known allergy to rabbits or rabbit proteins.

Immunogenicity was not reported in any participants in the SEVENFACT clinical trials prior to licensure (i.e., no participant developed inhibitors/neutralizing antibodies). The SEVENFACT prescribing information includes instructions for monitoring patients for development of neutralizing antibodies. Neutralizing antibodies to other Factor VIIa-containing products have been observed in patients with congenital Factor VII-deficiency (SEVENFACT has not been studied in this patient population).

Thromboembolic events are potential risks for any exogenous factor that involves the clotting cascade, including factor FVII/FVIIa. There were no thrombotic events reported during the SEVENFACT clinical trials. The SEVENFACT prescribing information addresses the risk of thrombosis, including a boxed warning stating that serious arterial and venous thrombotic events may occur following administration of SEVENFACT. The Warnings and Precautions Section identifies patients at higher risk for thrombosis including patients with atherosclerotic disease, coronary artery disease, cerebrovascular disease, crush injury, septicemia, or history of thrombosis/ thromboembolism, history of congenital or acquired hemophilia receiving concomitant prothrombic complex or other hemostatic agents (i.e., addressing also the potential risk of drug-drug interactions which may increase risk of thrombosis). The prescribing information also provides instructions for monitoring patients for development of thrombosis.

There are no safety-related postmarketing studies as postmarketing requirement or commitment (PMR/PMC) for SEVENFACT and there is no requirement for a Risk Evaluation and Mitigation Strategy (REMS).

5.2 Postmarketing Study

The initial approval of SEVENFACT included a PMR under PREA to evaluate the use of SEVENFACT in congenital Hemophilia A or B patients from birth to <12 years old with Inhibitors to Factor VIII or IX.

Study status: Study completed and PREA PMR was fulfilled with approval of November 22, 2022, approval of sBLA 125641/67 (see sections 1.1 and 1.3 of this memorandum). No new safety concerns were identified from this study.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of SEVENFACT received between April 01, 2020 (initial approval) and June 30, 2025 (date of query). FAERS stores 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.

6.2 Results

The results of the FAERS search of adverse event reports for SEVENFACT during the review period are listed in Table 3 below. There were 14 reports, including 11 from the US.

Table 3: FAERS Reports for SEVENFACT (April 01, 2020, through June 30, 2025)

Age	U.S. Serious* Non-fatal	Non-U.S. Serious Non-Fatal	U.S. Deaths	Non-U.S. Deaths	U.S. Non-Serious	Non-U.S. Non-Serious	U.S. Total	Non-U.S. Total
<18 years	1	1	0	0	3	0	4	1
≥18 years	1	1	0	0	2	0	3	1
Unknown	0	1	0	0	4	0	4	1
Total	2	3	0	0	9	0	11	3

*Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions as defined in 21CFR600.80

**Note: Based on review of case narratives, two of the reports with “unknown age” in Table 3 were determined to involve pediatric patients.

6.2.1 Deaths

There were no deaths following SEVENFACT reported to FAERS during the PAC review period.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were five serious, non-fatal reports representing 4 unique cases. One report with unknown age was determined on further examination to involve a pediatric patient. The 4 unique cases involved two pediatric patients and two adults, further described below. No new safety concerns are identified from review of these reports.

Pediatric serious non-fatal reports (n = 2)

- Foreign report of a 14-year-old male with a complex medical history including VACTERL syndrome[3], asthma, idiopathic short stature, scoliosis, thrombosis, and esophageal atresia, who received multiple products, including SEVENFACT, status post scoliosis surgery and was reported to have a complicated clinical course with multiple AEs, including anaphylactic shock, hemorrhage, left hemothorax, pleural effusion, pneumothorax, and mechanical ventilation complications. SEVENFACT was included as one of multiple suspect products (including ketamine, propofol, aprotinin, calcium chloride, fibrinogen/human thrombin, sulfentanil citrate, and tranexamic acid, desmopressin, budesonide, famotidine, alburex, FXIII/von Willebrand Factor, gabapentin, dexamethasone, red blood cell transfusions). The patient was also reported to have experienced urticaria during treatment with intravenous DDAVP (desmopressin). The temporal relationship between each of AEs and the administration of SEVENFACT or the other suspect products listed was not reported.

  Reviewer Comment: While SEVENFACT appears among the list of suspect products in the report, there is no mention of SEVENFACT or coagulation Factor VIIa recombinant Human-JNCW in the narrative, and there are no AEs specified in association/temporal association with SEVENFACT. Of note, this report was submitted by the manufacturers of desmopressin, budesonide, and famotidine. The paucity of temporal latency information, confounding from multiple suspect products, co-morbidities and underlying conditions precludes further causality assessment.

- Report of a 13-year-old male with hemophilia A receiving SEVENFACT periodically to treat bleeding episodes, and concomitant ELOCTATE and HEMLIBRA for prophylactic prevention of bleeding, experienced four episodes of hemarthrosis of the knees and associated hospitalizations. It was not specified if bleeds occurred on scheduled SEVENFACT dosing days or not. Dosage of

[3] VACTERL Syndrome is a syndrome characterized by a constellation of birth defects including at least three of: vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.

SEVENFACT was either daily or every other day during periods of active bleeding. The manufacturer assessed the events as common complications of the patient's underlying condition (Hemophilia).

Reviewer Comment: Review of the case finds hemarthrosis likely related to and confounded by the patient's underlying condition, increased risk of hemorrhage and/or possible lack of effect of ELOCTATE and HEMLIBRA used prophylactically. Additionally, as per SEVENFACT USPI, during bleeding episodes SEVENFACT should be administered every 2-3 hours. If patient received SEVENFACT daily or every other day during bleeding episodes, he may have been underdosed leading to ineffective control of bleeding episodes.

Adult serious non-fatal reports (n = 2)

- Foreign report of a 49-year-old male with hemophilia A receiving SEVENFACT and CLONAZEPAM experienced AEs at the injection site including bruising, erythema and decreased joint range of motion, as well as AEs relating to mental health including anxiety, panic attack, somnolence, depression, excitability, and irritability. Additional details about the clinical circumstances of these events or the temporal relationship between administration of SEVENFACT and CLONAZEPAM and these events were not available.

  Reviewer Comment:
  The patient's underlying hemophilia A may be contributory to decreased joint range of motion, as patients with hemophilia A may bleed into joints resulting in joint damage. Panic attack is an indication for clonazepam use. CLONAZEPAM is associated with AEs of skin rash and an underlying mental health condition may be associated with the reported AEs of somnolence, depression, anxiety, excitability, and irritability. Of note, this report was submitted by the CLONAZEPAM manufacturer. The paucity of clinical details and lack of information pertaining to latency precludes further causality assessment. The events of injection site irritation, injection site bruising, vessel puncture site erythema can occur with intravenously administered products and are related to the labeled PTs of infusion-related reaction, infusion site hematoma, and infusion site discomfort.

- Report of a 33-year-old male with hemophilia A and history of inhibitors, was treated with SEVENFACT and experienced thrombosis. The patient's medical history included a left upper extremity catheter (removed 5 years prior to report) and a history of thrombosis. Since an unknown date, he had been treated with NOVOSEVEN and received HEMLIBRA weekly for bleeding prophylaxis. The patient was switched from NOVOSEVEN to SEVENFACT. Approximately 2 months after the last administration of SEVENFACT, the patient experienced left arm swelling after working out and received SEVENFACT, to treat pain and swelling presumptively due to bleeding. Discomfort and pain continued and additional SEVENFACT was administered. The pain continued and intensified

and eventually radiated to left clavicle and left lateral neck, and the patient also experienced occasional headaches. Per the report, over the next 2 months, the patient received 8 infusions of SEVENFACT. An ultrasound identified a nonocclusive brachial venous thrombus, and SEVENFACT was stopped. The patient was switched back to NOVOSEVEN and underwent balloon pulmonary angioplasty.

Reviewer Comment: The patient had received SEVENFACT due to erroneous assessment of hemorrhage while the patient's symptoms were due to thrombosis. Thrombotic events are labeled AEs for FVII products, including SEVENFACT. HEMLIBRA (emicizumab) can also increase risk of thrombosis, however, it is unclear from the information available in the report whether or not HELIMBRA was concomitantly administered with SEVENFACT. The risk of serious arterial and venous thrombotic events is included in the Warnings and Precautions Section of the prescribing information for SEVENFACT, and as a boxed warning. The prescribing information advises that patients who receive SEVENFACT should be monitored for the development of signs and symptoms of activation of the coagulation system or thrombosis, and when there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the dose of SEVENFACT should be reduced or stopped, depending on the patient's condition.

6.2.3 Non-serious Reports

During the reporting period, there were 9 non-serious reports. One of the reports with unknown age was determined upon further examination to involve a pediatric patient, resulting in 4 pediatric cases, 2 adult cases, and 3 with unspecified age.

The adverse events in the 4 pediatric cases included the PTs: *drug ineffective*, *injury associated with device, international normalized ratio increased, Factor VII inhibition, off label use*, and *no adverse event*. In the case involving injury associated with a device, a 17-year-old experienced an injection site injury (vein rupture) while self-administering SEVENFACT using a small gauge canula. Switching to a larger canula allowed better flow of SEVENFACT while being administered intravenously. The PTs *off-label use*, *international normalised ratio (INR) increased*, and *Factor VII inhibition* occurred in a 2-year-old that experienced an elevation in INR due to Factor VII inhibitors while receiving SEVENFACT daily as prophylaxis. (This patient had a previous history of Factor VII inhibitor while receiving Novoseven prophylactically).

Among the remaining 5 cases, the PTs included intentional product misuse, feeling cold, tremor, drug ineffective, hypersensitivity, and no adverse event. The PT of no adverse event was reported in conjunction with the PT of drug ineffective.

Reviewer comment: Review of these cases does not raise new safety concerns. Inhibitor (neutralizing antibody) formation and hypersensitivity are labeled AEs.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of SEVENFACT were disproportionally reported compared to other products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point of June 29, 2025. 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 (S) run identified 2 preferred terms (PTs), “no adverse event” (5 reports) and “drug ineffective” (6 reports), with a disproportional reporting alert for SEVENFACT (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).

Review of these reports found that all 5 reports with the PT “no adverse event” also contained the PT “drug ineffective.” Of the 6 reports of PT “drug ineffective,” 3 were reported in pediatric patients, 2 were in adults, and 1 had no age reported. Review of these reports found that they involved bleeding related to the patients’ underlying conditions and no new safety concerns were identified for SEVENFACT.

6.4 Periodic Adverse Event Reports (PAERs)

The manufacturer’s postmarketing periodic safety reports for SEVENFACT covering the surveillance period since licensure (April 01, 2020) to July 15, 2024 (latest periodic adverse event report received from the manufacturer) were reviewed. The adverse events reported were the same as/consistent with those seen in FAERS. 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 July 03, 2025, for peer-reviewed literature, with the search term “SEVENFACT” and then with the search term “coagulation factor VIIa (recombinant)-jncw” retrieved 5 publications. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety concerns for SEVENFACT were identified as a result of review of this publication.

Article	Author's Safety Conclusion
Pipe SW, Dunn AL, Young G. Efficacy and safety evaluation of eptacog beta (coagulation factor VIIa [recombinant]-jncw) for the treatment of hemophilia A and B with inhibitors. Expert Rev Hematol. 2023 Jul-Dec;16(10):715-729.	This review article describes findings from the phase 1b and phase 3 (PERSEPT) clinical trials which formed the basis for the regulatory approval of SEVENFACT for the indication of use in patients ages 12 and older with hemophilia A or B with inhibitors (PwHABI). There were no safety concerns identified by the authors in this review/publication.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for SEVENFACT does not indicate any new safety concerns. This review for the PAC was initiated due to the initial 2020 SEVENFACT 125641/0 approval in patients ≥12 years of age and 2022 approval of SEVENFACT sBLA 125641/67 to include data from PREA PMR to update labeling in section 8.4 of the USPI. AEs were generally consistent with known and labelled risks after use of Factor VII products, including SEVENFACT. Overall, there were few reports of adverse events, and there were no reports of death. 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 SEVENFACT.