Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

Pharmacovigilance Plan Review Memorandum
Sevenfact™ (BLA 125641/0)

From:	Firoozeh Alvandi, MD Medical Officer, Pharmacovigilance Branch Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE)
Through:	Wambui Chege, MD Acting Branch Chief, PVB, DE, OBE Scott Proestel, MD Division Director, DE, OBE
To:	Mikhail Ovanesov, PhD Chair, BLA Review Committee Office of Tissues and Advanced Therapies (OTAT)
STN:	Original BLA 125641/0
Product:	Proposed brand name: Sevenfact™ (product name: LR796); Coagulation Factor VIIa (Recombinant)
Proposed indication:	Sevenfact is indicated for on-demand treatment and control of bleeding episodes occurring in adolescent and adult patients with hemophilia A or B with inhibitors
Sponsor:	LFB USA, Inc.
Action Due Date:	October 13, 2017

1. INTRODUCTION

Objectives and Scope

The sponsor, LFB S.A., submitted an original BLA 125641/0 on 10/13/2016, seeking licensure for the product LR769, proposed proprietary name "Sevenfact™" for the on-demand treatment and control of bleeding episodes in adolescent and adult hemophilia A or B patients with inhibitors. The purpose of this memorandum is to review the pharmacovigilance plan proposed by the sponsor for postmarketing safety monitoring and to identify potential safety concerns that may require further additional postmarketing safety surveillance, studies, or other pharmacovigilance activities if the product is licensed.

Product Description

Sevenfact is the proposed trade name for LR769, Coagulation Factor VIIa (Recombinant), a recombinant coagulation factor VIIa. Sevenfact is produced using genetically engineered rabbits into which the DNA coding sequence for human factor VII has been introduced with a mammary gland specific DNA sequence, thus directing the expression of the human rFVII protein into milk. The amino acid sequence is reported to be identical to that of human plasma-derived factor VIIa (upon testing against the World Health Organization standard for human FVIIa, it was found to be >99% pure). FVII is enzymatically converted into FVIIa during purification and processing.

Mechanism of action

In pharmacologic plasma concentrations, factor VIIa is expected to support thrombin generation by binding to the surface of platelets and to tissue factor at the site of vascular disruption. Complexed with tissue factor, factor VIIa activates coagulation factor X to factor Xa, and coagulation factor IX to factor IXa. In complex with other factors, factor Xa then converts prothrombin to thrombin, leading to the formation of a hemostatic plug upon converting fibrinogen to fibrin and resulting in clot formation at the site of hemorrhage. Optimal factor VIIa function is dependent on the presence of an adequate quantity of functional platelets at the site of bleeding.

Proposed indication

The indication sought is for on-demand treatment and control of bleeding episodes occurring in adolescent and adult patients with hemophilia A or B with inhibitors.

Regulatory History

This product has not been approved in any part of the world. The initial IND (IND 15183) was submitted in July of 2012. In October of 2016 (10/13/2016) the sponsor submitted the BLA (BLA 125641) seeking initial licensure for Sevenfact (LR769).

2. MATERIALS REVIEWED

Materials reviewed in support of this pharmacovigilance plan assessment are listed below.

- Manufacturer's Submissions
  Original BLA submission 125641\0
    - Module 1.16.1: Pharmacovigilance Plan/Risk Management Plans

- Module 2.5: Clinical Overview
- Module 2.7.4: Summary of Clinical Safety
- Module 5.3.6: 120-day Safety Update
- Input from OTAT Clinical Reviewer: Dr. Poornima Sharma

3. CLINICAL STUDIES

The clinical trial data submitted in support of this BLA is based on 4 trials, one completed Phase Ib PK trial and three Phase 3 clinical trials - a completed Phase 3 safety/efficacy and PK trial "RB-FVIIa-006-13 (PERSEPT 1)" and 2 ongoing trials "LFB-FVIIa-007-14 (PERSEPT 2)" which is a phase 3 safety/efficacy and PK trial and "LFB-FVIIa-008-14 (PERSEPT 3)" which is a safety/efficacy trial. Of these 4 trials, the sponsor has opted to submit safety data from the 2 trials which are complete at the time of submission of this BLA. See section 4, Safety Database for additional details.

Clinical Trials/Studies

Study Name	Study Population	Study Status
GTC-FVIIa-005-11 (PK study) (Phase Ib)	A Phase Ib, Dose Escalation Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients	Completed
RB-FVIIa-006-13 (PERSEPT 1) (Phase 3 safety/efficacy, PK portion)	Adolescent/adult Hemophilia A or B patients with inhibitors	Completed
LFB-FVIIa-007-14 (PERSEPT 2) (Phase 3 safety, efficacy and PK)	Pediatric patients (birth to 12 years) with Hemophilia A and B with inhibitors	Ongoing
LFB-FVIIa-008-14 (PERSEPT 3) (Phase 3 safety and efficacy)	Adult and pediatric surgical patients (6 months to 75 years) with Hemophilia A or B with inhibitors	Ongoing

4. SAFETY DATABASE

Clinical Trial Safety Data

Data on clinical safety of Sevenfact (LR769) is derived from two clinical trials in a total of 42 patients with hemophilia A or B with or without inhibitors that included the treatment of 468 bleeding episodes, as follows:

- A Phase 1b clinical trial (GTC-FVIIa-005-11) evaluating PK and pharmacodynamics (PD) of 3 doses of LR769 (25 µg/kg, 75 µg/kg, and 225 µg/kg) in 15 male patients ages 18-75 years of age (range 20, 61; median 33 years of age) with hemophilia A or B.
- A Phase 3 trial (RB-FVIIa-006-13, "PERSEPT 1") assessing the safety and efficacy of 2 treatment regimens (75 µg/kg and 225 µg/kg) in the treatment of bleeding episodes in 27 male patients ages 12-75 years of age (range 12, 54; median 31 years of age) with hemophilia A or B with inhibitors to FVIII or FIX.

The results of the two trials were combined. In patients with hemophilia A or B with or without inhibitors who underwent treatment for 468 bleeding episodes, 23 (54.8%) patients experienced 64 adverse events (i.e., the proportion of subjects with at least one Treatment-Emergent Adverse Event (TEAE) was 54.8% (64 total TEAEs in 23 of 42 patients treated with Sevenfact (LR769)).

Treatment-Emergent Adverse Events (TEAEs)
Of the 64 TEAEs, 10 AEs, which included 6 “infusion site related”: infusion site discomfort, hematoma; 2 headache; 1 elevated body temperature; 1 dizziness, were considered treatment-related, and none were considered serious. The most common TEAEs (in >10%) of subjects reported for Sevenfact by preferred term (PT) was injection site related.

Reactions that occurred in more than 1 patient
From a total of 468 treatments in 42 patients, there were 10 reports of hemarthrosis (in 4 patients), 9 of headaches (in 6 patients), 3 of dizziness (in 2 patients), 3 of nasopharyngitis (in 3 patients), and 2 of fatigue (in 2 patients).

Serious Adverse Events
The only serious AEs (SAEs) were acute tonsillitis complicated by intracranial hemorrhage (reported as two SAEs) in a single patient, and requiring hospitalization. These SAEs were considered by the sponsor as unrelated to treatment. The case consisted of AEs of tonsillitis and intracranial hemorrhage in a 19-year-old male with severe hemophilia A and baseline FVIII level of 1% and inhibitor level of 12.5 Bethesda unit (BU), and right elbow joint hemorrhage, enrolled in trial RB-FVIIa-006-13). The patient’s past medical history included febrile convulsions (ongoing since 1994), cerebral hemorrhage, bilateral knee and ankle arthrosis (ongoing since 2006 and 2007, respectively), intracranial hemorrhage (2008), and chronic hepatitis (ongoing since October 2011), with positive test for hepatitis C virus at study entry screening. Immunogenicity data included negative anti-rFVIIa antibody test at Phase A, visit 1 and during Phase B, Weeks 3 to 36; and negative immunoglobulin G colloidal rabbit milk protein results during Phase B, Weeks 3 to 36 of the study. The patient was randomized to the 225 µg/kg LR769 treatment regimen and received the first study drug dose in Phase A on (b) (6), and the first dose of study drug in Phase B on (b) (6). The patient was reported to have experienced 10 mild/moderate bleeding episodes between October 8, 2014, and July 7, 2015. The first 4 episodes were treated with 225 µg/kg LR769, the next 2 episodes were treated with 75 µg/kg LR769, the next 2 episodes were treated with 225 µg/kg LR769, and the last 2 were treated with 75 µg/kg LR769. Four of the bleeding episodes were due to trauma and 6 were spontaneous. Patient-reported efficacy at 12 hours was “good” or “excellent” for all but the last bleeding episode when it was considered “moderate.” The last dose of 75 µg/kg LR769 was administered on (b) (6). On (b) (6), the patient experienced severe acute tonsillitis that was classified as an SAE by the investigator because it required hospitalization. The patient was febrile prior to hospital admission. On July 15, 2015, the patient became somnolent, febrile, and developed right arm paralysis. On (b) (6), brain MRI revealed a left-sided 6 mm to 8 mm subarachnoid hemorrhage. On (b) (6) CT revealed acute subdural hematoma of the left brain hemisphere compared to the (b) (6), scan. The patient thus

received tranexamic acid among other treatments, L-lysine, and Novo-Seven, and intracranial hemorrhage resolved on July 31, 2015. The patient was discharged from the hospital. No further study drug was given as this patient had already completed the study. Review of this case found that the hemorrhage was confounded by indication (patient had pre-existing hemorrhages and underlying hemophilia and tonsillitis (with fever) was unrelated to LR769 and possibly infectious etiology, as there was no evidence of product contamination and the mechanism of action of the product would not be expected to biologically plausibly be associated with development of tonsillitis. This case of tonsillitis and cerebral hemorrhage was likely related to the patient's underlying condition and does not raise any concerns regarding the safety of Sevenfact.

Deaths

No deaths occurred in the clinical trials (two completed trials) provided in support of Sevenfact BLA licensure. (b) (4)

Adverse Events of Special Interest (AESIs)

AEs of special interest for FVIIa-containing products are thrombotic/embolic, allergic, and immunogenic AEs. Thromboembolic events are the most common serious adverse events associated with previously approved rFVIIa-containing product (NovoSeven). In clinical studies submitted in support of Sevenfact BLA licensure, there were no thromboembolic, allergic, or immunogenic (antibody formation) events reported at doses 25 µg/kg – 225 µg/kg, for which licensure is being sought. Furthermore, there were no neutralizing antibodies to Sevenfact reported in 498 exposures, which included 456 repeat exposures.

Missing information

There were no adequate and well-controlled studies conducted using Sevenfact in pregnant women, during lactation (it is not known whether Sevenfact is excreted in the milk of lactating mothers), in children (younger than adolescents), or in patients with hemophilia A or B greater than 65 years of age.

Note: The sponsor considers pediatric information missing, as the clinical trials are ongoing and were not completed at the time of submission. The sponsor included safety data only from completed clinical trials, thus considering information regarding pediatric population missing, due to ongoing status of clinical trial in patients 12 years of age and younger. Per the sponsor (pdf page 6 of 17 of the *Pharmacovigilance Plan*), "*In the completed studies, no patients <18 year old has been included*."

> Reviewer Comment: The overall frequency of AEs and SAEs was low, and the data and information provided and reviewed do not raise safety concerns at this time. There is no indication for enhanced pharmacovigilance beyond routine surveillance.

120-Day Safety Update

The 120-day safety update, dated 02/07/2017, was received from the sponsor on 02/10/2017. As per the sponsor, currently Sevenfact is not marketed in any country. There are 2 Phase 3 clinical trials ongoing (LFB-FVIIa-007-14, "PERSEPT 2," and LFB-FVIIa-008-14, "PERSEPT 3"), PERSEPT 2 is a pediatric study of LR769 used in the treatment of bleeding episodes in children up to age 12 years of age with hemophilia A or B, similar in design to PERSEPT 1 (started December 2015 and is ongoing). PERSEPT 3 evaluates the use of LR769 in surgical and invasive procedures in adults and children (6 months to 75 years of age) with hemophilia A or B.

The safety population consists of 64 patients in all four clinical studies of LR769, of which 56.3% had completed their study participation as of the October 01, 2016, data lock for the 120-day safety update, with 32.8% of patients enrolled in active studies as of October 01, 2016. Seven (10.9%) patients have withdrawn, due to patients withdrawing consent (n=3), patients withdrawn by the sponsor due to noncompliance with the study protocol procedures (n=2), loss to follow up (n=1), and "investigator's decision" (not further described) (n=1). (b) (4), (b) (6)

Note: The safety data from completed studies, GTC-FVIIa-005-11 (PK) and PERSEPT 1, is derived from all 42 patients enrolled, as these patients received at least one study drug dose, however, not all 42 patients completed the study; 6 of the 42 patients withdrew, and there was (b) (4), as listed above. Per the sponsor (pdf page 26 of 126 of the *Summary of Clinical Safety*), "*The integrated analyses of safety included all 42 patients who received LR769…. 36 (85.7%) of the 42 patients who received study treatment completed their study*." Table 2 in the 120-day-safety-update (pdf page 14 of 77 of the *120-Day-Safety-Update*) also states that 36 of 64 patients completed the study (56.3%).

Below is a summary of the status of clinical trials, from the sponsor's 120-day safety update:

Status of Clinical Studies as of 120-Day Safety Update Data Lock of 10/1/2016

Type of Study	Study Identifier	Study Objectives	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects or Patients	Healthy Subjects or Diagnosed Patients	Treatment Duration	Study Status
PK, PD, and safety, dose-finding, Phase 1b	GTC-FVIIa-005-11	Safety, PK, and PD	Dose-escalation	LR769 at 25, 75, 225 µg/kg; Cohort 1: 1 dose of 25 µg/kg of LR769 Cohort 2: 1 dose of 75 µg/kg of LR769; Cohort 3: 1 dose of 225 µg/kg of LR769; Each dose was administered IV several weeks apart	15 subjects: 25 µg/kg = 10 75 µg/kg = 5 subjects from 25 µg/kg, and 5 newly enrolled 225 µg/kg = 5 subjects from 25 µg/kg, and 5 subjects from 75 µg/kg	Adult male subjects with Hemophilia A or B with or without inhibitors	2 administrations, at different dose levels, at different time points; participation varied from a few weeks to a few months	Completed
Safety and Efficacy in Adolescents and Adults, Phase 3	RB-FVIIa-006-13 PERSEPT 1	Assess efficacy and safety of 2 separate dose regimens (75µg/kg, 225 µg/kg) LR769 for treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or IX	Global, multicenter, Phase 3, prospective, open-label, randomized, crossover study. 2 dose regimens (75 and 225 µg/kg) LR769	75, 225 µg/kg LR769 IV; crossover every 3 months	27 randomized patients	Adolescent/ Adult Hemophilia A or B patients with inhibitors	No further treatment with study drug beyond the time point where a *Good* or *Excellent* response for this bleeding episode was noted	Completed
Safety and Efficacy in Pediatrics, Phase 3	LFB-FVIIa-007-14 PERSEPT 2	To assess efficacy and safety of 2 separate dose regimens (75 and 225 µg/kg) LR769 for treatment of bleeding episodes in patients from birth to 12 years with Hemophilia A and B with inhibitors	Global, multicenter, Phase 3, prospective, open-label, randomized, crossover study. Two dose regimens (75 and 225 µg/kg) LR769	75, 225 µg/kg LR769 IV; crossover every 3 months	22 patients enrolled as of 01 October 2016 (data-cut-off) N=24 planned (currently, 10 patients from birth to <6 years old, and 12 patients ≥6 years to <12 years old)	Pediatric patients from birth to 12 years with Hemophilia A and B with inhibitors	Until at least 352 treated mild or moderate bleeding episodes	Ongoing
Safety and Efficacy in Surgical Setting, Phase 3	LFB-FVIIa-008-14 PERSEPT 3	To assess the efficacy of LR769 to prevent excessive bleeding and to achieve hemostasis in patients with Hemophilia A or B patients with inhibitors who are undergoing elective surgical or other invasive procedure	Global, multicenter, Phase 3, single-arm, open label	(b) (4)				

IV = intravenous(ly); N/A = not applicable; PD = pharmacodynamics; PICC = peripherally inserted central catheter; PK = pharmacokinetics

Source: Module 5.3.6: *120-day Safety Update* pp 9-10.

*NOTE : The total number of patients included in the safety data is 64 as there was (b) (4) (b) (4) in study PERSEPT 3 which occurred after the 120-day safety report update data lock.

As of the 120-day safety update data lock date of October 01, 2016, there were no deaths in any of the trials. After the data lock date, on October 23, 2016, (b) (4), (b) (6)

(b) (4), (b) (6) 56-year-old male with hemophilia A with inhibitor and hypertension had previously participated in another clinical trial (RB-FVIIa-006-13) without any serious adverse event. In clinical trial LFB-FVIIa-008-14, the patient received (b) (4), (b) (6) do not alter the safety profile of LR769.

Additional AEs reported in the 120-day safety update are discussed below.
Four patients experienced 10 TEAEs that were considered by the investigator to be treatment-related, as follows, by assigned dose:

- 1 event each of dizziness and headache at LR769 dose of 25 µg/kg
- 4 events of infusion site discomfort and 2 events of infusion site hematoma (all in the same patient), and 1 event of dizziness at LR769 dose of 75 µg/kg
- 1 event of body temperature increased at LR769 dose of 225 µg/kg

Withdrawals from clinical trial due to SAEs include one patient (patient (b) (6) who withdrew from the clinical trial (RB-FVIIa-006-13) due to SAE of subarachnoid hemorrhage. Although the patient recovered from the event and completed the study, no further study drug was administered.

Summary of AEs (Safety Update Population) from 120-Day Safety Update Reporting Period*

	25 µg/kg (N=10)		75 µg/kg (N=54)		225 µg/kg (N=51)		Overall (N=64)	
Parameter	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
ANY TEAEs?	21	8 (80.0)	39	20 (37.0)	35	20 (39.2)	95	34 (53.1)
Any Treatment-associated AEs (TAAEs)? (1)	5	3 (30.0)	21	10 (18.5)	11	7 (13.7)	37	15 (23.4)
Any Serious TEAEs?	0	0 (0.0)	2	1 (1.9)	1	1 (2.0)	3	2 (3.1)
Any Serious TAAEs?	0	0 (0.0)	0	0 (0.0)	1	1 (2.0)	1	1 (1.6)
Any Treatment-related TEAEs? (2)	2	2 (20.0)	7	2 (3.7)	1	1 (2.0)	10	4 (6.3)
Any TEAEs leading to study drug withdrawal?	0	0 (0.0)	1	1 (1.9)	0	0 (0.0)	1	1 (1.6)
Any TEAEs leading to death?	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

AE = adverse event; N = number of patients in the Safety Population who had at least 1 treatment episode treated with the given treatment regimen; TAAE =treatment-associated adverse event; TEAE = treatment-emergent adverse event
(1) For AEs occurring in the 005 study or during Phase A of the 006 and 007 studies, an AE was considered to be a TAAE if it occurred within 24 hours after administration of study drug. For AEs occurring during Phase B of the 006 and 007 studies, an AE was considered to be a TAAE if it occurred between the start of treatment of a bleeding episode and the end of treatment of the bleeding episode, up to and including the 24 hours after the last administration of study drug for that bleeding episode, or if it occurred within 24 hours after study drug administration for PK purposes.
(2) An AE was considered treatment related if it had a definite, probable, or possible relationship to the study treatment or if the relationship to study treatment was missing.
Note: AEs are assigned to the last treatment regimen received prior to the start of the AE.
Source: Module 5.3.6: *120-day Safety Update* p 32.

*NOTE: The above table does not include the (b) (4) in study PERSEPT 3 which occurred after the 120-day safety report update data lock.

Review of the 120-day safety update did not raise safety concerns.

Foreign Post-licensure Safety Data
Sevenfact (LR769) is not commercially available anywhere in the world.

Conclusion
The sponsor provided an integrated summary of identified risks associated with LR769 from clinical trial data. Review of these clinical trials did not identify any safety risks.

> Reviewer Comment: In conjunction with the clinical review, discussions with the review team, and overall assessment of the safety database, there are no safety issues identified that would require additional pharmacovigilance measures, should the product be approved in the US.

5. PHARMACOVIGILANCE PLAN

Proposed Pharmacovigilance Plan
The Pharmacovigilance Plan (PVP) (dated 11/15/2016) includes the sponsor's assessment of identified and potential risks and missing information based on the pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information.

Safety concerns and Proposed Actions
No safety concerns were identified based on clinical studies/related to administration of Sevenfact.

Potential risks
The potential risks are the same as those associated with the use of previously approved rFVIIa-containing product (NovoSeven) and include thrombotic/embolic, allergic, and immunogenic AEs. No thromboembolic, immunogenic (including formation of inhibiting antibodies to Factor VII), or allergic events occurred in any study participants during the conduct of the clinical trials for Sevenfact.

Reviewer comment: The proposed PVP is acceptable.

Missing information
The populations studied were limited to 18 to 75-year-old congenital hemophilia A or B patients with inhibitors to FVIII or FIX. However, no elderly patients enrolled. Pediatric patients (<18 year old), patients >65 year old (elderly), and patients with severe comorbidities (diabetes, heart failure, hepatic failure, and/or renal failure) were not included in the clinical trials. The sponsor is conducting ongoing clinical trial LFB-FVIIa-007-14 (PERSEPT 2) in the pediatric population, and ongoing phase 3 trial LFB-FVIIa-008-14 (PERSEPT 3) in patients in the surgical/invasive procedure settings. Please see the table titled "Status of Clinical Studies as of 120-Day Safety Update Data Lock of 10/1/2016," above. The sponsor considers pediatric information missing, as the clinical trials are ongoing and were not completed at the time of submission. The sponsor included safety data only from completed clinical trials, thus considering information regarding pediatric population missing, due to ongoing status of PERSEPT 2.

Proposed actions by the sponsor are summarized in the table from the sponsor titled "Summary of Safety Concerns and Planned Pharmacovigilance Actions," below:

Summary of Safety Concerns and Planned Pharmacovigilance Actions

Safety concerns and overview of planned pharmacovigilance actions		
Areas requiring confirmation or further investigation	**Proposed routine and additional pharmacovigilance activities Milestones, etc.**	**Objectives**
IMPORTANT IDENTIFIED RISKS		
Not applicable		
IMPORTANT POTENTIAL RISKS		
Allergic/anaphylactic type reactions		
None	Routine pharmacovigilance.	To ensure a continuous monitoring of the safety profile of the medicinal product.
Inhibiting antibodies to factor VII		
None	Routine pharmacovigilance.	To ensure a continuous monitoring of the safety profile of the medicinal product.
Thromboembolic events		
None	Routine pharmacovigilance.	To ensure a continuous monitoring of the safety profile of the medicinal product.
IMPORTANT MISSING INFORMATION		
Pediatric (<12 years)	Routine pharmacovigilance. Clinical trial monitoring; DMC data reviews, data analysis and final study report	To ensure a continuous monitoring of the safety profile of the medicinal product. To determine safety and efficacy of LR769 in pediatric hemophilia A or B patients with inhibitors
Surgical patients	Routine pharmacovigilance. Clinical trial monitoring; DMC data reviews, data analysis and final study report	To ensure a continuous monitoring of the safety profile of the medicinal product. To determine safety and efficacy of LR769 in pediatric and adult hemophilia Aor B patients with inhibitors undergoing surgical or other invasive procedures
Elderly population	Routine pharmacovigilance.	To ensure continuous monitoring of the safety profile of the medicinal product.
Patients with co-morbidities	Routine pharmacovigilance.	To ensure continuous monitoring of the safety profile of the medicinal product.
Patients with hepatic or renal failure	Routine pharmacovigilance.	To ensure continuous monitoring of the safety profile of the medicinal product.
Females, pregnant women	Routine pharmacovigilance	To ensure continuous monitoring of the safety profile of the medicinal product.

PVP plan submission BLA 125461/0 Module 1.16.1 Pharmacovigilance Plan dated November 15, 2016, pp. 15-16.

Reviewer comment: The sponsor's proposed action regarding missing information is adequate.

6. OTHER MANAGED REVIEW INFORMATION

There are no outstanding safety issues, based on results of the clinical trials. Discussions with primary clinical reviewers, Dr. Poornima Sharma and Dr. Bindu George from the product office (OTAT) did not reveal any safety concerns.

Postmarketing requirement (PMR) pediatric study under PREA: The sponsor submitted a pediatric study plan (PSP) including study PERSEPT-2, the review and determination of adequacy of which will be deferred to the product office primary clinical reviewer(s).

7. DE ASSESSMENT AND RECOMMENDATIONS

Final determination of the benefit/risk profile of Sevenfact is pending the clinical, statistical and product reviews. Safety-related data and the proposed pharmacovigilance plan submitted in BLA 125641/0 have been reviewed. The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. A pediatric study plan was submitted by the sponsor to evaluate the safety and efficacy of Sevenfact in children (clinical study PERSEPT 2) in children aged birth to 12 years, and the determination of whether this will be a PMR pediatric study under PREA is deferred to the primary product office clinical reviewer(s).

Routine pharmacovigilance is recommended to evaluate potential risks and missing information associated with Sevenfact should the product be licensed. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80. Routine surveillance includes 15-day expedited reports for serious, unlabeled/ unexpected adverse events, and quarterly periodic safety reports for 3 years and annually thereafter. Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.