CLINICAL REVIEW MEMO OF LABELING SUPPLEMENT

Application Type	CBE-Labeling Supplement
STN	125641-67
CBER Received Date	05/24/2022
PDUFA Goal Date	11/24/2022
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Kavita Natrajan
Review Completion Date / Stamped Date	11/14/2022
Supervisory Concurrence	Tejashri Purohit-Sheth MD
Applicant	LFB S.A
Established Name	LR 769, coagulation factor VIIa [(recombinant-jncw]
Trade Name	**SEVENFACT®**
Pharmacologic Class	Recombinant coagulation FVIIa (activated)
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single use vials of 1mg or 5mg for reconstitution with sterile water For Intravenous administration after reconstitution only
Dosing Regimen	For Mild/Moderate bleeds: 75 mcg/kg every 3 hours until hemostasis is achieved OR initial loading dose of 225 mcg/kg followed by a repeat doses of 75 mcg/kg every 3 hours if hemostasis is not achieved within 9 hours of the loading dose For Severe bleeds: 225 mcg/kg loading dose followed by 75 mcg/kg every 2 hours if needed starting 6 hours after the loading dose Administer intravenously only
Indication(s) and Intended Population(s)	For use in children 12 years and older, and adults with Hemophilia A or B with inhibitors for on-demand treatment and control of bleeding episodes
Orphan designation	No

Background

SEVENFACT® (LR 769, recombinant factor VIIa) is a recombinant, human coagulation factor VIIa (activated factor VII) produced from the expression of human Factor VII gene under the control of (b) (4) specific promoter in mammary glands of transgenic rabbits. It is isolated and purified from the milk of transgenic rabbits and is activated during the purification process. SEVENFACT® was licensed in April 2020 for the on-demand treatment and control of bleeding

episodes in children 12 years and older, and adults with hemophilia A or B with inhibitors. An efficacy supplement for the indications of use in the perioperative management of hemophilia A or B subjects with inhibitors of all age groups and for the on-demand treatment and control of bleeding episodes in children < 12 years of age was submitted on August 7, 2020. However, both indications received a complete response due to failure to demonstrate efficacy in the respective subject populations.

Request for Changes Being Effected (CBE) Labeling Supplement:

The PERSEPT 2 study that enrolled subjects < 12 years of age for the on-demand treatment and control of bleeding episodes was the PREA (Pediatric Research Equity Act) PMR (post Marketing Requirement) study. Although Applicant had done the study as agreed upon, it failed to show efficacy in this subject population. PREA PMR would not be considered fulfilled until the Applicant included the negative results of the study in the pediatric section (section 8.4) of the package insert. Failure to comply with the PREA PMR was communicated to the Applicant on April 19,2022 in response to which the Applicant submitted the current CBE labeling supplement updating section 8.4 of the label and fulfill their PREA PMR obligation as requested by the Agency.

.

Review of CBE Labeling Supplement:

The Applicant submitted clean and redline versions of the draft label with proposed changes to section 8.4 of the label. We reviewed the proposed label, made changes, and sent it back to the Applicant who agreed to our changes. Applicant was also requested to make the label 508 compliant. The changes to the label were discussed at an internal meeting and included input from Dr. Adrienne Hornatko-Munoz in CBER IOD.

Proposed revisions to the US Prescribing Information (USPI) by Applicant:

Proposed changes by Applicant are in Red

8.4 Pediatric Use

Limited clinical data for SEVENFACT in the pediatric population were collected in an adult and adolescent study (Study 1). A total of 5 subjects aged ≥12 to <18 years of age (range 13-17 years) were dosed with SEVENFACT. These 5 subjects were treated for a total of 79 bleeding episodes (all mild or moderate) that occurred while subjects were still under 18 years of age. Hemostatic efficacy in this subgroup (n=5) was comparable to efficacy observed in the overall population [*See Clinical Studies (14)*].

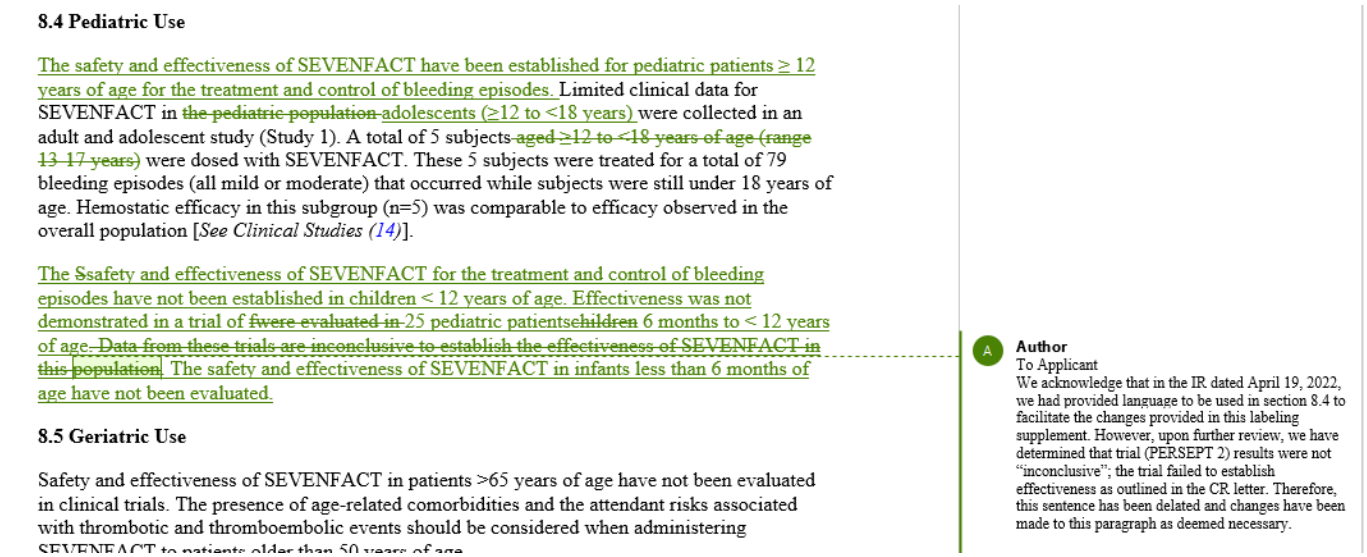
Safety and effectiveness of SEVENFACT were evaluated in children 6 months to < 12 years of age. Data from these trials are inconclusive to establish the effectiveness of SEVENFACT in this population. The safety and effectiveness of SEVENFACT in infants less than 6 months of age have not been evaluated.

Reviewer Comment

We did not agree with Applicant's conclusion that data from the PREA PMR study were inconclusive. The PREA PMR (PERSEPT 2) study did not meet its primary efficacy endpoint since the lower bounds of the 95% CI (confidence interval) did not cross the pre-specified primary efficacy endpoint threshold of 0.55. Hence, the results were negative and not inconclusive as suggested by the Applicant. Hence, we made the necessary changes to section 8.4 to reflect this fact as shown below. We also reflected the fact that efficacy had not been studied in children < 6 months of age in the PREA PMR study.

FDA Revisions to the Label

FDA changes to the label are shown below



8.4 Pediatric Use

The safety and effectiveness of SEVENFACT have been established for pediatric patients ≥ 12 years of age for the treatment and control of bleeding episodes. Limited clinical data for SEVENFACT in ~~the pediatric population~~ adolescents (≥12 to <18 years) were collected in an adult and adolescent study (Study 1). A total of 5 subjects ~~aged ≥12 to <18 years of age (range 13-17 years)~~ were dosed with SEVENFACT. These 5 subjects were treated for a total of 79 bleeding episodes (all mild or moderate) that occurred while subjects were still under 18 years of age. Hemostatic efficacy in this subgroup (n=5) was comparable to efficacy observed in the overall population [*See Clinical Studies (14)*].

The ~~S~~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 ~~fwere evaluated in~~ 25 pediatric patients~~children~~ 6 months to < 12 years of age. ~~Data from these trials are inconclusive to establish the effectiveness of SEVENFACT in this population.~~ The safety and effectiveness of SEVENFACT in infants less than 6 months of age have not been evaluated.

8.5 Geriatric Use

Safety and effectiveness of SEVENFACT in patients >65 years of age have not been evaluated in clinical trials. The presence of age-related comorbidities and the attendant risks associated with thrombotic and thromboembolic events should be considered when administering SEVENFACT to patients older than 50 years of age

Author
To Applicant
We acknowledge that in the IR dated April 19, 2022, we had provided language to be used in section 8.4 to facilitate the changes provided in this labeling supplement. However, upon further review, we have determined that trial (PERSEPT 2) results were not "inconclusive"; the trial failed to establish effectiveness as outlined in the CR letter. Therefore, this sentence has been delated and changes have been made to this paragraph as deemed necessary.

The Applicant accepted our changes and the clean version of the label submitted on 10/11/2022 is reflective of this fact (see below). The Applicant is thus considered to have fulfilled the PREA PMR obligation with section 8.4 reflecting the results of the PREA PMR study.

8.4 Pediatric Use

The safety and effectiveness of SEVENFACT have been established for pediatric patients ≥ 12 years of age for the treatment and control of bleeding episodes. Limited clinical data for SEVENFACT in adolescents (≥12 to <18 years) were collected in an adult and adolescent study (Study 1). A total of 5 subjects were dosed with SEVENFACT. These 5 subjects were treated for a total of 79 bleeding episodes (all mild or moderate) that occurred while subjects were still under 18 years of age. Hemostatic efficacy in this subgroup (n=5) was comparable to efficacy observed in the overall population [*See Clinical Studies (14)*].

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.