Division Director Memo
Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapies

APPLICATION:	BLA 125641/0	**TRADE NAME:**	SevenFact
APPLICANT/SPONSOR:	Laboratoire Francais du Fractionnement et des Biotechnologies SA LFB, USA Inc.	**ESTABLISHED NAME:**	Coagulation Factor VIIa (Recombinant) (rVIIa)
CBER RECEIVED DATE	10/13/16		
PDUFA DATE	10/13/17	**PRODUCT CLASS:**	Clotting Factor Replacement
REVIEW DATE:	10/13/17	**ROUTE:**	Intravenous infusion

INDICATION: On-demand treatment and control of bleeding in adolescent and adult patients with hemophilia A or B with inhibitors to Factor VIII and IX

Review Team

Clinical: Dr. Poornima Sharma; **Statistical:** Dr. Boris Zaslavsky; **Pharm/Tox**: Dr. Wei Liang; **Clin Pharm**: Xiaofei Wang; **CMC**: Dr. Mikhail Ovanesov, Dr. Alexey Khrenov, Dr. Yideng Liang, Dr. Andrey Sarafanov

REVIEW SUMMARY:

LFB submitted this original BLA to seek marketing approval for SevenFact for the on-demand treatment of bleeding episodes in adolescent and adult hemophilia A or B patients with inhibitors to Factor VIII or Factor IX, respectively.

The primary evidence of safety and efficacy comes from Study RB-FVIIa-006-13, which was a Phase 3, multicenter, randomized, open label, crossover study that tested two treatment regimens comprised of 75 or 225 mcg/kg doses in 27 subjects. The primary efficacy analysis evaluated the proportion of successfully treated bleeding episodes at 12 hours after the first administration of SevenFact in each of the two treatment arms as compared to the pre-specified objective performance criterion (OPC) of 55%. Treatment was considered successful if a patient had a "good" or "excellent" response on the 4-point hemostasis scale, did not require additional study drug, blood products or other hemostatic agent for bleeding beyond the 12-hour time point, and there was no increase in pain beyond the 12- hour time point.

The primary efficacy analysis demonstrated that treatment with both doses resulted in statistically significant treatment success in comparison the to the OPC of 55%. The proportion of successfully treated bleeds was significantly greater than the OPC of 55%: 84.9% (95% CI: 74.0%, 95.7%) for the 75 μg/kg regimen and 93.2% (95% CI: 88.1%, 98.3%) for the 225 μg/kg regimen. However, the clinical review team had concerns regarding how some of the endpoint events were classified with respect to success and failure. The clinical reviewer considered 10 treatment successes as failures that were assessed as successes by the Applicant, and 22 bleeding episodes that had missing values as failures. Re-analysis of the primary endpoint data with these failures still resulted in a significantly greater proportion of successfully treated bleeds compared the OPC.

SevenFact was well tolerated and there were no observed thromboembolic events, development of neutralizing antibodies, or hypersensitivity reactions. Overall, the benefit risk profile of SevenFact is favorable based on review of the clinical data.

Please see primary reviews from the clinical and statistical reviewers for details of the review. I concur with the clinical review team's recommendation of Approval based on the clinical data. However, there are significant CMC issues related to manufacturing that are outstanding that will need to be resolved prior to Approval. Therefore, the Applicant will be issued a Complete Response Letter.

OUTSTANDING ISSUES:

The Applicant will need to address the numerous manufacturing related deficiencies identified in the Complete Response Letter. If and when the manufacturing deficiencies are resolved, and they are determined to not impact the validity of the clinical data reviewed in support of this BLA, the BLA should be able to be approved based on this current clinical review.

RECOMMENDED REGULATORY ACTION

BLA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	___	**APPROVAL**	___	**COMPLETE RESPONSE**	**X** **FOR CMC ISSUES ONLY**
OTHER ACTION:					

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