

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



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Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR
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Subject: Rationale for waiving CSL BLA for Antihemophilic Factor (Recombinant), Single Chain [AFSTYLA], STN 125591/0, from referral to the Blood Products Advisory Committee

BACKGROUND

STN 125591/0 is an original biologics license application (BLA) submitted by CSL Recombinant Facility for *Antihemophilic Factor (Recombinant), Single Chain* with the proprietary name AFSTYLA. It is a recombinant analogue of human Factor (F) VIII in which most of the B-domain occurring in the wild-type FVIII and 4 amino acids of the adjacent acidic A3 domain were removed (amino acids 765 to 1652 of full-length FVIII). It has ^{(b) (4)} amino acids in one single glycopeptide with a molecular weight of approximately (b) (4). Once activated, AFSTYLA has a structure identical to that of FVIIIa formed from full-length, two-chain FVIII. AFSTYLA is manufactured by CSL Behring in Marburg, Germany with the first stages of the manufacturing process performed at (b) (4).

AFSTYLA is supplied as a preservative-free, lyophilized formulation presented in five dosage strengths at 250, 500, 1000, 2000 and 3000 international units (IU) per vial. The dosage sizes are presented in either 6-mL (250, 500 and 1000 IU) or 10-mL (2000 and 3000 IU) single-use glass vials.

Before intravenously administration to patients, AFSTYLA is reconstituted using sterile Water for Injection (sWFI) and a needleless Mix2vial™ transfer device, giving volumes of 2.5 mL (for 250, 500 and 1000 IU) or 5 mL (for 2000 and 3000 IU).

The proposed indications for AFSTYLA are: (1) on-demand treatment and control of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in adults and children with hemophilia A.

REASONS FOR WAIVING REFERRAL TO BPAC

The *Division of Hematology Research and Review* and the *Division of Hematology Clinical Review* in the *Office of Blood Research and Review* reviewed the information in this application and determined that referral to the *Blood Products Advisory Committee* prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The new molecular entity provision (NME) does not apply to AFSTYLA as it does not represent a novel product class. Recombinant FVIII products have been licensed in the United States since 1992 and have been used to control and prevent bleeding in patients with hemophilia A. The first product in this class, RECOMBINATE, was approved by the FDA in 1992, and currently there are several full-length and B-domain-deleted FVIII products licensed in the United States.
- The mechanism of action of FVIII and its function in blood coagulation are well studied and understood. Upon activation of FVIII by thrombin, FVIIIa acts as a cofactor for activated Factor IX triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen results in the formation of a fibrin clot that stops bleeding. When administered into a patient with hemophilia A, FVIII products temporarily replace the missing or defective endogenous FVIII.
- The amino acid sequence of AFSTYLA is based on that of a B-domain-deleted human FVIII, with only minor modifications, which are related to the removal of a processing site in the acidic region of the A3 domain. The resulting single-chain molecule possesses the same functional characteristics as other FVIII molecules. The hemostatic activity of AFSTYLA is consistent with that of other licensed FVIII products and enables the formation of a fibrin clot via the intrinsic coagulation pathway.
- The manufacturing process for AFSTYLA includes two viral clearance steps – (b) (4) – that meet the current requirements for assuring product safety with regard to adventitious viruses.
- The proposed indications for AFSTYLA are similar to those of other U.S.-licensed FVIII products.
- The design of the pivotal clinical study to evaluate the safety and efficacy of AFSTYLA was adequate, and the results of the studies did not raise any concerns.

- Review of information submitted in the BLA for AFSTYLA did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations. The sole significant issue was related to the use of a chromogenic substrate assay for AFSTYLA potency assignment, and was resolved at the Office level.