Application Type	BLA Supplement (Labeling)
STN	125591/383
CBER Received Date	December 9, 2022
PDUFA Goal Date	June 9, 2023
Division / Office	OTP
Committee Chair	Karl Kasamon, MD
Clinical Reviewer(s)	Karl Kasamon, MD
Project Manager	Leyish Minie
Priority Review	No
Reviewer Name(s)	Hairong Shi, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lin Huo, Ph.D. Team Lead, FDA/CBER/OBPV/DB/TEB2
	Lihan Yan, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB2
Applicant	CSL Behring Lengnau AG
Established Name	Antihemophilic Factor (Recombinant), Single Chain
(Proposed) Trade Name	AFSTYLA
Dosage Form(s) and Route(s) of Administration	White or slightly yellow lyophilized powder supplied in single-dose vials containing nominally 250, 500, 1000, 1500, 2000, 2500, or 3000 IU. To be given intravenously.
Dosing Regimen	Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) For routine prophylaxis: Children (<12 years old): 30 to 50 IU per kg administered 2 to 3 times weekly Adults and adolescents (≥ 12 years old): 20 to 50 IU per kg administered 2 to 3 times weekly. For on-demand Repeat injection every 12 to 24 hours to maintain required Factor VIII level Perioperative management: Repeat injection every 8 to 24 hours to maintain required Factor VIII level

Indication(s) and Intended Population(s)	Indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for: on-demand treatment and control of bleeding episodes, routine prophylaxis to reduce the frequency of bleeding episodes, and perioperative management of bleeding. Note: The purpose of this submission is to update the labeling with previously untreated patients' safety data.

1. Executive Summary

AFSTYLA, the recombinant Antihemophilic Factor, is indicated in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, routine prophylaxis to reduce the frequency of bleeding episodes, and perioperative management of bleeding. The results of clinical studies for AFSTYLA in previously treated patients (PTPs) were reported in the original regulatory submission STN 125591/0 (approved on 25 May 2016). In this supplemental Biologics License Application (sBLA), the applicant submitted the final study report for previously untreated patients (PUPs) in Study CSL627_3001. The applicant proposes label updates to include additional safety data from PUPs.

Study CSL627_3001 was a non-randomized, open-label, multiple-arm extension study to assess the safety and efficacy of AFSTYLA in subjects with severe Hemophilia A. The safety profile of AFSTYLA in PUPs was evaluated in 24 PUPs (boys ≤5 years of age) who received at least one dose of AFSTYLA during the study. Of the 24 subjects, 19 (79.2%) subjects completed the study, 3 (12.5%) subjects discontinued as per physician's decision, 1 (4.2%) subject discontinued because of an AE (high-titer inhibitor), and 1 (4.2%) subject discontinued because of overseas relocation. The total number of exposure days (EDs) for the 24 subjects was 5,909. Twenty-one subjects (87.5%) attained ≥ 50 EDs.

There were 12 (50%) subjects who developed inhibitors during the study. Three of the 24 PUPs discontinued before reaching 50 EDs: 1 subject developed inhibitor at ED 5 and dropped out at ED 8, the other 2 subjects dropped out at ED 5 and ED 22, respectively. Among all subjects with at least 50 EDs (including the subject who developed inhibitor at ED 5 prior to dropping out), the incidence rate of inhibitor to FVIII was 54.5% (12/22) with a 95% confidence interval of (32.2%, 75.6%). Six subjects (27.3% [6/22]) had a high-titer inhibitor (≥ 5.0 BU), and 6 subjects (27.3% [6/22]) had a low-titer inhibitor (< 5.0 BU).

The median EDs for initial inhibitor development was 10 EDs (range 4 to 23 EDs). Eleven inhibitor-positive subjects enrolled into the immune tolerance induction (ITI) substudy. Nine of 11 had inhibitor eradication at the end of study. The median (range) EDs to inhibitor eradication was 37 (16 to 194). The median (range) time to inhibitor eradication was 14.3 (7.7 to 64.4) weeks. None of the PUPs developed antibodies against Chinese hamster ovary host cell proteins.

The most commonly reported treatment-emergent adverse events (TEAEs) were Pyrexia in 15 subjects (44 events), Nasopharyngitis in 9 subjects (15 events), Upper Respiratory Tract Infection in 7 subjects (18 events). There were no deaths, anaphylactic reactions, thromboembolic events. No AEs associated with double or higher dose than prescribed occurred were reported.

In summary, it appears that the observed inhibitor rate among PUPs who received AFSTYLA may be numerically higher than usual when compared to some rates reported in the literature (e.g., Gouw et al. [2013] reported about 30%). However, the inhibitor level is within the range of statistical uncertainty and no inhibitors were seen in previously treated patients (PTPs), which provides some reassurance. I defer to the clinical reviewer on whether this raises concerns under the benefit and risk considerations of the product.

Reference:

Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368(3):231-9.