Saudi Public Assessment Report

(Summary Report)

Afstyla®

Type of Application: New Drug Application

Type of Product: Biological Drug

Active Pharmaceutical Ingredient(s): Lonoctocog Alfa

ATC code: B02BD02 (Anti-hemophilic Factor)

Dosage Form: Preservative-free, lyophilized powder

Dosage Strength: 250, 500, 1000, 2000, and 3000 IU

Pack Size: 1 vial plus 1 vial 5 ml of water for injection as a reconstituting solution

Shelf life: 24 Months

Storage Conditions: Store in a refrigerator (2°C – 8°C), do not freeze

Reference Product in SA (if applicable): NA

Marketing Authorization Holder: CSL Behring GmbH, Marburg, Germany

Manufacturer: CSL Behring GmbH, Görzhäuser Hof, 35041, Marburg, Germany

Registration No.: 2505222064 - 2505222065 - 2505222066 - 2505222067 - 2505222063

Decision and Decision Date: Approved on 15/11/2021

Proposed Indications: Treatment of Hemophilia A (coagulation FVIII deficiency)

Product Background

Hemophilia A (coagulation FVIII deficiency) is a rare and serious X-linked hereditary disorder of blood coagulation due to decreased levels of FVIII that results in bleeding into joints, muscles, or internal organs, either spontaneously or as a result of accidental or surgical trauma. Afstyla® is considered a novel medicinal product administered intravenously for the treatment and prophylaxis of hemorrhagic episodes in patients with Haemophilia A, the product is developed, manufactured, and provided by CSL Behring. The active ingredient (recombinant single-chain coagulation Factor VIII) is a single-chain recombinant Factor VIII (rVIII-Single Chain) produced in Chinese hamster ovary (CHO) cells. It is a construct where most of the B-domain occurring in wild-type, full-length FVIII and 4 amino acids of the adjacent acidic , a 3 domain were removed (amino acids 765 to 1652 of full-length FVIII).

This product is qualified to follow the SFDA's normal submission regulatory pathway.

The SFDA approval for Afstyla® (Lonoctocog Alfa) is based on a review of the quality, safety and efficacy data as summarized hereinafter:

Quality Aspects

The proposed medicine powder and solvent for solution for injection quality assessment were undertaken to meet the last version of *GCC Data Requirements for Human Drugs Submission* and related guidelines. The drug product is a preservative-free sterile, lyophilized formulation presented in seven dosage strengths of 250, 500, 1000, 1500, 2000, 2500, and 3000 IU. Each individual dosage size is presented in single-use glass vials of 6 ml (250, 500, and 1000 IU) or 10 ml (1500, 2000, 2500, and 3000 IU) nominal capacity. The active pharmaceutical ingredient, recombinant, single-chain coagulation factor VIII (rVIII-Single Chain), is formulated in a histidine buffer containing stabilizers and a bulking agent. For use, the lyophilized powder is reconstituted using sterile WFI giving volumes of 2.5 ml (for 250, 500, and 1000 IU) and 5 ml (for 1500, 2000, 2500, and 3000 IU). Instructions for the reconstitution of CSL627 are supplied with the product.
The submission included manufacturing processes for both drug substance and drug product were described narratively and in sufficient detail, according to the manufacturing development data. Satisfactory validation data pertaining to the commercial manufacturing process and process control are provided. Appropriate stability data following the GCC stability guidelines generated from commercial batches packed in vials intended for commercial use were submitted. The stability data show the finished product is stable for 24 months when stored in a refrigerator (2°C-8°C), without freezing , and when kept in the outer carton in order to be protected from light.

Clinical Aspects

The clinical development program for Afstyla® consisted of two pivotal clinical studies in adult and pediatric subjects with hemophilia A (FVIII activity < 1%):

- (CSL627_1001) phase I/III Safety, Efficacy, and Pharmacokinetics study.
- (CSL627_3002) Phase III Safety, Efficacy, and Pharmacokinetics study.

Summary of the clinical studies presented hereafter:

CSL627_1001: A phase I/III, open-label, prospective, non-randomized, multicenter study, to determine the safety, efficacy, and pharmacokinetics (PK) comparing Octocog Alfa (Advate®) to recombinant single-chain coagultion factor VIII (rVIII-Single Chain). The study aim to determine the rate of coagulation factor VIII inhibitors formation, evaluate the PK profile of 50 IU/kg rVIII-SingleChain compared to Advate, demonstrate the efficacy of rVIII-SingleChain in the prevention and treatment of bleeding events and indicate the efficacy in surgical prophylaxis. The primary efficacy endpoints include treatment success for bleeding episodes based on a 4-point rating scale "excellent, good, moderate or poor/no response", efficacy ratings of "excellent" or "good" were defined as treatment success for this endpoint. Other primary endpoints are the number of subjects who develop inhibitors to coagulation factor VIII and annualized spontaneous bleeding rate (AsBR), comparison of on-demand regimen to prophylaxis regimen.

The study consists of three parts; a PK period (Part 1), a continuation of dosing safety and efficacy period (Part 2), and safety, efficacy, and repeat PK period (Part 3) and also includes a surgical sub-study for subjects enrolled in Parts 2 and 3. A total of 175 subjects with severe hemophilia A were included in the study.

- **Part 1:** Included 30 males subjects at least 18 years of age diagnosed with severe hemophilia A. This part of the study included a single-sequence crossover PK comparison of Advate® and rVIII-Single Chain. Subjects received a single intravenous (IV) dose of 50 IU/kg Advate followed by the same dose of rVIII-SingleChain after a 4-day wash-out period. The PK data from Part I confirmed that the dosing selection and schedules for Part 3 of the study (based on the World Federation of Hemophilia [WFH] guidelines) were appropriate.
- **Part 2:** This part of the study assessed the efficacy and safety of rVIII-SingleChain with continued dosing from Part 1. The first 5 subjects had to receive on-demand treatment to confirm the hemostatic potential of rVIII-Single Chain, while the remaining subjects received either on-demand or prophylaxis treatment based on their preference and investigator discretion.
- **Part 3:** Eligible 100 males subjects included ≥ 12 to 65 years of age, who had been diagnosed with severe hemophilia A. This part of the study assessed the safety and efficacy of rVIII-SingleChain with continued dosing of new subjects and included a

repeat PK assessment for at least 13 subjects. After PK assessment, subjects then began on-demand or prophylaxis treatment for at least 50 Exposure Days (EDs).

- **A surgical sub-study** was conducted with a minimum of 5 subjects from either Part 2 or 3. In this sub-study, dosing regimens with rVIII-SingleChain were individualized based on the type of surgery and clinical status of the subject.

CSL627_3002: A phase III, international, open-label, prospective, multicenter, safety, efficacy, and a pharmacokinetic study conducted to assess the efficacy, safety, and characterize the PK of rVIII-SingleChain in a total of 84 subjects 0 to < 12 years of age with severe hemophilia A. The main objective is to evaluate the efficacy of recombinant single-chain FVIII (rVIII-SingleChain) in the treatment of major and minor bleeding episodes using the investigator's 4-point assessment scale as the primary endpoint. The study consisted of a PK evaluation period (single-dose PK of 50 IU/kg rVIII-SingleChain) and a treatment period.
In the PK period of this study, the PK of rVIII-SingleChain in children 0 to < 6 years and 6 to < 12 years of age was assessed after a single infusion of rVIII-SingleChain at a dose of 50 IU/kg body weight. After completion of the PK period, subjects were dosed on either an on-demand or prophylactic basis for a minimum of 3-6 months (treatment period).

In the treatment period, subjects received rVIII-SingleChain until they had achieved 50 exposure days (EDs). Subjects refer to clinics for follow-up on a monthly basis (28 days ± 7 days) for up to 6 months. Then every 3 months until at least 50 EDs. Once there were 50 subjects with 50 EDs, the remaining subjects were allowed to roll over directly into the extension Study 3001, regardless of the number of EDs.

The clinical pharmacology, efficacy and safety results from the above studies were assessed by the SFDA efficacy and safety department. Based on the efficacy and safety review of the submitted evidence, the benefit/risk balance of Afstyla® (Lonoctocog Alfa) is considered positive. Therefore, we recommend the approval of the marketing authorization of Afstyla®.

Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published at (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa