

Clinical Memorandum: BLA STN 125251/389, von Willebrand Factor/Coagulation Factor VIII Complex (Human)

DATE: March 22, 2024

FROM: Courtney Johnson, Medical Officer, BHB/DCEH/OCE/OTP/CBER

THROUGH: 'Lola Fashoyin-Aje, Office Director, OCE/OTP/CBER

SUBJECT: Prior Approval Supplement (PAS) Labeling Supplement

PRODUCT: von Willebrand Factor/Coagulation Factor VIII Complex (Human)

Recommendations: Approval of PI

Product: von Willebrand Factor/Coagulation Factor VIII Complex (Human)- Wilate

Wilate is a plasma-derived, stable, double virus inactivated, highly purified concentrate of freeze-dried active human FVIII and VWF for treatment of patients suffering from VWD or hemophilia A. It is prepared from (b) (4) (b) (4) plasma.

Wilate is indicated in children and adults with von Willebrand disease for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes in children 6 years of age and older and adults with von Willebrand disease.

Wilate is indicated in adolescents and adults with hemophilia A for:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes

History of BLA

On December 2009, Wilate was licensed in the United States for the treatment of spontaneous and trauma induced bleeding episodes (BEs) in patients with severe VWD as well as in patients with mild or moderate VWD in whom the use of DDAVP is known or suspected to be ineffective or contraindicated. The initial biologics license application (BLA) was approved based on studies TMAE-101, TMAE-102, TMAE-108, and TMAE-110.

In August 2015, FDA approved an indication expansion to include the prevention of excessive bleeding during and after minor and major surgery in patients.

In September 2019, FDA approved the indications hemophilia A in adolescents and adults for routine prophylaxis to reduce the frequency of BEs and on-demand treatment and control of BEs.

In December 2023, FDA approved the indication of routine prophylaxis to reduce the frequency of bleeding episodes in children 6 years of age and older and adults with von Willebrand disease in the United States.

Purpose of Labeling Supplement: To fulfill an outstanding PREA PMR to add the study results of WIL-30 to Section 8.4 Pediatric Use of the PI.

History of PREA PMR which led to this current labeling supplement

125251/244 - Efficacy Supplement to add new indication for prophylaxis use in patients 12 years and older with Hemophilia A. Efficacy supplement approved September 2019.

- PMR created (WIL-30 study) to evaluate the use of Wilate for prophylaxis use in patients <12 years of age

125251/^{(b) (4)} – Final study report for WIL-30 submitted on December 18, 2019- ^{(b) (4)}
^{(b) (4)} children less than 12 years of age for the treatment of Hemophilia A based on results from Study WIL-30, intended to fulfill the PREA PMR, and to extend the shelf-life after reconstitution of the WILATE powder in diluent from immediately to 4 hours.

- First Complete Response Letter sent on October 16, 2020
 - CMC review memo approved shelf-life extension
 - October 16, 2020- First CR Letter- The Agency reviewed the final study report of WIL-30 and found the data inadequate to fulfill the PREA PMR. The agency's assessment of the annualized bleeding rate (ABR) for routine prophylaxis with Wilate was substantially higher than would be expected for patients on prophylaxis. Additionally, none of the subjects on the study who experienced major bleeding had successful outcomes following treatment. The cause was hypothesized to be attributable to PK differences in the clearance of Wilate between children <12 yo when compared to adolescents and adults. Accordingly, FDA requested that the sponsor conduct a new clinical trial designed to evaluate safety and efficacy in patients <12yo with an appropriate starting dose and dosing regimen based on the PK data.
 - Octapharma's response to this first CR letter- Octapharma stated that the sample size (n = 10) in WIL-30 was sufficient for their primary PK endpoint, and that only a descriptive approach was taken for the secondary objectives- ABR and spontaneous annualized bleeding rate (SABR), as they were not the main focus of the study. Consequently the small sample size resulted in ABRs with wide confidence intervals and variability around efficacy estimates. Additionally, the sponsor stated that the majority of breakthrough bleeding events (BEs) were due to trauma and the traumatic ABR was higher in WIL-30 when compared to other studies, so the efficacy outcomes were due to a higher proportion of traumatic bleeds.
- Second Complete Response sent on August 6, 2021
 - The Agency responded to Octapharma's response to our initial Complete Response letter and stated that we do not consider their rationale sufficient to demonstrate evidence of the efficacy of Wilate used for prophylaxis for patients < 12yo with Hemophilia A. Additionally, Octapharma did not submit new clinical/clinical pharmacology data to support ^{(b) (4)} We re-

iterated our request to conduct a new pediatric study to evaluate the PK, efficacy, and safety in this population.

- Notification of Non-Compliance with PREA sent on September 8, 2021

125251/278 - Annual Status Report of Post marketing Study Requirement/Commitments for PREA PMR associated with STN 125251/244

125251/333 - Annual Status Report December 2019 to December 2020 for PMR Study WIL-30 commitment to STN 125251/244

125251/(b) (4) - Request for Waiver from PREA, Product Correspondence referring to STN 125251/(b) (4)

- Denied July 18, 2022.

125251/358 - Annual Status Report for PMR Study WIL-30 - commitment to STN 125251/244

125251/384 - Annual Status Report for PMR Study WIL-30 - commitment to STN 125251/244

- In response to this annual status report, FDA stated that in order to fulfill the outstanding PREA PMR, the Sponsor would need to add negative or inconclusive results of WIL-30 to Section 8.4 of the label (can be submitted as a labeling submitted). However, due to the limited nature of the data, (b) (4) for Hemophilia A in children younger than 12 years of age (b) (4)

125251/389- Current label supplement submitted.

Changes to the Label

Changes to the label include:

- Addition of the definition of mild, moderate, major, and life-threatening hemorrhages as a footnote to Table 5 in Section 2.1-Dose
- Addition of the negative study results of WIL-30 stated as "The safety and effectiveness of WILATE have not been established for pediatric patients <12 years of age with Hemophilia A. In a clinical study that evaluated the pharmacokinetics of WILATE in 10 pediatric patients (2 to 11 years of age) with hemophilia A, effects on annualized bleeding rate were inconclusive." to Section 8.4 Pediatric Use
- Removal of data from one patient <12 years of age from the last paragraph of Section 14-Clinical Studies, under Hemophilia A- Treatment of Bleeding Episodes
- Addition of "chest discomfort" under adverse reactions in the Highlights of the PI to align with Section 6.1- Clinical Trials Experience
- Minor changes to Section 17-Patient Information to align this section with Section 5- Warnings and Precautions and Section 6.1-Clinical Trials Experience.

Clinical Reviewer Comments:

This labeling supplement was submitted to fulfill an outstanding PREA PMR. As the study results of WIL-30 were inconclusive, the applicant chose not to conduct a new pediatric study to evaluate the efficacy, PK and safety in this population or submit new clinical/clinical pharmacology data to support the requested indication. The label was updated to include a statement indicating that the study results are inconclusive in demonstrating safety and

effectiveness in patients ages 2 to 11 years of age. (b) (4)
(b) (4)

This reviewer agrees to the additional proposed changes to the label to include:

- Addition of the definition of mild, moderate, major, and life-threatening hemorrhages as a footnote to Table 5 in Section 2.1-Dose
- Removal of data from one patient <12 years of age from the last paragraph of Section 14-Clinical Studies, under Hemophilia A- Treatment of Bleeding Episodes
- Addition of “chest discomfort” under adverse reactions in the Highlights of the PI to align with Section 6.1- Clinical Trials Experience
- Minor changes to Section 17-Patient Information to align this section with Section 5- Warnings and Precautions and Section 6.1-Clinical Trials Experience.

Recommendations

Approval of this PAS Labeling Supplement with agreed upon PI submitted on 3/15/24. The sponsor has fulfilled their outstanding PREA PMR.