Clinical/Clinical Pharmacology Memorandum:
BLA STN 125555/318, NUWIQ (antihemophilic factor, recombinant)

DATE: December 18, 2024

FROM: Fadi Nossair, Clinical Reviewer, CBER/OTP/OCE/DCEH-BHB

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THROUGH: Megha Kaushal, Branch Chief, CBER/OTP/OCE/DCEH-BHB

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SUBJECT: PAS Labeling Supplement

PRODUCT: NUWIQ (antihemophilic factor, recombinant)

Recommendations: Approval of Prior Approval Labeling Supplement (PAS)

Nuwiq is a B-domain-deleted recombinant coagulation factor VIII product, produced in a human cell line, and approved on 9/4/2015 for the treatment of children and adults with hemophilia A for:

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

The current U.S. Prescribing Information (USPI) provides dosing recommendations for routine prophylaxis of patients 2 years and older. Dosing recommendation for children < 2 years were not included because results of trials GENA-5 and GENA 15, which involve previously untreated patients (PUP) with hemophilia A, of which the majority are patients < 2 years, were not available at the time of the initial approval. The results of these trials were submitted as a PAS labeling supplement (125555/173), which was approved on 9/29/2020.

The Applicant submitted this PAS labeling supplement to update the dosage and administration section (section 2.1) to include dosing recommendations for routine prophylaxis for children < 2 years, based on trial data on 81 children < 2 years of age obtained in GENA-05 and GENA-15. Specifically, the recommended dose is 20-50 IU/kg, with a frequency of infusion from once per week to every other day, individually adjusted based on the discretion of the treating physician.

The proposed dosing approach for children < 2 years was used in the GENA-05 and GENA-15 trials, which established comparable safety and efficacy profile in children < 2 years, including comparable immunogenicity. The Applicant provided details of their sub-group analysis of children < 2 years for our review, which is summarized as follows:

- There were 65 patients who were treated for bleeding events, for a total of 738 treated bleeding events. Excellent or good control (i.e., successful treatment) was achieved in ~92% (678/738) of treated bleeding events, with similar rates observed regardless of site of bleeding and type of bleeding (i.e., spontaneous vs. traumatic). These results were comparable to previously treated children (PTPs) aged 2-12 years, who had success rates of ~83%.

- There were 46 patients who were on continuous prophylaxis for at least 3 months, with an observation period of 27.6 months (16-38). The annualized bleeding rate (ABR) for this cohort was 3.99 (1.30-5.69). These results were comparable to PTPs aged 2-12 years, who had an ABR of 4.12 (5.22).
- There were 17 patients, who underwent 18 surgical procedures, of which 10 were major surgeries and 8 were minor surgeries. Of the 14 procedures with an efficacy assessment performed, 100% (14/14) had excellent or good control. These results were comparable to PTPs aged 2-12 years, who had a 100% (21/21) excellent control assessment rate.
- In vivo recovery (IVR) measurement was performed as an optional assessment, by measuring baseline, 15-min post-infusion and 1-hour post-infusion, using both a chromogenic and one-stage assays. This was evaluated in 39 patients, who received a dose of 40 IU FVIII/kg BW. The mean (standard deviation) IVR for children < 2 years was 1.7 (0.6) and 1.1 (0.4), based on the chromogenic assay and one-stage assay, respectively. Using the one-stage assay, IVR for this age group was lower than IVR observed in adults and adolescents (IVR 2.1) and children aged 2-12 years (IVR 1.6). The IVR data in pediatric patients aged <2 years indicate that the recovery in this age group is lower than in all other age groups.
- The GENA-05 trial contains immunogenicity assessments as part of the primary objective of the study, and evaluation of incremental Factor VIII (AVIII) recovery. There were no further PK assessments to fully evaluate half-life and clearance in children < 2 years.
- Inhibitor development occurred in 30.9% (25/81) of children < 2 years of age at exposure day (ED) 1. If all enrolled PUPs were considered, regardless of age at time of enrollment, the inhibitor development rate was 26.7% (28/105). Children < 2 years with inhibitors developed them at a median (range) ED of 10.5 (4-34), with 92% (23/25) occurring with ≤ 20 ED. The rate of inhibitor formation in PUPs is comparable to the rates observed with other recombinant B-domain-deleted coagulation factor VIII product in patients with severe hemophilia A (i.e., up to 30%).
- Review of treatment-emergent adverse events that occurred in ≥ 5% of children < 2 years showed a comparable safety profile to that observed in children aged 2-12 years. There was one SAE (pyrexia) due to hospitalization and there were no deaths.

The review team recommends the addition of dosing for routine prophylaxis for children < 2 years in the section 2.1 of the NUWIQ USPI. This will provide prescribers and patients with important product-specific dosing and in vivo recovery information for the youngest patients with hemophilia A.

In addition, we recommendthe following additions/modifications to the USPI:
- Modifying the indication statement from “indicated in adults and children with Hemophilia A” to “indicated in pediatric and adult patients with Hemophilia A”.
- Modifying “single-use vials” to “single-dose vials” throughout the USPI.
- Modifying “subjects” to “patients” throughout the USPI.
- Removing uninformative statement “NUWIQ should be given to a pregnant woman only if clearly needed” from section 8.1.
- Modifying age categories in the pediatric use section to eliminate the lower boundary of 2 years, given the availability of appropriate data to inform recommendations in patients < 2 years of age. This is applicable in the highlight section and in section 8.4.
- Updated section 8.4 and section 12.3 to include IVR data for children < 2 years:
    - Section 8.4 had the following addition: “IVR in pediatric patients aged <2 years is lower than in all other age groups.”
    - Section 12.3 had the following addition: “In 39 PUPs <2 years of age, a dose of 40 IU FVIII/kg BW was administered for recovery determinations. The mean IVR in children <2 years of age

was 1.1 %/IU/kg, lower than in adults and adolescents (IVR 2.1 %/IU/kg) and children aged 2–11 years (IVR 1.6 %/IU/kg).”

Division Director Addendum:
I concur with the review team’s assessment of the data submitted in the PAS and with their recommendations for approval.

‘Lola Fashoyin-Aje, MD, MPH
Director (acting), Division of Clinical Evaluation- Hematology
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