CLINICAL UPDATE

Brand Name	Nuwiq®
Generic Name	antihemophilic factor (recombinant)
Drug Manufacturer	Octapharma USA Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength

FDA APPROVAL DATE

December 12, 2021

LAUNCH DATE

March 21, 2022

REVIEW DESIGNATION

N/A

TYPE OF REVIEW

Biologic License Application (BLA)- 125555

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Nuwiq® is a recombinant antihemophilic factor [blood coagulation factor VIII (Factor VIII)] indicated in adults and children 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

Nuwiq® is not indicated for the treatment of von Willebrand disease.

MECHANISMS OF ACTION

Nuwiq® temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis.

DOSAGE FORM(S) AND STRENGTH(S)

Nuwiq® is available as a white sterile, non-pyrogenic, lyophilized powder for reconstitution in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 2500, 3000 or 4000 IU Factor VIII potency.

DOSE & ADMINISTRATION

For intravenous use after reconstitution

- Each vial of Nuwiq® is labeled with the actual amount of Factor VIII potency in international units (IU).

- Determine dose using the following formula for adolescents and adults:
- Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL).
- Dose and duration of therapy depends on severity of the FVIII deficiency, the location and extent of bleeding, FVIII level, and patient's clinical condition.
- Dosing for routine prophylaxis:

EFFICACY

The efficacy of Nuwiq® was evaluated in three multi-center, open-label, prospective clinical trials in PTPs with severe Hemophilia A. For routine prophylaxis, the efficacy of Nuwiq®was evaluated in two multi-center studies, one in adult patients (n = 32) and one in pediatric patients (n = 59). For the treatment of bleeding episodes, efficacy was evaluated in one multi-center study in adolescents (n = 2) and adults (n = 20) who were treated on-demand only, and also in patients who experienced breakthrough bleeding episodes in the two prophylaxis studies. Across all studies, subjects undergoing surgical procedures were evaluated for hemostatic efficacy during perioperative management.

On-demand Treatment and Control of Bleeding Episodes

A total of 1124 bleeding episodes in 69 subjects (35 adults, 2 adolescents, and 32 children) were treated with Nuwiq®. Response to each treatment was assessed by the patients using an ordinal scale of excellent (abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion), good (definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an infusion requiring up to 2 infusions for complete resolution), moderate (probable or slight beneficial effect within approximately 12 hours after the first infusion requiring more than two infusions for complete resolution), or none (no improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution).

The majority of treated bleeding episodes (n = 986) was from the study where patients only received on-demand treatment. 642 (65%) bleeding episodes occurred spontaneously, 341 (35%) were traumatic, and 3 (0.3%) bleeding episodes were due to other causes. The mean dose per injection used to treat a bleeding episode was 32 IU/kg. Hemostatic efficacy in response to Nuwiq® treatment was rated as excellent or good in 94% and as moderate in 6% of the bleeds.

In case of breakthrough bleeding episodes, the mean dose per injection used to treat a bleeding episode was 33.3 IU/kg in adults (n=15 with 30 bleeding episodes) and 45 IU/kg in pediatric patients (n=32 with 108 bleeding episodes). The median number of injections to treat a bleeding episode was 1. Hemostatic efficacy was excellent or good in 100% of bleeds in adults and 82% of bleeds in pediatric patients.

Perioperative Management of Bleeding

Across all studies, the efficacy of Nuwiq® in surgical prophylaxis was assessed in a total of 60 surgical procedures in 36 patients; 32 procedures in 16 patients were classed as minor and 28 procedures in 23 patients were classed as major. Nuwiq® pre-operative dosing ranged from 33 IU/kg to 90 IU/kg per infusion. The total number of infusions administered ranged from one to 19 for minor procedures and three to 76 for major procedures; three procedures required an injection of Nuwiq® during surgery.

The efficacy of surgical prophylaxis was rated for each case by a surgeon and a hematologist, taking into account both the intra- and postoperative assessment. Hemostasis efficacy was rated at the end of the surgery by the surgeon and postoperatively by the surgeon and hematologist using ordinal scales as follows:

- Excellent: Intra-operative: intra-operative blood loss lower than or equal to the average expected blood loss for the type of procedure performed in a patient with normal hemostasis; Postoperative: No postoperative

bleeding or oozing that was not due to complications of surgery. All postoperative bleeding (due to complications of surgery) was controlled with Nuwiq® as anticipated for the type of procedure.

- Good: Intra-operative: intra-operative blood loss was higher than average expected blood loss but lower than or equal to the maximal expected blood loss for the type of procedure in a patient with normal hemostasis; Postoperative: No postoperative bleeding or oozing that was not due to complications of surgery. Control of postoperative bleeding due to complications of surgery required increased dosing with Nuwiq® or additional infusions, not originally anticipated for the type of procedure.
- Moderate: Intra-operative: Intra-operative blood loss was higher than maximal expected blood loss for the type of procedure performed in a patient with normal hemostasis, but hemostasis was controlled. Postoperative: Some postoperative bleeding and oozing that was not due to complications of surgery; control of postoperative bleeding required increased dosing with Nuwiq® or additional infusions, not originally anticipated for the type of procedure.
- None: Intra-operative: Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen. Postoperative: Extensive uncontrolled postoperative bleeding and oozing. Control of postoperative bleeding required use of an alternate FVIII concentrate.

Efficacy for 28 major surgeries was rated as excellent in 23 (82%) cases, good in 4 (14%) cases, and moderate in 1 (4%) case. The efficacy of all 30 rated minor surgeries was excellent.

Routine Prophylaxis and Bleeding Control

In the study evaluating the efficacy and safety of Nuwiq® for routine prophylaxis in 32 adult subjects (29 White, 3 Asian), the product was given every other day with a dose of 30-40 IU/kg for at least 6 months. In another study evaluating the safety, immunogenicity and hemostatic efficacy in 59 pediatric subjects aged 2 to 12 years (all White, 29 were 2 to 5 years old, and 30 between 6 and 12 years), subjects received Nuwiq® prophylactically every other day or 3 times per week for at least 6 months. Clinical outcomes are summarized in below Table.

Table 1: Clinical Outcomes in Adult and Pediatric Subjects

	Adults (N=32)	Children (N=59)
Mean dose (± standard deviation)	32.8 ± 2.8 IU/kg	38.9 ± 7.2 IU/kg
Subjects with 0 bleeding episodes	16 (50.0%)	20 (33.9%)
Subjects with 1 bleeding episode	11 (34.4%)	14 (23.7%)
Subjects with 2 bleeding episodes	-	3 (5.1%)
Subjects with ≥ 3 bleeding episodes	-	22 (37.3%)
Subjects with ≥5 bleeding episodes	5 (15.6%)	
Annualized bleeding rate (per subject) - spontaneous bleeds	1.16 ± 2.57 (median 0, range 0-8.6)	1.50 ± 3.32 (median 0, range 0-13.8)
Annualized bleeding rate (per subject) for all types of bleeds	2.28 ± 3.73 (median 0.9, range 0-14.7)	4.12 ± 5.22 (median 1.90, range 0-20.7)
Reduction in annualized bleeding rate compared to on-demand treatment in a different study*	96%	93%

Severity of bleeds (% of bleeds) in the adults were major 16 (36.4%), minor – 28 (63.6%), life threatening 0. Severity of bleeds in the children was moderate or major 64 (42.6%), minor 61 (56.5%), unknown 1 (0.9%), life threatening 0.
* Based on a negative binomial model.

In a study of 59 previously treated pediatric patients ages 2-12 years, the children received a total of 5746 infusions. Of these infusions, 5316 (93%) were for prophylaxis, 216 (4%) for the treatment of bleeding episodes, 41 (0.7%) for peri-operative management and 173 (3%) for pharmacokinetic (PK) and recovery assessments.

Long-term treatment with routine prophylaxis was evaluated in an extension of the pediatric study in which 49 children (2-5 years [N=26] and 6-12 years [N=23]) who had completed the original pediatric study were treated with an additional 20,518 infusions of Nuwiq® over a mean of an additional 29.4 months. Across both studies, a total of 26,289 infusions and 33,724,769 IU (990,927 IU/kg) were given. Of these infusions, 25,040 (95.2%) were for

prophylaxis, 700 (2.7%) for treatment of bleeding episodes, 304 (1.2%) for peri-operative management, 247 (0.9%) for recovery assessments, and 189 (0.7%) for pharmacokinetic analyses. The median dose per prophylactic infusion was 37 IU/kg (range 12.8-124 IU/kg).

The mean annualized bleeding rate was 3.5 ± 4.4 (median 2.2, range 0.0 – 24.7). Eight of the 59 children (14%) had no bleeds.