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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUWIQ safely and effectively. See full prescribing information for NUWIQ.

NUWIQ®, Antihemophilic Factor (Recombinant)

Lyophilized Powder for Solution for Intravenous Injection

Initial U.S. Approval: 2015

---------- INDICATIONS AND USAGE ----------

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. (1)

---------- DOSAGE AND 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)
- Dosing for routine prophylaxis:

Subjects	Dose (IU/kg)	Frequency of infusions
Adolescents [12 - 17 yrs] and adults	30 - 40	Every other day
Children [2 - 11 yrs]	30 - 50	Every other day or three times per week

- Frequency and duration of therapy depends on severity of the FVIII deficiency, location and extent of bleeding, and patient's clinical condition.

---------- DOSAGE FORMS AND STRENGTHS ----------

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

---------- CONTRAINDICATIONS ----------

NUWIQ is contraindicated in patients who have manifested life-threatening hypersensitivity reactions, including anaphylaxis, to the product or its components (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue NUWIQ and administer appropriate treatment. (5.1)
- Development of Factor VIII neutralizing antibodies (inhibitors) may occur. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. (5.2)
- Monitor all patients for Factor VIII activity and development of Factor VIII inhibitor antibodies. (5.3)

---------- ADVERSE REACTIONS ----------

The most frequently occurring adverse reactions (>0.5%) in clinical trials were paresthesia, headache, injection site inflammation, injection site pain, non-neutralizing anti-Factor VIII antibody formation, back pain, vertigo, and dry mouth. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at 1- 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Pediatric Use: Lower recovery, shorter half life and faster clearance in children aged 2 - ≤12 years. Higher doses and/or a more frequent dosing schedule for prophylactic treatment should be considered in pediatric patients aged 2 to 5 years. (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: July 7, 2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution.

2.1 Dose

- Each vial of NUWIQ is labeled with the actual Factor VIII potency expressed in international units (IU). One IU of Factor VIII activity is defined by the quantity of Factor VIII in one mL of normal human pooled plasma. Calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by approximately 2% of normal activity or 2 IU/dL when assessed using the one stage clotting assay. Use the following formulae to determine the required dose:

Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)

$$\textit{Expected Factor VIII rise (\% of normal)} = \frac{2 \times \textit{administered IU}}{\textit{body weight (kg)}}$$

- Dose and duration of therapy depend on the severity of the Factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition.

On-demand Treatment and Control of Bleeding Episodes

A guide for dosing NUWIQ for the on-demand treatment and control of bleeding episodes is provided in

Table 1. Selected dosing regimen should maintain plasma Factor VIII activity levels at or above the plasma levels (in % of normal or in IU/dL) outlined in the table.

Table 1: Dosing for Treatment and Control of Bleeding Episodes

Type of Bleeding Episodes	Required peak post-infusion Factor VIII activity (% of normal or IU/dL)	Frequency of Dosing (hours)	Duration of Therapy (days)
Minor: Superficial muscle or soft tissue and oral bleeds	20–40	12-24	At least 1 day, until the bleeding episode is resolved,
Moderate to Major: Hemorrhage into muscles, into oral cavity, hemarthrosis, known trauma	30–60	12-24	For 3–4 days or more until bleeding episode is resolved.
Life-threatening: Intracranial, intra-abdominal, gastro-intestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or iliopsoas sheath, eyes/retina, fractures or head trauma	60–100	8-24	Until bleeding risk is resolved.

Perioperative Management

A guide for dosing NUWIQ during surgery (perioperative management) is provided in Table 2. Dosing should aim at maintaining a plasma Factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in the table.

Table 2: Dosing for Perioperative Management

Type of Surgery	Required post-infusion Factor VIII activity (% of normal or IU/dL)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor including tooth extraction	30–60 (pre- and post-operative)	24	At least 1 day, until healing is achieved.
Major Intracranial, intra-abdominal, or joint-replacement therapy	80–100 (pre- and post-operative)	8-24	Until adequate wound healing, then continue therapy for at least another 7 days to maintain a Factor VIII activity of 30% to 60% (IU/dL).

Routine Prophylaxis

A guide for dosing NUWIQ for routine prophylaxis to reduce the frequency of bleeding is provided in Table 3. Exact dosing should be defined by the patient's clinical status and response.

Table 3: Dosing for Routine Prophylaxis

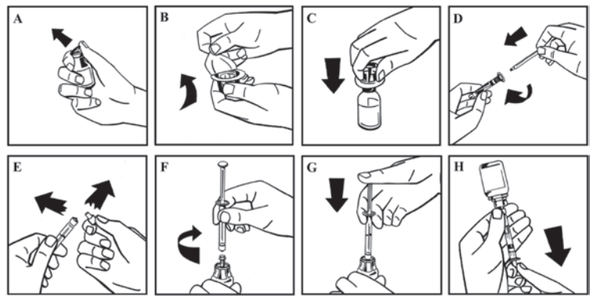
Subjects	Dose (IU/kg)	Frequency of infusions
Adolescents [12 - 17 yrs] and adults	30 - 40	Every other day
Children [2 - 11 yrs]	30 - 50	Every other day or three times per week

2.2 Preparation and Reconstitution

NUWIQ package contents:

- single-use vial of NUWIQ concentrate
- pre-filled syringe containing 2.5 mL Sterile Water for Injection
- vial adapter
- butterfly needle
- two alcohol swabs.

1. Always work on a clean surface and wash your hands before performing the procedure.
2. Allow the vial of NUWIQ and the pre-filled syringe to come to room temperature.
3. Remove the plastic flip-top cap from the NUWIQ vial to expose the rubber stopper. (Figure A).
4. Wipe the top of the vial with an alcohol swab and allow the rubber stopper of the vial to dry.
5. Peel back the paper cover from the vial adapter package revealing the adapter spike without removing the adapter from the package (Figure B).
6. With the concentrate vial on an even surface, insert the adapter spike into the rubber stopper. The adapter snaps to the vial when done (Figure C).
7. Peel back the paper cover from the pre-filled syringe package. Connect plunger rod attaching the threaded end of the plunger rod to the solvent syringe, turning clockwise until a slight resistance is felt (Figure D). Avoid contact with shaft.
8. Break off the tamper-proof plastic tip from the syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip (Figure E).
9. Remove the adapter packaging and connect the syringe to the vial adapter by turning clockwise until resistance is felt (Figure F).
10. Slowly inject all liquid from syringe into the concentrate vial (Figure G).
11. Without removing the syringe, dissolve the concentrate powder in the vial by gently moving or swirling a few times. DO NOT SHAKE. Wait until all the powder dissolves completely.
12. Inspect the final solution for particles. The solution should be clear, colorless, and free from visible particles. Do not use if solution is cloudy or has particulate matter.
13. Turn the vial and syringe upside down (still attached).
14. Slowly withdraw the solution into the syringe. Make sure that all liquid is transferred to the syringe (Figure H).
15. Detach the filled syringe from the vial adapter by turning counter clockwise.



Do not refrigerate the solution after reconstitution. Use the solution within 3 hours after reconstitution. If solution is not used within this time period, close the filled syringe with the tamper-proof plastic tip, and discard.

2.3 Administration

For intravenous use after reconstitution only.

1. Inspect the reconstituted NUWIQ solution for visible particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.
2. Do not administer NUWIQ in the same tubing or container as other medications
3. Clean the chosen injection site with an alcohol swab.
4. Attach the provided infusion set to the syringe. Insert the needle of the infusion set into the chosen vein.
5. Perform intravenous bolus infusion. The rate of administration should be determined by patient's comfort level, at a maximum rate of 4 mL per minute.
6. After infusing NUWIQ, remove and properly discard the infusion set. After the infusion, remove the peel-off label containing the batch number from the factor concentrate vial and place it in the log book for record keeping.

3 DOSAGE FORMS AND STRENGTHS

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

The actual Factor VIII potency is labeled on each NUWIQ vial.

4 CONTRAINDICATIONS

NUWIQ is contraindicated in patients who have manifested life-threatening hypersensitivity reactions, including anaphylaxis, to the product or its components.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, are possible with NUWIQ. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, or pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies

The formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following the administration of NUWIQ. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the plasma Factor VIII level fails to increase as expected, or if bleeding is not controlled after NUWIQ administration, suspect the presence of an inhibitor (neutralizing antibody) [*see Warnings and Precautions (5.3)*].

5.3 Monitoring and Laboratory Tests

- Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained [*see Dosage and Administration (2.1)*].
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of NUWIQ. Use Bethesda Units (BU) to report inhibitor levels.

6 ADVERSE REACTIONS

The most common adverse reactions (>0.5% of subjects) reported in clinical trials were paresthesia, headache, injection site inflammation, injection site pain, non-neutralizing anti-Factor VIII antibody formation, back pain, vertigo, and dry mouth.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rate in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of NUWIQ was evaluated in five prospective, open-label clinical studies in previously treated patients (PTPs - exposed to a Factor VIII containing product for ≥150 exposure days (EDs) in the case of adolescents and adults or ≥50 EDs in the case of subjects below 12 years of age) with severe Hemophilia A (Factor VIII ≤ 1%). Subjects who had a history of detectable Factor VIII inhibitor, severe liver or kidney disease, were not immune competent (CD4+ count <200/µL), or scheduled to receive immunomodulating drugs, were excluded.

Across all clinical studies, 135 patients were stratified, among them, 74 were adults, 3 adolescents between 12 and 17 years old, and 58 pediatric patients between 2 and 11 years old. A total of 127 (94.1%) subjects were treated for at least 180 days. Collectively, patients received between 24,005 and 996,550 IU (555 to 8629 IU/kg) from14 to 319 infusions over 14 to 299 exposure days, over a period of 33 to 563 days. An exposure day was defined as any day on which at least one infusion was started.

With a total of 16,134 infusions over 15,950 EDs, reported adverse reactions included paresthesia, headache, injection site inflammation, injection site pain, back pain, vertigo, and dry mouth. Each of these adverse reactions occurred once in the study population of 135, and thus each had a rate of 0.7%. Non-neutralizing anti-Factor VIII antibodies (without inhibitory activity as measured by the modified Bethesda assay) were reported in four patients, giving a rate of 3%. Three of four subjects had pre-existing non-neutralizing antibodies prior to exposure with NUWIQ. The binding antibodies were transient in two of these three subjects. In one subject who was tested negative at screening, the non-neutralizing antibody was measured once at study end.

Immunogenicity

All clinical trial subjects (N = 135) were monitored for neutralizing antibodies (inhibitors) to Factor VIII by the modified Bethesda assay using blood samples obtained prior to the first infusion of NUWIQ, at defined intervals (at ED 10 to 15, at 3 months, and every further 3 months) during the studies and at the completion visit. No subject developed neutralizing antibodies to Factor VIII. Four subjects (3%) developed a non-neutralizing antibody without any inhibitory activity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NUWIQ with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with NUWIQ use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with NUWIQ. It is not known whether NUWIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NUWIQ should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of NUWIQ in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUWIQ and any potential adverse effects on the breastfed infant from NUWIQ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy studies were performed in 59 previously treated pediatric patients (58 patients 2 to 11 years old) who received at least one dose of NUWIQ for routine prophylaxis. Efficacy in routine prophylaxis and on-demand treatment of bleeding episodes is comparable between children and adults [*see Clinical Studies (14)*]. 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. For two adverse events (mild back pain, mild headache) in two (3%) subjects, causality was rated as possibly related to NUWIQ administration.The pediatric pharmacokinetic data of NUWIQ were obtained in 29 children between 2 and 5 years of age and 30 children between 6 and ≤12 years of age. Half-life (T1/2) and incremental in vivo recovery (IVR) are lower in children than in adults and systemic drug clearance is substantially higher in the pediatric age group 2 to 5 yrs compared to adults [*see Clinical Pharmacology (12.3)*]. Higher doses and/or a more frequent dosing schedule for prophylactic treatment should be considered in pediatric patients aged 2 to 5 yrs.

8.5 Geriatric Use

Clinical studies of NUWIQ did not include sufficient numbers of subjects age 65 and over to provide conclusive evidence as to whether or not they respond differently than younger subjects.

11 DESCRIPTION

NUWIQ, Antihemophilic Factor (Recombinant), is a sterile, non-pyrogenic, lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-use vials containing nominal Factor VIII potencies of 250, 500, 1000, 2000, 2500, 3000 or 4000 IU. When reconstituted with 2.5 mL of solvent (Sterile Water for Injection), the respective nominal concentrations are 100, 200, 400, 800, 1000, 1200 or 1600 IU/mL. The reconstituted product contains the following excipients per mL: 18 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium chloride dihydrate, 1.2 mg poloxamer 188, and 1.2 mg sodium citrate dihydrate. The concentration of each of the excipients is the same for all potencies. NUWIQ contains no preservatives. Each vial of NUWIQ is labeled with the actual Factor VIII potency expressed in IU determined using one-stage clotting assay, using a reference material calibrated against a World Health Organization (WHO) International Standard for Factor VIII concentrates. One IU, as defined by the WHO standard for human Factor VIII concentrates, is approximately equal to the level of Factor VIII activity in 1 mL of fresh pooled, normal, human plasma. The mean specific activity of NUWIQ is 8124 IU/mg total protein.

B-domain deleted recombinant coagulation Factor VIII (BDD-rFVIII) is the active ingredient in NUWIQ. BDD-rFVIII is a recombinant glycoprotein (a heterodimer) with an approximate molecular mass of 170 kDa, comprising the Factor VIII domains A1-A2 (so-called heavy chain of ~90 kDa) and A3-C1-C2 (so-called light chain of ~80 kDa), whereas the B-domain, present in the full-length plasma-derived Factor VIII, has been deleted. The purified protein consists of 1440 amino acids. The amino acid sequence is comparable to the B-domain deleted form of human plasma Factor VIII(90 + 80 kDa).

BDD-rFVIII is produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) 293F cells with no animal or human derived materials added during the manufacturing process or to the final product. As NUWIQ is produced using a human cell-line, it contains post-translational modifications comparable to human plasma-derived Factor VIII and is devoid of Neu5Gc or α-1,3-Gal epitopes[1] that may be present in products produced in animal cells. Furthermore, BDD-rFVIII is fully sulfated at Tyr1680 [1]. The active substance is concentrated and purified by a series of chromatography steps, which also includes two dedicated viral clearance steps: solvent/detergent (S/D) treatment for virus inactivation and 20 nm nanofiltration for removal of viruses.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation Factor VIII, resulting in a prolonged plasma clotting time as measured by the activated partial thromboplastin time (aPTT) assay. Treatment with NUWIQ normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of NUWIQ were evaluated in an open-label, multicenter clinical study of 22 (20 adults and 2 adolescents) previously treated patients (PTPs) with severe Hemophilia A. The PK parameters (Table 4) were based on plasma Factor VIII activity measured by the one-stage clotting assay after a single intravenous infusion of a 50 IU/kg dose.

The PK profile obtained after 6 months of repeated dosing was comparable with the PK profile obtained after the first dose.

Table 4: Pharmacokinetic Parameters of NUWIQ in 22 PTP Adults/Adolecents (Dose: 50 IU/kg)

PK Parameters	Mean ± SD
AUC (h·IU/mL)	18.0 ± 5.6
AUC_{norm} (h·IU/mL/(IU/kg))	0.4 ± 0.1
$C_{maxnorm}$ (IU/mL/(IU/kg))	0.022 ± 0.003
$T_{1/2}$ (h)	17.1 ± 11.2*
IVR (%/IU/kg)	2.1 ± 0.3
MRT (h)	22.5 ± 14.2
CL (mL/h/kg)	3.0 ± 1.0
V_{ss} (mL/kg)	59.8 ± 19.8

AUC = Area under the curve (Factor VIII:C); AUC_{norm} = AUC divided by the dose; $C_{maxnorm}$ = Maximal plasma concentration divided by the dose; CL = Clearance; Factor VIII:C = Factor VIII coagulation activity; IVR = Incremental *in vivo* recovery; MRT = Mean residence time; PK = Pharmacokinetics; SD = Standard deviation; $T_{1/2}$ = Terminal half-life; V_{ss} = Volume of distribution at steady state; *Median, lower/upper quartile: 13.7, 12.0/17.5

Pediatric Pharmacokinetics

PK of pediatric patients is presented in Table 5 for the age groups 2 to 5 years and 6 to 12 years. They were based on plasma Factor VIII activity measured by the one-stage clotting assay after a single intravenous infusion of 50 IU/kg dose. Compared to adults and adolescents, IVR and $T_{1/2}$ were lower and systemic drug clearance (based on per kg bodyweight) was substantially higher in children 2 to 5 yr of age.

IVR analysis after 3 and 6 months of prophylactic treatment yielded comparable results with the IVR after the first dose.

As in the adult population, similar PK values were obtained using the chromogenic and the one-stage assay.The values in Table 5 reflect those obtained using the one-stage assay.

Table 5: Pharmacokinetic Parameters of NUWIQ in 26 PTP Children Age 2 to 5 Years and 6 to 12 Years (Dose: 50 IU/kg)

PK Parameters	2 to 5 years (N = 13) Mean ± SD	6 to ≤12 years (N = 13) Mean ± SD
AUC (h·IU/mL)	10.1 ± 4.6	11.8 ± 2.7
AUC_{norm} (h·IU/mL/(IU/kg))	0.2 ± 0.1	0.3 ± 0.1
$C_{maxnorm}$ (IU/mL/(IU/kg))	0.016 ± 0.002	0.017 ± 0.004
$T_{1/2}$ (h)	11.9 ± 5.4*	13.1 ± 2.6#
IVR (%/IU/kg)	1.6 ± 0.2	1.6 ± 0.4
MRT (h)	15.1 ± 7.4	16.5 ± 2.9
CL (mL/h/kg)	5.4 ± 2.3	4.1 ± 0.9
V_{ss} (mL/kg)	68.3 ± 10.4	66.1 ± 16.0

AUC = Area under the curve (Factor VIII:C); AUC_{norm} = AUC divided by the dose; $C_{maxnorm}$ = Maximal plasma concentration divided by the dose; CL = Clearance; Factor VIII:C = Factor VIII coagulation activity; IVR = Incremental in vivo recovery; MRT = Mean residence time; PK = Pharmacokinetics; SD = Standard deviation; $T_{1/2}$ = Terminal half-life; V_{ss} = Volume of distribution at steady state; *Median, lower/upper quartile: 10.1, 9.4/13.7; #Median, lower/upper quartile: 12.8, 11.2/15.9

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of NUWIQ or studies to determine the effects of NUWIQ on genotoxicity or fertility have not been performed.

13.2 Animal Toxicology and/or Pharmacology

Local tolerance assessment of NUWIQ in rabbits following single perivenous administration at dosage strengths up to 4000 IU did not result in adverse findings.

14 CLINICAL STUDIES

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 as surgical prophylaxis was assessed in a total of 33 surgical procedures in 19 patients; 20 procedures in 7 patients were classed as minor and 13 procedures in 12 patients were classed as major. NUWIQ pre-operative dosing ranged from 35 IU/kg to 50 IU/kg per infusion. The total number of infusions administered ranged from 1 to 5 for minor and 4 to 35 for major surgeries; one surgery 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 major surgeries was rated as excellent in 9 (69%) cases and as good in 3 (23%) cases. In 1 (8%) case, efficacy was rated as moderate. The efficacy of all minor surgeries was rated as excellent.

Routine Prophylaxis

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 Table 6.

Table 6. 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 were moderate or major 64 (42.6%), minor 61 (56.5%), unknown 1 (0.9%), life threatening 0.
* Based on a negative binomial model.

15 REFERENCES

1. Kannicht C, Ramström M, Kohla G, Tiemeyer M, Casademunt E, Walter O, Sandberg H. Characterisation of the post-translational modifications of a novel, human cell line-derived recombinant human factor VIII. Thromb Res. 2013;131:78-88

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- NUWIQ is supplied in packages comprising a single-use vial containing nominally 250, 500, 1000, 2000, 2500, 3000 or 4000 international units (IU) of Factor VIII potency, a pre-filled syringe with 2.5 mL solvent (Water for Injection), a vial adapter, a butterfly needle and two alcohol swabs. The actual amount of NUWIQ in IU is stated on each carton and vial.
- Components used in the packaging of NUWIQ are not made with natural rubber latex.

		Container NDC	Carton NDC
pale blue	NUWIQ 250 IU	68982-140-01	68982-139-01
pale pink	NUWIQ 500 IU	68982-142-01	68982-141-01
green blue	NUWIQ 1000 IU	68982-144-01	68982-143-01
orange	NUWIQ 2000 IU	68982-146-01	68982-145-01
brown	NUWIQ 2500 IU	68982-148-01	68982-147-01
dark grey	NUWIQ 3000 IU	68982-150-01	68982-149-01
dark green	NUWIQ 4000 IU	68982-152-01	68982-151-01

Storage and Handling

- Store NUWIQ in the original package to protect the NUWIQ vials from light.
- Store NUWIQ in powder form at 2 – 8°C (35 – 46°F) for up to 24 months. Do not freeze.
- During the shelf life, the product may be kept at room temperature [up to 25°C (77°F)] for a single period not exceeding 3 months. After storage at room temperature, do not return the product to the refrigerator.
- Do not use after the expiration date.
- Keep the reconstituted solution at room temperature. Do not refrigerate after reconstitution. Use the reconstituted solution immediately or within 3 hours after reconstitution. Discard any remaining solution.

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use)
- Because hypersensitivity reactions are possible with NUWIQ, inform patients of the early signs of hypersensitivity reactions, including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Advise patients to stop the injection if any of these symptoms arise and contact their physician, and seek prompt emergency treatment.
- Advise patients to contact their physician or treatment center for further treatment and/or assessment if they experience a lack of clinical response to Factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to consult with their healthcare provider prior to traveling. While traveling, patients should be advised to bring an adequate supply of NUWIQ based on their current treatment regimen.

Manufactured by:
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SE-112 75, Sweden
U.S. License No. 1646

Distributed by:
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FDA-APPROVED PATIENT LABELING

Patient Information

NUWIQ /nu' veek /
Antihemophilic Factor (Recombinant)

Please read this Patient Information carefully before using NUWIQ and each time you get a refill, as there may be new information. This Patient Information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is NUWIQ ?

NUWIQ is an injectable medicine that is used to help treat and control bleeding in adults and children with Hemophilia A (congenital clotting Factor VIII deficiency). NUWIQ can reduce the number of bleeding episodes in children and adults when used regularly (prophylaxis). Usually, Hemophilia A treatment is life-long.

Your healthcare provider may also give you NUWIQ when you have surgery.

NUWIQ is NOT used to treat von Willebrand disease.

Who should not use NUWIQ ?

You should not use NUWIQ if you had an allergic reaction to it in the past.

Tell your healthcare provider if you are (or are planning to become) pregnant and/or breastfeeding because NUWIQ may not be right for you.

What should I tell my healthcare provider before using NUWIQ ?

Talk to your healthcare provider about any medical conditions that you have or have had, including if you have been told that you have inhibitors to Factor VIII, because NUWIQ may not work for you.

Tell your healthcare provider about all of the prescription and non-prescription medicines you take, including over-the-counter medicines, dietary supplements, and/or herbal medicines.

How should I use NUWIQ ?

You get NUWIQ as an infusion into your vein. NUWIQ is sold as a powder in a vial. The powder is mixed with sterile water supplied in a prefilled syringe. See instructions for reconstitution and injection of NUWIQ.

Your healthcare provider will instruct you on how to do reconstitutions and infusions on your own or with the help of a family member. Your healthcare provider may watch you give yourself the first dose of NUWIQ.

You must carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing NUWIQ so that your treatment will work optimally for you.

NUWIQ comes in different dosage strengths. The actual number of international units (IU) of Factor VIII in the vial will be printed on the label and box. Always check the actual number of IU of Factor VIII printed on the label to make sure you are using the strength prescribed by your healthcare provider.

Contact your healthcare provider right away if bleeding is not controlled after using NUWIQ.

Talk to your healthcare provider before travelling. Plan to bring enough NUWIQ for your treatment during this time.

Do not stop using NUWIQ without consulting with your healthcare provider.

What are the possible side-effects of NUWIQ ?

Allergic reactions may occur with NUWIQ. Stop the injection immediately and call your healthcare provider or emergency department right away if you have any of the following symptoms: dizziness, loss of consciousness, difficulty breathing, wheezing, chest tightness, swelling of lips and tongue, rash, or hives.

Your body can also make antibodies (known as inhibitors) against Factor VIII, which may stop NUWIQ from working properly. Your healthcare provider may test your blood to check for inhibitors at regular intervals.

Side-effects that have been reported with NUWIQ include: injection site inflammation, injection site pain, prickling or tingling sensation, headache, back pain, dizziness, and dry mouth.

These are not all the possible side effects of NUWIQ. Talk to your healthcare provider about any side-effect that bothers you or that does not go away.

How should I store NUWIQ ?

Keep NUWIQ in its original box to protect it from exposure to light. Do not freeze NUWIQ.

You can store NUWIQ in the refrigerator for up to 24 months at 2-8°C (36-46°F). NUWIQ can be kept at room temperature [up to 25°C (77°F)] for a single period not exceeding 3 months (note on the carton the date when the product was removed from the refrigerator). After storage at room temperature, the product must be used or discarded, and it must not be put back into the refrigerator.

Do not use NUWIQ after the expiration date printed on the vial.

Do not use NUWIQ if the reconstituted solution is cloudy, contains particles, and/or is not colorless.

NUWIQ should be used as soon as possible after reconstitution. Protect reconstituted NUWIQ from light and temperatures above 25°C (77°F). Discard any product not used within three hours.

Dispose of all materials, including any unused NUWIQ, in an appropriate container.

What else should I know about NUWIQ ?

Do not use NUWIQ for a medical condition for which it was not prescribed. Do not share NUWIQ with other people, even if they have the same diagnosis and symptoms that you have.

Resources at Octapharma available to patients

For more product information on NUWIQ, please visit www.NUWIQ.com.

For more information on patient assistance programs that are available to you, please contact the Octapharma Patient Support Center at 1-800-554-4440.

For more information on additional Octapharma patient resources, please visit www.NUWIQ.com.

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