NUWIQ® Antihemophilic Factor (Recombinant)
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. (3)

DOSE AND ADMINISTRATION

1. Dosing
- Each vial of NUWIQ is labeled with the actual amount of Factor VIII potency in international units (IU) per vial.
- Determine dose using the following formula for adolescents and adults:
  \[ \text{Required IU} = \text{body weight (kg)} \times \text{dose per IU (IU/kg per IU/kg)} \]
- For children 2 - 11 years of age:
  \[ \text{Required IU} = \text{body weight (kg)} \times \text{dose per IU (IU/kg per IU/kg)} \]

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

FOSAMAX FORMS AND STRENGTHS
NUWIQ is available as a white sterile, non-pyrogenic, lyophilized powder for reconstitution.
- Lyophilized Powder for Solution for Intravenous Injection
NUWIQ®, Antihemophilic Factor (Recombinant)

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. CONTRAINDICATIONS
- Hypersensitivity reactions, including anaphylaxis, to the product or its components (4)
- Known or suspected pregnancy

2. WARNINGS AND PRECAUTIONS
- Neutralizing antibodies (inhibitors) to Factor VIII can occur following the first infusion of NUWIQ, at defined intervals (at ED 10 to 15, at 3 months, and every further 3 months) during the study and at the completion of the study. No subject developed neutralizing antibodies to NUWIQ. Four subjects (3.9%) developed a non-neutralizing antibodies without any inhibitory activity.

- The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. 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.

3. USE IN SPECIFIC POPULATIONS

3.1 Pregnancy
- 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 known, however, that the use of exogenous Factor VIII in children aged 2 - 12 years old may affect neutralizing antibodies in the mother. It is not known whether NUWIQ may affect the potential to become pregnant.

3.2 Lactation
- These clinical studies of NUWIQ did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, geriatric patients should be monitored for adverse reactions.

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

5. 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) [2.3].

- Monitor for plasma Factor VIII activity at least 3 days before starting the next dose of NUWIQ. Use Bethesda Units (BU) to report inhibitor levels.

6. Adverse Reactions
- The most common adverse reactions (≥25% of subjects) reported in clinical trials were headache, injection site inflammation, injection site pain, non-neutralizing anti-Factor VIII antibody formation, back pain, arthralgia, and dry mouth.

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

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

16. HOW SUPPLIED/STORAGE AND HANDLING
- NUWIQ is available in single-use vial for intravenous injection.
- NUWIQ package contents:
  - single-use vial of NUWIQ concentrate
  - prefilled syringe containing 2.5 mL Sterile Water for Injection
  - vial adapter
  - butterfly needle
  - two alcohol swabs.

2.2 Preparation and Reconstitution
NUWIQ package contents:
- single-use vial of NUWIQ concentrate
- prefilled 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 prefilled syringe to come to room temperature.
3. Remove the plastic stopper from the vial using the rubber stopper to keep the vial from spilling.
4. While holding the vial top with an alcohol swab and allow the rubber stopper of the vial to dry.
5. Place the prefilled syringe from the vial adapter releasing the adapter slot without removing the adapter from the package (Figure B).
6. With the vial concentrate on an even surface, insert the adapter into the rubber stopper. The adapter snaps to the vial when done (Figure C).
7. Peel back the paper cover from the prefilled syringe. Connect plunger rod to the adapter by pushing the threads of the and of the plunger rod to the solvent syringe, turning (counterclockwise) until a slight resistance is felt (Figure D). Avoid contact with shaft.
8. From the plunger rod to the adapter by pushing the threads of the and of the plunger rod to the solvent syringe, turning (counterclockwise) until a slight resistance is felt (Figure D).
9. Slowly withdraw the solution into the syringe. Make sure that all liquid is transferred to the syringe (Figure E).

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12.1 Mechanism of Action

NUWIQ temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis. 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 long-term. NUWIQ 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. NUWIQ has been produced using a human cell-line, it contains post-translational modifications comparable to human plasma-derived Factor VIII. NUWIQ is packaged in vials which are manufactured under Good Manufacturing Practice (GMP) conditions and are filled aseptically.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vss (mL/kg)</td>
<td>59.8 ± 19.8</td>
</tr>
<tr>
<td>CL (mL/h/kg)</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td>Cmaxnorm (IU/mL/(IU/kg))</td>
<td>0.016 ± 0.002</td>
</tr>
<tr>
<td>Area under the curve (AUC) (IU/mL)</td>
<td>32.8 ± 2.8</td>
</tr>
<tr>
<td>Mean ± SD (mL/kg)</td>
<td>17.8 ± 2.8</td>
</tr>
</tbody>
</table>

Table 5. Clinical Outcomes in Adult and Pediatric Subjects

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Mean ± SD</th>
<th>Median (range)</th>
<th>CI 95% CI 90%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (%)</td>
<td>100%</td>
<td>0.9 (0.2-3.2)</td>
<td>0.9 (0.1-3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Without (%)</td>
<td>35%</td>
<td>1.1 (0.3-3.0)</td>
<td>1.1 (0.1-3.0)</td>
<td>&lt;0.001</td>
</tr>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vss (mL/kg)</td>
<td>68.3 ± 16.4</td>
</tr>
<tr>
<td>CL (mL/h/kg)</td>
<td>6.1 ± 2.4</td>
</tr>
<tr>
<td>Cmaxnorm (IU/mL/(IU/kg))</td>
<td>4.1 ± 0.9</td>
</tr>
</tbody>
</table>

13.2 Animal Toxicology and/or Pharmacology

Leporine hydrochloride is a 10% solution of Leporine for reconstitution. Leporine is a non-ionic, polyoxyethylene-lipophilized polyethylene glycol for reconstitution. Leporine is provided in vials containing 15 mL of a 10% solution of Leporine for reconstitution. Leporine is a non-ionic, polyoxyethylene-lipophilized polyethylene glycol for reconstitution.