NUWIQ® is available as a white sterile, non-pyrogenic, lyophilized powder for reconstitution.

Subjects

<table>
<thead>
<tr>
<th>Dose (IU/kg)</th>
<th>Frequency of Infusions</th>
</tr>
</thead>
</table>
| Adults and children (12 - 17 years) | 30 – 50
| Every other day or three times per week, if necessary |
| Children (2 - 11 years) | 30 – 50
| Every other day or three times per week, if necessary |

Table 1: Dosing for Treatment and Control of Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Bleeding Episode</th>
<th>Required peak Factor VIII activity (% normal or OK)</th>
<th>Frequency of Dosing (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor: Superficial muscle or soft tissue and oral</td>
<td>50 – 70</td>
<td>12 – 24</td>
<td>Until at least 1 day after the bleeding episode has resolved.</td>
</tr>
<tr>
<td>Moderate to Major: Herniorrhaphy</td>
<td>50 – 70</td>
<td>12 – 24</td>
<td>Until at least 1 day after the bleeding episode has resolved.</td>
</tr>
<tr>
<td>Severe intraperitoneal or intracranial bleeding, lacerations, burn, or chemical burns</td>
<td>70 – 90</td>
<td>12 – 24</td>
<td>Until at least 1 day after the bleeding episode has resolved.</td>
</tr>
<tr>
<td>Severe intra-abdominal, gastrointestinal, genitourinary, or retroperitoneal bleeding, or active or recurrent intracranial hemorrhage</td>
<td>90–100</td>
<td>8 – 24</td>
<td>Until bleeding risk is resolved.</td>
</tr>
<tr>
<td>Life-threatening: Major: Deep intramuscular or subcutaneous muscle, or soft tissue and oral</td>
<td>50–100</td>
<td>3–4 or more times per day</td>
<td>For 3–4 days or more, until adequate wound healing is achieved.</td>
</tr>
<tr>
<td></td>
<td>100–120</td>
<td>3–4 or more times per day</td>
<td>For 3–4 days or more, until adequate wound healing is achieved.</td>
</tr>
</tbody>
</table>

Table 2: Dosing for Periprocedural Management

Type of Bleeding Episode | Required peak Factor VIII activity (% normal or OK) | Frequency of Dosing (hours) | Duration of Therapy (days) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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<td>8 – 24</td>
<td>Until bleeding risk is resolved.</td>
</tr>
<tr>
<td>Life-threatening: Major: Deep intramuscular or subcutaneous muscle, or soft tissue and oral</td>
<td>50–100</td>
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<td></td>
<td>100–120</td>
<td>3–4 or more times per day</td>
<td>For 3–4 days or more, until adequate wound healing is achieved.</td>
</tr>
</tbody>
</table>

Table 3: Dosing for Routine Prophylaxis

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Dose (IU/kg)</th>
<th>Frequency of Infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children (12 - 17 years)</td>
<td>30 – 50</td>
<td>Every other day or three times per week, if necessary</td>
</tr>
<tr>
<td>Children (2 - 11 years)</td>
<td>30 – 50</td>
<td>Every other day or three times per week, if necessary</td>
</tr>
</tbody>
</table>

A regimen may be further individually adjusted to less or more frequent dosing at the discretion of the treating physician.

2.2 Preparation and Reconstitution
NUWIQ is a recombinant antihemophilic factor (blood clotting factor VIII [Factor VIII]) indicated in adults and children with Hemophilia A for:

- single-use vial of NUWIQ concentrate
- prefilled syringes containing 2.5 mL Sterile Water for Injection

• vial
• butterfly needle
• two alcohol swabs

1. Open the vial on a clean, flat 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 flat-top cap from the vial and use the rubber stopper.
4. Wipe the tip of the vial with an alcohol swab and allow the rubber stopper of the vial to hydrolyze by adding approximately 2 mL of Sterile Water for Injection to the vial for 2 minutes.
5. Place the attached vial adapter into the vial and center the bottle.
6. Push the paper cover from the vial adapter package to remove the adapter without tapping the adapter into the vial or into the prefilled syringe package.
7. Place the prefilled syringe on an even surface, invert the adapter and snap the rubber stopper into the rubber stopper adapter. Snap the adapter to the vial when done (Figure C).
8. Push the paper cover from the prefilled syringe package. Connect plunger rod from the prefilled syringe to the plunger rod of the vial adapter. Pull back on the plunger until at least a 90-degree angle is felt (Figure D). Avoid contact with shaft.
9. Before use, check the syringe for the presence of bubbles or debris from the syringe. Do not touch the inside of the cap or the syringe tip (Figure E).
10. Remove the packaging adapter and connect the syringe to the vial by turning clockwise until resistance is felt (Figure F). Until all the powder dissolves completely.
11. Do not mix final solution for particles. The solution should be clear, colorless, and free from visible debris. Do not use it if it is cloudy or has particulate matter.
12. Turn the vial and syringe upside down (still attached).
13. Slowly withdraw the solution from the vial into the syringe. Make sure that all liquid is transferred to the transfusion set (Figure H).
14. Detach the filled syringe from the vial adapter by turning counter clockwise.

2.3 Administration

For on-demand treatment and control of bleeding episodes:

1. Insert the needle of the syringe into the chosen vein.
2. Remove the adapter packaging and connect the syringe to the vial adapter by turning clockwise until resistance is felt (Figure F).
3. Apply gentle pressure to the syringe to a maximum rate of 4 mL per minute by patient's comfort level, at a maximum rate of 4 mL per minute.
4. Attach the provided infusion set to the syringe. Insert the needle of the infusion set into the chosen vein. Continue to infuse at a maximum rate of 4 mL per minute until adequate wound healing is achieved. (Figure I).
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.

Intravenous infusion Factor VIII activity and development of Factor VIII inhibitor

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

NUWIQ is not indicated for the treatment of von Willebrand disease.

12.2 Pharmacodynamics

NUWIQ is a recombinant antihemophilic factor (blood clotting factor VIII [Factor VIII]) indicated in adults and children with Hemophilia A for:

• on-demand treatment and control of bleeding episodes

Routine prophylaxis

NUWIQ is available as a white sterile, non-pyrogenic, lyophilized powder for reconstitution.

NUWIQ® is a recombinant antihemophilic factor (blood clotting factor VIII [Factor VIII]) indicated in adults and children with Hemophilia A for:

• on-demand treatment and control of bleeding episodes

Routine prophylaxis

NUWIQ is available as a white sterile, non-pyrogenic, lyophilized powder for reconstitution.
8.4.3 Median, lower/upper quartile: 13.7, 12.0/17.5

11 DESCRIPTION

11.1 Mechanism of Action

The pharmacokinetic (PK) of NUWIQ were evaluated in an open-label, multicenter clinical study of 22 (20 adults and 2 adolescents) previously treated patients (PTP) with severe HAE. The PK parameters (Table 4) were based on plasma factor VIII activity measured by the use of a one-stage assay. The PK profile obtained after a 6-month dosing period was compared with the PK profile obtained after the first dose.

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 deficient production or function of factor VIII (FVIII) due to a reduction in its plasma levels.

12.3 Pharmacokinetics

The pharmacokinetics of NUWIQ were studied after single intravenous doses of 50 IU/kg dose in patients aged 2 to 5, 6 to 12 years and 12 to 17 years. The safety and efficacy of NUWIQ were assessed in a study in 110 previously untreated pediatric patients (PUP, age range 0-14 months). Of 110 PUP, 108 had evaluable data and were investigated to evaluate safety and efficacy (immunogenicity of the primary endpoint).

13 NONCLINICAL STUDIES

13.1 Carcinogenesis, Mutagenesis, Impairment of fertility

The potential for NUWIQ to induce local and systemic toxicity was assessed in studies involving single or multiple dosing to rabbits, monkeys, and dogs. NUWIQ was well tolerated at all the tested dose levels. The results of these studies suggest that NUWIQ is safe in the rabbit, monkey, and dog models.

14 CLINICAL STUDIES

14.1 Study Design

The pharmacokinetic parameters of NUWIQ in 26 PTP Children Age 2 to 5 Years and 6 to 12 Years (N=13) and 6 to 12 Years (N=13) are presented in Table 5.

14.2 Study Population

Across all studies, the efficacy of NUWIQ in surgical prophylaxis was assessed in a total of 60 pediatric patients (n=32 with 108 bleeding episodes). The median number of injections to achieve a clinical benefit was 1.

14.3 Efficacy

Across all studies, the efficacy of NUWIQ in surgical prophylaxis was assessed in a total of 60 pediatric patients (n=32 with 108 bleeding episodes). The median number of injections to achieve a clinical benefit was 1.

15 ADVERSE REACTIONS

15.1 Adverse Reactions in Clinical Studies

A total of 1124 bleeding episodes in 69 subjects (35 adults, 2 adolescents, and 32 children) were investigated to determine the immunogenicity of NUWIQ.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUWIQ is supplied in packages comprising a single-use vial containing nominally 250, 500, 1000, 2000 IU of FVIII concentrates. One IU, as defined by the WHO (International Standard for Factor VIII concentrates), contains 1 IU of FVIII in 1 mL of fresh pooled, normal, human plasma. The mean specific activity of NUWIQ is 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium chloride dihydrate, 1.2 mg sodium chloride, 5.4 mg aspartic acid, 5.4 mg L-glutamic acid, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium 12-hydroxy acid, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride.

In a study of 59 previously treated pediatric patients aged 2-12 years, the children received a total of 5468 IU doses. Of these IU doses, 3135 (57%) were for prophylaxis, 2346 (43%) for the treatment of bleeds. Across all studies, 78% of the patients were on prophylactic treatment, 22% on demand treatment. The specific activity of NUWIQ was 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium chloride dihydrate, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium hydroxide, 1.2 mg sodium chloride.

A total of 1124 bleeding episodes in 69 subjects (35 adults, 2 adolescents, and 32 children) were investigated to determine the immunogenicity of NUWIQ.

2.28 ± 3.73 (median 0.9, range 0-8.6)