Product Information Form for Hospitals

Indications and Usage

Novoeight® (antihemophilic factor, recombinant) is indicated for use in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes.

- Novoeight® is not indicated for the treatment of von Willebrand disease

Important Safety Information

Contraindications

- Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components, including hamster proteins

Warnings and Precautions

- Anaphylaxis and severe hypersensitivity reactions are possible. Patients may develop hypersensitivity to hamster proteins, which are present in trace amounts in the product. Should symptoms occur, discontinue Novoeight® and administer appropriate treatment

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novoeight®
Antihemophilic Factor (Recombinant)

Product Information Form for Hospitals

1 AHFS CLASSIFICATION NUMBER

20:28.16

2 GENERIC NAME

Antihemophilic Factor (Recombinant)

3 SOURCE OF SUPPLY

Novoeight® is manufactured by Novo Nordisk A/S. Novoeight® is distributed by Novo Nordisk Inc.

4 BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

BL 125466/0, October 15, 2013

5 PHYSICAL PROPERTIES

a. Macroscopic appearance

Novoeight® is supplied as white, lyophilized powder in single-dose vials, one vial per carton. The diluent for reconstitution of Novoeight® is 0.9% sodium chloride solution and is supplied in a pre-filled diluent syringe. Novoeight® is available in single-dose vials that contain nominally 250, 500, 1000, 1500, 2000 or 3000 international units (IU) per vial.

b. Solubility

Novoeight® is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (0.9% sodium chloride).

6 CHEMICAL PROPERTIES

a. Structural similarities to other available compounds or groups of compounds

The active ingredient in Novoeight® is a recombinant (r) analogue of human coagulation factor VIII (FVIII) with a molecular mass of 166 kDa, calculated excluding post-translational modifications. The rFVIII molecule in Novoeight® is a glycoprotein containing a heavy chain and a light chain, with 21 of the 908 amino acids of the B-domain of endogenous FVIII connected to the C-terminus of the heavy chain. Once activated, the resulting rFVIIIa has a comparable structure to endogenous FVIIIa.

b. Recommended storage conditions for Novoeight®

Store Novoeight® in the original package in order to protect from light.

Store Novoeight® under refrigeration at a temperature of 36°F to 46°F (2°C to 8°C) for up to 30 months from the date of manufacture until the expiration date stated on the carton. During the 30 month shelf life, Novoeight® may be kept at room temperature up to 86°F (≤30°C) for no longer than 12 months or up to 104°F (≤40°C) for no longer than 3 months.

Use Novoeight® within 4 hours after reconstitution when stored at <86°F (30°C) or within 2 hours when stored between 86°F (30°C) to 104°F (40°C). Store the reconstituted product in the vial.

Discard any unused reconstituted product.

c. Excipients contained in the commercially available product

When reconstituted with the appropriate volume of diluent, the product contains the following components per mL: 18 mg sodium chloride, 1.5 mg L-histidine, 3 mg sucrose, 0.1 mg polysorbate 80, 0.055 mg L-methionine and 0.25 mg calcium chloride dihydrate. The product contains no preservative.

7 PHARMACOLOGIC CLASSIFICATION

a. Pharmacologic class

Novoeight® is a hemostatic.

b. Mechanism of action

Novoeight® temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis in hemophilia A.

c. Pharmacokinetic data

All pharmacokinetic studies with Novoeight® were conducted in previously treated patients with severe hemophilia A (factor VIII ≤1%). Analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

In a multi-center, multi-national, open-label, single dose pharmacokinetic study, 23 patients with severe hemophilia A received 50 international units/kg of Novoeight® intravenously. Two patients were below the age of 18 years (13 and 17 years). The pharmacokinetic parameters for 20 patients who completed the study are summarized in the following table.

Pharmacokinetics of Novoeight® in 20 adult and adolescent patients with hemophilia A

Parameters	Clotting Assay	Chromogenic Assay
	Mean (SD)	Mean (SD)
Incremental Recovery (IU/mL)/(IU/kg)	0.020 (0.002)	0.028 (0.006)
AUC (IU*h/mL)	14.2 (3.8)	18.7 (5.1)
CL (mL/h/kg)	3.74 (0.95)	2.87 (0.80)
t½ (h)	10.8 (4.9)	12.0 (9.3)
Vss (mL/kg)	53.4 (10.9)	44.3 (28.2)
C_{max} (IU/mL)	1.07 (0.16)	1.54 (0.29)
MRT (h)	15.4 (6.4)	16.4 (10.1)

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7 PHARMACOLOGIC CLASSIFICATION (cont'd)

In a separate pharmacokinetic study, 28 pediatric patients with severe hemophilia A (14 patients were below 6 years of age and 14 patients were between 6 to <12 years of age) received a single dose of 50 international units/kg Novoeight®. The pharmacokinetic parameters of Novoeight® are summarized in the following table for both age groups.

Pharmacokinetics of Novoeight® in 28 pediatric patients with hemophilia A

Parameters	Clotting Assay		Chromogenic Assay	
	0 to <6 years	6 to <12 years	0 to <6 years	6 to <12 years
	Mean (SD)		Mean (SD)	
Incremental Recovery (IU/mL)/(IU/kg)	0.018 (0.007)	0.020 (0.004)	0.022 (0.006)	0.025 (0.006)
AUC (IU*h/mL)	9.9 (4.1)	11.1 (3.7)	12.2 (4.4)	14.4 (3.5)
CL (mL/h/kg)	6.26 (3.73)	5.02 (1.67)	4.60 (1.75)	3.70 (1.00)
t½ (h)	7.7 (1.8)	8.0 (1.9)	10.0 (1.7)	9.4 (1.5)
Vss (mL/kg)	57.3 (26.8)	46.8 (10.6)	55.8 (23.7)	41.2 (6.0)
C_{max} (IU/mL)	1.00 (0.58)	1.07 (0.35)	1.12 (0.31)	1.25 (0.27)
MRT (h)	9.7 (2.5)	9.9 (2.6)	12.1 (1.9)	11.6 (2.3)

The pharmacokinetic parameters were comparable between younger (0 to <6 years) and older (6 to <12 years) children. The mean clearance of Novoeight® in younger and older children was 67% and 34% higher (based on per kg body weight) than in adults (3.74 mL/h/kg) when using the clotting assay, and 60% and 29% higher than in adults (2.87 mL/h/kg) when using the chromogenic assay. The mean half–life of Novoeight® in younger and older children was 29% and 26% shorter than in adults (10.8 hours) when using the clotting assay, and 16% and 21% shorter than in adults (12 hours) when using the chromogenic assay.

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novoeight®
Antihemophilic Factor (Recombinant)

8 DOSAGE RANGE

a. Dosage range and route of administration

Novoeight® is for intravenous injection after reconstitution only.

- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, on the location and extent of bleeding, and the patient's clinical condition. Careful monitoring of replacement therapy is necessary in cases of major surgery or life-threatening bleeding episodes.
- **Each vial of Novoeight® contains the labeled amount of recombinant factor VIII in international units (IU). One IU of factor VIII activity corresponds to the quantity of factor VIII in one milliliter of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that one IU of factor VIII per kg body weight raises the plasma factor VIII activity by two IU/dL. This relationship causes a factor of 0.5 to be present in the dose calculation formula shown below.**
- The required dosage can be determined using the following formula:
  Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL)
  The final dose calculated is expressed as IU
- Base the dose and frequency of Novoeight® on the individual clinical response. Patients may vary in their pharmacokinetic and clinical responses.

On-demand treatment and control of bleeding episodes

A guide for dosing Novoeight® for on-demand treatment and control of bleeding episodes is provided in the following table. Dose to maintain a plasma factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in this table.

Dosing for Control and Prevention of Bleeding Episodes

Type of Bleeding Episodes	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Early hemarthrosis, minor muscle or oral bleeding	20-40	12-24	At least 1 day until bleeding resolution is achieved
Moderate Muscle bleeding, bleeding into the oral cavity or mild head trauma	30-60	12-24	Until pain and acute disability are resolved (approximately 3-4 days)
Major Life or limb threatening hemorrhage, gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, fractures	60-100	8-24	Until resolution of bleed (approximately 7-10 days)

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8 DOSAGE RANGE (cont'd)

Perioperative management

A guide for dosing Novoeight® during surgery (perioperative management) is provided in the following table. Consider maintaining a plasma factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in this table.

Dosing for Perioperative Management

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

Routine prophylaxis

A guide for dosing Novoeight® for routine prophylaxis is included in the following table.

Dosing for Routine Prophylaxis

Patient Population	Factor VIII Dose Required (IU/kg)	Frequency of Doses (days)
Adults and adolescents (≥12 years)	20-50	3 times weekly
	20-40	Every other day
Children (<12 years)	25-60	3 times weekly
	25-50	Every other day

b. Use in specific populations

Pregnancy

As hemophilia mainly affects males, there are no adequate and well-controlled studies using Novoeight® in pregnant women to determine whether there is a drug-associated risk. Animal reproduction studies have not been conducted with Novoeight®. 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. There is no reliable data on the incidences specific to the hemophilia A population.

8 DOSAGE RANGE (cont'd)

Lactation

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

Pediatric use

Children have shorter half–life and lower recovery of factor VIII than adults. Because clearance (based on per kg body weight) has been demonstrated to be higher in the pediatric population, higher or more frequent dosing based on body weight may be needed.

Safety and efficacy studies have been performed in 146 pediatric patients <18 years of age. Ninety (including all 59 PUPs) of these subjects (62%) were <6 years of age, 32 (22%) were 6 to <12 years of age, and 24 (16%) were adolescents (12 to <18 years of age). Subjects during routine prophylaxis and treatment of bleeds received Novoeight® at the dose levels described previously in the Dosing for Routine Prophylaxis table. A total of 1290 bleeds in 127 subjects were treated with Novoeight®. The majority of the bleeds 1162 (90%) were of mild/moderate severity. Of these 1290 bleeds, 1140 (88%) were rated excellent or good in their response to treatment with Novoeight® and in 17 (1%) the response to treatment was unknown. A total of 1100 (85%) of the bleeds were resolved with one or two injections of Novoeight®. Routine prophylactic treatment has been shown to reduce joint bleeding.

Geriatric use

Clinical studies of Novoeight® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Obesity

In the extension trial, in six adult patients with body mass index (BMI) ≥ 30 kg/m^2, the AUC was higher and clearance lower than in patients with BMI < 30 kg/m^2. There is insufficient data to recommend specific dose adjustments for patients with BMI ≥ 30 kg/m^2. Adjust dose as necessary and per prescriber's discretion for patients with BMI ≥ 30 kg/m^2.

9 SAFETY

a. Adverse reactions, toxicities, and special precautions

Adverse reactions

The most frequently reported adverse reactions observed in clinical trials (≥1%) were injection site reactions, and pyrexia.

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9 SAFETY (cont'd)

Clinical trials 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 with rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the clinical development of Novoeight®, 301 male patients (242 previously treated patients (PTPs); exposed to a factor VIII-containing product for ≥150 days and 59 Previously Untreated Patients (PUPs) with severe hemophilia A (factor VIII level ≤1%) received at least one dose of Novoeight® as part of either routine prophylaxis, on-demand treatment of bleeding episodes, perioperative management of major and minor surgical, dental, or other invasive procedures, Immune Tolerance Induction (ITI) or pharmacokinetic evaluation of Novoeight® with more than 140,000 exposure days (corresponding to over 900 patient years). During prophylaxis treatment subjects received a median of 468 injections of Novoeight® (range 1-1317).

Immunogenicity

Subjects were monitored for neutralizing antibodies to factor VIII and binding antibodies to CHO and murine protein. No PTPs developed confirmed neutralizing antibodies to factor VIII. One twenty-two month old previously treated child had a positive neutralizing antibody to factor VIII of 1.3 BU in the Bethesda assay after 15 exposure days that was not confirmed when checked after 20 exposure days. *In vivo* recovery was normal for this child and no clinical adverse findings were observed. In the completed main phase of the clinical trial in PUPs, 24 of 56 (42.9%) patients developed inhibitors with a mean of 14.1 exposure days at the time of the first positive inhibitor test; 15 (26.8%) PUPs developed high titer (≥ 5 BU) inhibitors. High risk genetic mutations were identified in 91.7% of the overall inhibitors and 93.3% of the high titer inhibitors.

The inhibitor rate observed in PUPs is consistent with results observed in the SIPPET study and in patients at mutational risk of developing inhibitors. Overall, there is a favorable benefit-risk assessment for use of Novoeight® in all studied populations in the currently approved indications.

No patients developed *de novo* anti-murine antibodies. Nineteen subjects were positive for anti-Chinese hamster ovary (CHO) cell protein antibodies. Two of these subjects changed from anti-CHO negative to anti-CHO positive and 6 subjects changed from anti-CHO positive to anti-CHO negative. The remaining 11 subjects were either positive throughout the trials (n=6), negative at baseline and end-of trial but with transient positive samples (n=2), or positive at baseline and end-of trial but with negative samples in between (n=3). No clinical adverse findings were observed in any of these subjects.

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, it may be misleading to compare the incidence of antibodies to Novoeight® with the incidence of antibodies to other products.

9 SAFETY (cont'd)

b. Contraindications, Warnings and Precautions

Contraindications

Novoeight® is contraindicated in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components (including traces of hamster proteins).

Warnings and precautions

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylaxis, are possible with Novoeight®. Novoeight® contains trace amounts of hamster proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins. Early signs of hypersensitivity reactions that can progress to anaphylaxis include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if allergic- or anaphylactic-type reactions occur.

Neutralizing antibodies

Formation of neutralizing antibodies (inhibitors) to factor VIII can occur following administration of Novoeight®. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all factor VIII products. Inhibitors have been reported following administration of Novoeight® in PUPs. In the completed main phase of the clinical trial in PUPs, 24 of 56 (42.9%) patients developed inhibitors with a mean of 14.1 exposure days at the time of the first positive inhibitor test; 15 (26.8%) PUPs developed high titer (≥ 5 BU) inhibitors. Monitor all patients for the development of inhibitors by appropriate clinical observation and laboratory testing. If the expected plasma levels of factor VIII activity are not attained, or if bleeding is not controlled with an appropriate dose, perform testing for factor VIII inhibitors.

Monitoring laboratory tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay or the chromogenic substrate assay to confirm that adequate factor VIII levels have been achieved and maintained, when clinically indicated.
- Perform assay to determine if factor VIII inhibitor is present if expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with the expected dose of Novoeight®. Determine inhibitor levels in Bethesda Units.

c. List potential drug-drug interactions if deemed clinically significant

N/A

10 COMPARISONS

N/A

Indications and Usage

Novoeight® (antihemophilic factor, recombinant) is indicated for use in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes.

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Important Safety Information

Contraindications

- Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components, including hamster proteins

Warnings and Precautions

- Anaphylaxis and severe hypersensitivity reactions are possible. Patients may develop hypersensitivity to hamster proteins, which are present in trace amounts in the product. Should symptoms occur, discontinue Novoeight® and administer appropriate treatment
- Development of activity-neutralizing antibodies (inhibitors) may occur. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all factor VIII products. Inhibitors have been reported following administration of Novoeight® in PUPs. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform testing for factor VIII inhibitors

Adverse Reactions

- The most frequently reported adverse reactions (≥1%) were inhibitors in Previously Untreated Patients (PUPs), injection site reactions, and pyrexia.

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novoeight®
Antihemophilic Factor (Recombinant)

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