

novoeight®

Antihemophilic Factor (Recombinant)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Novoeight®, Antihemophilic Factor (Recombinant) For Intravenous Injection. Lyophilized Powder for Solution Initial U.S. Approval: 2013

INDICATIONS AND USAGE

Novoeight® is an Antihemophilic Factor (Recombinant) indicated for use in adults and children with hemophilia A for:

- Control and prevention of bleeding
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

Novoeight® is not indicated for the treatment of von Willebrand disease. (1)

DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only (2)

- Each vial of Novoeight® contains the labeled amount of recombinant Factor VIII in international units (IU). (2)
- The required dosage is determined using the following formula: $\text{Dosage Required (IU)} = \text{Body Weight (kg)} \times \text{Desired Factor VIII Increase (IU/dL or \% normal)} \times 0.5 \text{ (IU/kg per IU/dL)}$
- Frequency of Novoeight® administration is determined by the type of bleeding episode and the recommendation of the treating physician. (2.1)

DOSAGE FORMS AND STRENGTHS

Novoeight® is available as a lyophilized powder in single-use vials of 250, 500, 1000, 1500, 2000 and 3000 international units. (3)

CONTRAINDICATIONS

Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components, including hamster proteins. (4)

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. (5.1)
- Development of activity-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, 5.3)

ADVERSE REACTIONS

The most frequently reported adverse reactions ($\geq 0.5\%$) were injection site reactions, increased hepatic enzymes, and pyrexia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-844-303-4448 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pediatric Use: Clearance (based on per kg body weight) is higher in children. Higher or more frequent dosing may be needed. (8.4)

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

11/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Novoeight®, Antihemophilic Factor (Recombinant), is indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency or classic hemophilia) for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

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

2 DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only.

2.1 Dose

• 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:

$$\text{Dosage (IU)} = \text{Body Weight (kg)} \times \text{Desired Factor VIII Increase (IU/dL or \% normal)} \times 0.5$$

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.

Control and Prevention of Bleeding Episodes

A guide for dosing Novoeight® for the control and prevention of bleeding episodes is provided in Table 1. 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 Table 1.

Table 1: 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)

Perioperative Management

A guide for dosing Novoeight® during surgery (perioperative management) is provided in Table 2. Consideration should be given to maintaining a plasma factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 2.

Table 2: 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, intra-abdominal, 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 below in Table 3.

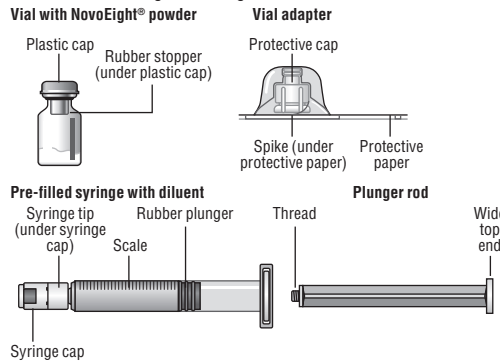
Table 3: Dosing for Routine Prophylaxis

Patient Population	Factor VIII Dose Required (IU/kg)	Frequency of Doses
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

2.2 Preparation and Reconstitution

- Always wash hands and ensure that the area is clean before performing the procedures.
- Use aseptic technique during the reconstitution procedures.
- If the patient uses more than one vial of Novoeight® per injection, reconstitute each vial according to the following instructions.

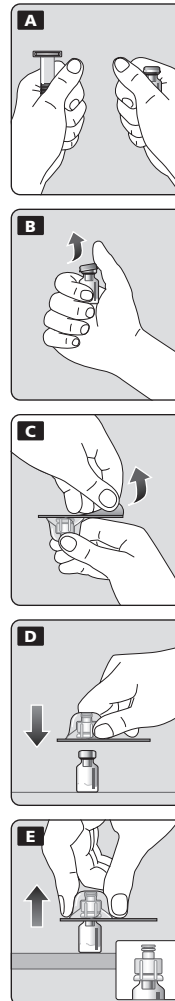
Overview of Novoeight® Package



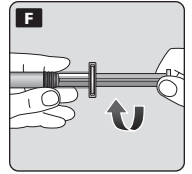
The instructions below serve as a general guideline for preparation and reconstitution of Novoeight®. For full instructions, refer to the FDA-approved patient information and Instructions for Use.

Reconstitution

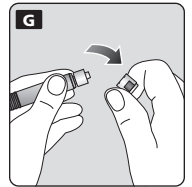
1. Bring the Novoeight® vial and the pre-filled diluent syringe to room temperature.
2. Remove the plastic cap from the Novoeight® vial.
3. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to dry prior to use.
4. Remove the protective paper from the vial adapter. **Do not remove the vial adapter from the protective cap.**
5. Place the vial on a flat and solid surface. While holding the protective cap, place the vial adapter over the Novoeight® vial and press down firmly on the protective cap until the vial adapter spike penetrates the rubber stopper.
6. Remove the protective cap from the vial adapter.



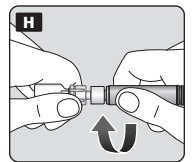
7. Grasp the plunger rod as shown in the diagram. Attach the plunger rod to the syringe by holding the plunger rod by the wide top end. Turn the plunger rod clockwise into the rubber plunger inside the pre-filled diluent syringe until resistance is felt.



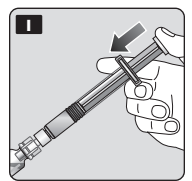
8. Break off the syringe cap from the pre-filled diluent syringe by snapping the perforation of the cap.



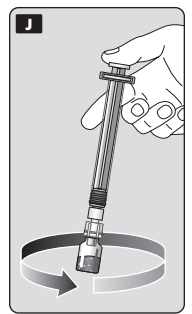
9. Connect the pre-filled diluent syringe to the vial adapter by turning it clockwise until it is secured.



10. Push the plunger rod to slowly inject all the diluent into the vial.



11. Without removing the syringe, gently swirl the Novoeight® vial until all of the powder is dissolved. The reconstituted solution should be inspected visually for particulate matter before administration. Do not use if particulate matter or discoloration is observed.



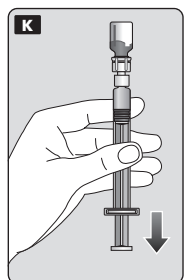
12. Use the Novoeight® solution immediately. If not, store the solution in the vial with the vial adapter and the syringe attached, at room temperature ≤ 86°F (30°C) for no longer than 4 hours.

2.3 Administration

For intravenous injection only.

- Accidental needle stick with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single-use.
- Inspect the reconstituted Novoeight® solution visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.
- Do not administer Novoeight® in the same tubing or container with other medicinal products.

1. Invert the Novoeight® vial and slowly draw the solution into the syringe.



2. Detach the syringe from the vial adapter by turning the syringe counterclockwise.
3. Attach the syringe to the luer end of an infusion needle set.
4. Inject the reconstituted Novoeight® intravenously slowly over 2 to 5 minutes.
5. After injection, safely dispose of the syringe with the infusion set, the vial with the vial adapter, any unused Novoeight® and other waste materials.

Caution:

The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector.

Some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave® /MicroClave®, InVision-Plus®, InVision-Plus CS®, Invision-Plus Junior®, Bionector®), and their use can damage the connector and affect administration. To administer Novoeight® through incompatible needleless connectors, withdraw the reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe.

If you encounter any problems with attaching the pre-filled sodium chloride diluent syringe to any Luer-lock compatible device, please contact Novo Nordisk at (844) 303-4448.

3 DOSAGE FORMS AND STRENGTHS

Novoeight® is available as a white lyophilized powder in single-use vials containing 250, 500, 1000, 1500, 2000 and 3000 international units per vial.

After reconstitution with 4 mL of 0.9% sodium chloride solution, each mL of reconstituted solution contains approximately 62.5, 125, 250, 375, 500 or 750 international units of Novoeight®, respectively.

4 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).

5 WARNINGS AND PRECAUTIONS**5.1 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.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to factor VIII can occur following administration of Novoeight®. 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.

5.3 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. [See *Dosage and Administration (2.1)*]
- 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.

6 ADVERSE REACTIONS

The most frequently reported adverse reactions ($\geq 0.5\%$) were injection site reactions, increased hepatic enzymes, and pyrexia.

6.1 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 to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the clinical development of Novoeight®, 214 male previously treated patients (PTPs; exposed to a factor VIII-containing product for ≥ 150 days) with severe hemophilia A (factor VIII level $\leq 1\%$) 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, or pharmacokinetic evaluation of Novoeight®. Thirty-one subjects (14%) were <6 years of age, 32 (15%) were 6 to <12 years of age, 16 (7%) were adolescents (12 to <16 years of age), and 135 (63%) were adults (16 years of age and older). The subjects received a total of 33,272 injections with a median of 127 injections of Novoeight® (range 1-442) per subject, and had a total of 32,929 exposure days during prevention and treatment of bleeds.

The most frequently reported adverse reactions in previously treated patients was injection site reactions (2.3%), increased hepatic enzymes (1.4%), and pyrexia (0.9%).

6.2 Immunogenicity

Subjects were monitored for neutralizing antibodies to factor VIII and binding antibodies to CHO and murine protein. No subjects developed confirmed neutralizing antibodies to factor VIII. One twenty-two month old 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.

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.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Risk Summary**

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.

8.2 Lactation**Risk Summary**

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.

8.4 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. [See *Clinical Pharmacology (12.3)*]

Safety and efficacy studies have been performed in 79 previously treated pediatric patients <16 years of age. Thirty-one of these subjects (39%) were <6 years of age, 32 (41%) were 6 to <12 years of age, and 16 (20%) were adolescents (12 to <16 years of age). All subjects received preventive treatment every other day or three times weekly at the dose levels described in Table 3. A total of 244 bleeds in 54 subjects were treated with Novoeight®. The majority of the bleeds (91%) were of mild/moderate severity, 41% of the bleeds were spontaneous and 58% of the bleeds were localized in joints. Of these 244 bleeds, 210 (86%) were rated excellent or good in their response to treatment with Novoeight® and 3 (1.2%) were rated as having no response. A total of 222 (91%) of the bleeds were resolved with one or two injections of Novoeight®. Routine prophylactic treatment has been shown to reduce joint bleeding. [See *Clinical Studies (14)*]

8.5 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.

11 DESCRIPTION

Novoeight® is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (0.9% sodium chloride). Novoeight® is available in single-dose vials that contain nominally 250, 500, 1000, 1500, 2000 or 3000 international units (IU) per vial. 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. Each vial of Novoeight® is labeled with the actual rFVIII activity expressed in IU determined by the one-stage clotting assay, using a reference material calibrated against a World Health

Organization (WHO) International Standard for FVIII Concentrates. One IU, as defined by the WHO standard for human FVIII, is approximately equal to the level of FVIII activity in 1 mL of fresh pooled human plasma. The specific activity of Novoeight® is approximately 8340 IU per milligram of protein.

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 the endogenous FVIIIa.

Novoeight® is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line which secretes rFVIII into the cell culture medium. The rFVIII protein is purified using a series of chromatography steps, one of which is the use of an immunoaffinity column in which a monoclonal antibody, produced in CHO cells and directed against FVIII, is employed to selectively isolate the rFVIII from the medium. The production process includes two dedicated viral clearance steps - a detergent treatment step for inactivation and a 20-nm filtration step for removal of viruses. No additives of human or animal origin are used in the cell culture, purification and formulation of Novoeight®.

12 CLINICAL PHARMACOLOGY**12.1 Mechanism of Action**

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

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Determination of aPTT is a conventional *in vitro* assay for the biological activity of FVIII. Treatment with Novoeight® normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

All pharmacokinetic studies with Novoeight® were conducted in previously treated patients with severe hemophilia A (factor VIII $\leq 1\%$). 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 Table 4.

Table 4: 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* <i>h</i> /mL)	14.2 (3.8)	18.7 (5.1)
CL (mL/h/kg)	3.74 (0.95)	2.87 (0.80)
<i>t</i> _{1/2} (h)	10.8 (4.9)	12.0 (9.3)
V _{ss} (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)

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 Table 5 for both age groups.

Table 5: 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* <i>h</i> /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)
<i>t</i> _{1/2} (h)	7.7 (1.8)	8.0 (1.9)	10.0 (1.7)	9.4 (1.5)
V _{ss} (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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Novoeight®, or studies to determine the effects of Novoeight® on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of Novoeight® was completed, and no carcinogenic risk from product use has been identified.

14 CLINICAL STUDIES

Three multi-center, open-label, non-controlled trials have been conducted to evaluate the safety and efficacy of Novoeight® in the control and prevention of breakthrough bleeds, routine prophylaxis and perioperative management in previously treated patients with hemophilia A. The analysis included 213 exposed subjects: 150 adolescents or adult subjects from the age of 12 years (≥150 exposure days) and 63 pediatric subjects below the age of 12 years (≥50 exposure days). Immunocompetent patients with severe hemophilia A (factor VIII activity ≤1%) and no history of FVIII inhibitors were eligible for the trials. A total of 187 out of 213 subjects continued in the safety extension trial. All subjects received preventive treatment every other day or three times weekly at the dose levels described in Table 3. Breakthrough bleeds were treated at the investigator's discretion aiming for a FVIII activity level above 0.5 IU/mL. Treatment during surgery was at the investigator's discretion aiming for a FVIII trough activity level above 0.5 IU/mL.

Control and Prevention of Bleeding Episodes

A total of 991 bleeds in 158 subjects were treated with Novoeight®. The majority of the bleeds (89%) were of mild/moderate severity, 62% of the bleeds were spontaneous and 72% of the bleeds were localized in joints.

An overall assessment of efficacy was performed by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using a four-point scale of excellent, good, moderate, or none. If the hemostatic response was rated as "excellent" or "good", the treatment of the bleed was considered a success. If the hemostatic response was rated as "moderate or none" the treatment was considered a failure. Of these 991 bleeds, 838 (84%) were rated excellent or good in their response to treatment with Novoeight® and 17 (1.7%) were rated as having no response. A total of 898 (91%) of the bleeds were resolved with one or two injections of Novoeight®.

Clinical trials of Novoeight® included 79 previously treated patients between one to 16 years of age. The hemostatic efficacy in treatment of bleeds was rated as either "excellent" or "good" on a pre-specified rating scale for 86% of the 244 bleeds reported in 54 subjects.

Routine Prophylaxis

All 213 subjects received Novoeight® for routine prophylaxis. The prophylactic regimen for the 150 adolescent and adult subjects consisted of 20-40 IU/kg every other day or 20-50 IU/kg three times per week. The prophylactic regimen for the 63 pediatric subjects consisted of 25-50 IU/kg every other day or 25-60 IU/kg three times per week. The majority of the subjects (>80%) were treated with the three times per week regimen.

The median annualized bleeding rates are provided in Table 6.

Table 6: Annualized Bleeding Rate in All Patients

	Small children 0 – <6 years	Older children 6 – <12 years	Adolescents 12 – <16 years	Adults ≥16 years	Total
Annualized bleeding rate (median) (IQR)	2.9 (6.3)	4.1 (8.6)	4.4 (6.9)	3.1 (5.6)	3.1 (7.3)

A total of 68 subjects were treated with Novoeight® for at least 12 months, including seven subjects <12 years. The ABR was similar for the subjects treated for 12 months when compared to the ABR for the total trial population.

Perioperative Management

A total of 11 surgeries were performed in 11 previously treated subjects between 14 and 55 years of age, of which 10 were major

surgeries (five synovectomies, two total hip arthroplasties, one knee replacement, arthroscopy, and circumcision), and one was minor (tooth extraction).

The investigator's ratings of intra- and post-operative quality of hemostasis for these subjects were "excellent" or "good" for all cases.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- Novoeight® is supplied in packages comprised of a single-use vial containing nominally 250, 500, 1000, 1500, 2000, or 3000 international units (IU) of FVIII potency, a MixPro® pre-filled diluent syringe containing 0.9% sodium chloride solution, and sterile vial adapter with 25 micrometer filter, which serves as a needleless reconstitution device.
- The actual amount of FVIII potency in IU is stated on each carton and vial.

Presentation (Nominal Product Strength)	Carton NDC Number	Components
250 International Units	NDC 0169 7825 01	
500 International Units	NDC 0169 7850 01	
1000 International Units	NDC 0169 7810 01	
1500 International Units	NDC 0169 7815 01	
2000 International Units	NDC 0169 7820 01	
3000 International Units	NDC 0169 7830 01	

- The Novoeight® vials are made of glass, closed with a chlorobutyl rubber stopper not made with natural rubber latex, and sealed with an aluminum cap.
- The pre-filled diluent syringes are made of glass, with a siliconised bromobutyl rubber plunger not made with natural rubber latex.
- The closed vials and pre-filled diluent syringes are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Storage and Handling

- 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 label. Within the 30-month period, Novoeight® may also be stored at room temperature not to exceed 86°F (30°C) for up to twelve (12) months.
- If you choose to store Novoeight® at room temperature, clearly record the date when the product was removed from the refrigerator in the space provided on the outer carton. The total time of storage at room temperature should not exceed 12 months. Do not return the product to the refrigerator.
- Do not use Novoeight® after the end of the 12-month period at room temperature storage, or after the expiration date stated on the vial, whichever occurs earlier.
- Do not freeze Novoeight®.

- Use Novoeight® within 4 hours after reconstitution when stored at room temperature. Store the reconstituted product in the vial.
- Discard any unused reconstituted product stored at room temperature for more than 4 hours.

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Allergic-type hypersensitivity reactions or anaphylaxis are possible with use of Novoeight®. Inform patients of the early signs of hypersensitivity reactions including rash, hives, itching, facial swelling, tightness of the chest and wheezing. Advise patients to discontinue use of Novoeight® immediately and contact their physician, and go to the emergency department if these symptoms occur.
- Advise patients to contact their physician or treatment facility for further treatment and/or assessment if they experience a lack of a 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 Novoeight® based on their current treatment regimen.
- Advise patients to follow the recommendations regarding proper sharps disposal provided in the FDA-approved Instructions for Use.

Version: 5

License Number: 1261

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Patent Information: <http://novonordisk-us.com/patients/products/product-patents.html>

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For information contact:

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800 Scudders Mill Road
Plainsboro, NJ 08536, USA
1-844-30-EIGHT

Manufactured by:
Novo Nordisk A/S
Novo Allé, DK-2880 Bagsvaerd
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USA16HDM05031 12/2016



Patient Product Information

Novoeight® (Nō-vō-eyt)

Antihemophilic Factor (Recombinant)

Read the Patient Product Information and the Instructions For Use that come with Novoeight® before you start taking this medicine and each time you get a refill. There may be new information.

This Patient Product Information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have questions about Novoeight® after reading this information, ask your healthcare provider.

What is the most important information I need to know about Novoeight®?

Do not attempt to do an infusion yourself unless you have been taught how by your healthcare provider or hemophilia center.

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

What is Novoeight®?

Novoeight® is an injectable medicine used to replace clotting factor VIII that is missing in patients with hemophilia A. Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

Novoeight® is used to control and prevent bleeding in people with hemophilia A.

Your healthcare provider may give you Novoeight® when you have surgery.

Novoeight® is not used to treat von Willebrand Disease.

Who should not use Novoeight®?

You should not use Novoeight® if you

- are allergic to factor VIII or any of the other ingredients of Novoeight
- if you are allergic to hamster proteins

Tell your healthcare provider if you are pregnant or nursing because Novoeight® might not be right for you.

What should I tell my healthcare provider before I use Novoeight®?

You should tell your healthcare provider if you

- Have or have had any medical conditions.
- Take any medicines, including non-prescription medicines and dietary supplements.
- Are nursing.
- Are pregnant or planning to become pregnant.
- Have been told that you have inhibitors to factor VIII.

How should I use Novoeight®?

Treatment with Novoeight® should be started by a healthcare provider who is experienced in the care of patients with hemophilia A.

Novoeight® is given as an injection into the vein.

You may infuse Novoeight® at a hemophilia treatment center, at your healthcare provider's office or in your home. You should be trained on how to do infusions by your hemophilia treatment center or healthcare provider. Many people with hemophilia A learn to infuse the medicine by themselves or with the help of a family member.

Your healthcare provider will tell you how much Novoeight® to use based on your weight, the severity of your hemophilia A, and where you are bleeding.

You may need to have blood tests done after getting Novoeight® to be sure that your blood level of factor VIII is high enough to clot your blood. This is particularly important if you are having major surgery.

Your healthcare provider will calculate your dose of Novoeight® (in international units, IU) depending on your condition and body weight.

Call your healthcare provider right away if your bleeding does not stop after taking Novoeight®.

Development of factor VIII inhibitors

Your body can also make antibodies called "inhibitors" against Novoeight®, which may stop Novoeight® from working properly.

If your bleeding is not adequately controlled, it could be due to the development of factor VIII inhibitors. This should be checked by your healthcare provider. You might need a higher dose of Novoeight® or even a different product to control bleeding. Do not increase the total dose of Novoeight® to control your bleeding without consulting your healthcare provider.

Use in children

Novoeight® can be used in children. Your healthcare provider will decide the dose of Novoeight® you will receive.

If you forget to use Novoeight®

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injections as scheduled and continue as advised by your healthcare provider.

If you stop using Novoeight®

If you stop using Novoeight® you are not protected against bleeding. Do not stop using Novoeight® without consulting your healthcare provider.

If you have any further questions on the use of this product, ask your healthcare provider.

What if I take too much Novoeight®?

Always take Novoeight® exactly as your healthcare provider has told you. You should check with your healthcare provider if you are not sure. If you inject more Novoeight® than recommended, tell your healthcare provider as soon as possible.

What are the possible side effects of Novoeight®?

Common Side Effects Include:

- swelling or itching at the location of injection
- changes in liver tests
- fever

Other Possible Side Effects:

You could have an allergic reaction to coagulation factor VIII products. **Call your healthcare provider right away and stop treatment if you get any of the following signs of an allergic reaction:**

- rashes including hives
- difficulty breathing, shortness of breath or wheezing
- tightness of the chest or throat, difficulty swallowing
- swelling of the lips and tongue
- light-headedness, dizziness or loss of consciousness
- pale and cold skin, fast heart beat which may be signs of low blood pressure
- red or swollen face or hands

These are not all of the possible side effects from Novoeight®. Ask your healthcare provider for more information. You are encouraged to report side effects to FDA at 1-800-FDA-1088.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

What are the Novoeight® dosage strengths?

Novoeight® comes in six different dosage strengths. The actual number of international units (IU) of factor VIII in the vial will be imprinted on the label and on the box. The six different strengths are as follows:

- Dosage strength of approximately 250 IU per vial
- Dosage strength of approximately 500 IU per vial
- Dosage strength of approximately 1000 IU per vial
- Dosage strength of approximately 1500 IU per vial
- Dosage strength of approximately 2000 IU per vial
- Dosage strength of approximately 3000 IU per vial

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your doctor.

How should I store Novoeight®?

Prior to Reconstitution:

Store in original package in order to protect from light. Do not freeze Novoeight®.

Novoeight® vials can be stored in the refrigerator (36°F to 46°F [2°C to 8°C]) for up to 30 months or up to the expiration date, or at room temperature (up to 86°F [30°C]) for a single period not exceeding 12 months.

If you choose to store Novoeight® at room temperature:

- Note the date that the product is removed from refrigeration on the box.
- The total time of storage at room temperature should not exceed 12 months. Do not return the product to the refrigerator.
- Do not use after 12 months from this date or the expiration date listed on the vial, whichever is earlier.

Do not use this medicine after the expiration date which is on the outer carton and the vial.

The expiration date refers to the last day of that month.

After Reconstitution (mixing the dry powder in the vial with the diluent):

The reconstituted Novoeight® should appear clear to slightly unclear without particles.

The reconstituted Novoeight® should be used immediately.

If you cannot use the Novoeight® immediately after it is mixed, it should be used within 4 hours when stored at ≤ 86°F (30°C). Store the reconstituted product in the vial.

Keep this medicine out of the sight and out of reach of children.

What else should I know about Novoeight® and hemophilia A?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use Novoeight® for a condition for which it is not prescribed. Do not share Novoeight® with other people, even if they have the same symptoms that you have.

For more information about Novoeight®, please call Novo Nordisk at 1-844-30-EIGHT.

Revised: 11/2016

Novoeight® is a registered trademark of Novo Nordisk Health Care AG.

Patent Information: <http://novonordisk-us.com/patients/products/product-patents.html>

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Manufactured by:
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USA16HDM05031 12/2016



Instructions on how to use Novoeight® MixPro®

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NOVOEIGHT®.

Novoeight® is supplied as a powder. Before injection (administration) it must be mixed (reconstituted) with the liquid diluent supplied in the syringe. The liquid diluent is a sodium chloride solution. The mixed Novoeight® must be injected into your vein (intravenous injection). The equipment in this package is designed to mix and inject Novoeight®.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads, and bandages.

⚠ **Don't use the equipment without proper training from your doctor or nurse.**

Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medication directly into the veins, it is important to **use a clean and germ free (aseptic) technique**. Improper technique can introduce germs that can infect the blood.

Don't open the equipment until you are ready to use it.

Don't use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Don't use the equipment if it is expired. Use a new package instead. The expiration date is printed on the outer carton and on the vial, the vial adapter and the pre-filled syringe.

Don't use the equipment if you suspect it is contaminated. Use a new package instead.

Don't dispose of any of the items until after you have injected the mixed solution.

The equipment is for single use only.

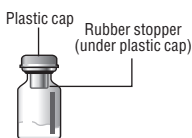
Content

The package contains:

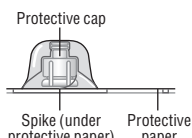
- Vial with Novoeight® powder
- Vial adapter
- Pre-filled syringe with diluent
- Plunger rod (placed under the syringe)

Overview

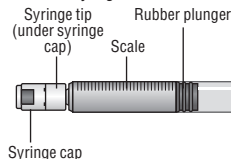
Vial with NovoEight® powder



Vial adapter



Pre-filled syringe with diluent

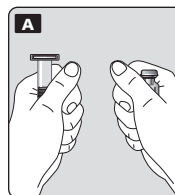


Plunger rod

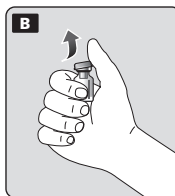


1. Prepare the vial and the syringe

- **Take out the number of Novoeight® packages you need.**
- **Check the expiry date.**
- **Check the name and the color of the package**, to make sure it contains the correct product.
- **Wash your hands** and dry them properly using a clean towel or air dry.
- Take the vial, the vial adapter and the pre-filled syringe out of the carton. **Leave the plunger rod untouched in the carton.**
- **Bring the vial and the pre-filled syringe to room temperature.** You can do this by holding them in your hands until they feel as warm as your hands.



- **Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, don't use the vial.**
- **Wipe the rubber stopper with a sterile alcohol swab** and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible.
- **Don't touch the rubber stopper with your fingers** as this can transfer germs.

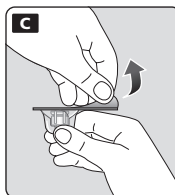


2. Attach the vial adapter

- **Remove the protective paper** from the vial adapter. **Don't take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter germs from your fingers can be transferred.

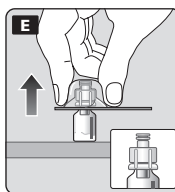
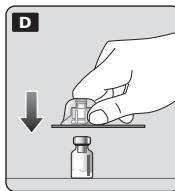
If the protective paper is not fully sealed or if it is broken, don't use the vial adapter.

- **Place the vial on a flat and solid surface.**
- **Turn over the protective cap**, and snap the vial adapter onto the vial. **Once attached, don't remove the vial adapter from the vial.**



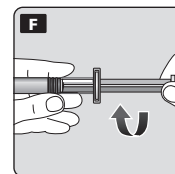
- Lightly **squeeze the protective cap** with your thumb and index finger as shown. **Remove the protective cap** from the vial adapter.

Don't lift the vial adapter from the vial when removing the protective cap.

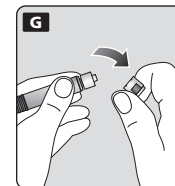


3. Attach the plunger rod and the syringe

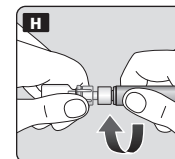
- Grasp the plunger rod by the wide top end and take it out of the carton. **Don't touch the sides or the thread of the plunger rod.** If you touch the sides or the thread germs from your fingers can be transferred.
- **Immediately** connect the plunger rod to the syringe by turning it clockwise into the rubber plunger inside the pre-filled syringe until resistance is felt.



- **Remove the syringe cap** from the pre-filled syringe by bending it down until the perforation breaks. **Don't touch the syringe tip under the syringe cap.** If you touch the syringe tip germs from your fingers can be transferred.
- **If the syringe cap is loose or missing, don't use the pre-filled syringe.**

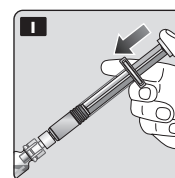


- **Screw the pre-filled syringe securely** onto the vial adapter until resistance is felt.

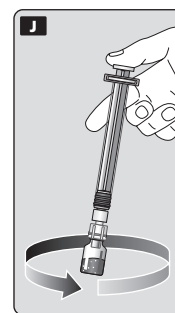


4. Mix the powder with the diluent

- **Hold the pre-filled syringe slightly tilted** with the vial pointing downwards.
- **Push the plunger rod** to inject all the diluent into the vial.



- **Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Don't shake the vial as this will cause foaming.**
- **Check the mixed solution.** It must be clear to slightly opalescent (slightly unclear). **If you notice visible particles or discoloration, don't use it.** Use a new package instead.



Novoeight® is recommended to be used immediately after it is mixed. This is because if left, the medicine may no longer be sterile and could cause infections.

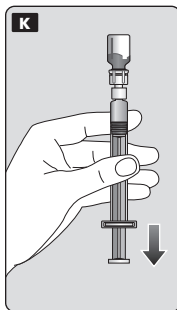
If you cannot use the mixed Novoeight® solution immediately, it should be used within 4 hours when stored at ≤ 86°F (30°C). Store the reconstituted product in the vial.

Do not freeze mixed Novoeight® solution or store it in syringes.

Keep mixed Novoeight® solution out of direct light.

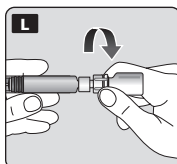
ⓘ If your dose requires more than one vial, repeat step A to J with additional vials, vial adapters and pre-filled syringes until you have reached your required dose.

- **Keep the plunger rod pushed completely in.**
- **Turn the syringe** with the vial upside down.
- **Stop pushing the plunger rod and let it move back** on its own while the mixed solution fills the syringe.
- **Pull the plunger rod slightly downwards** to draw the mixed solution into the syringe.
- **In case you only need part of the entire vial, use the scale on the syringe to see how much mixed solution you withdraw, as instructed by your doctor or nurse.**
- While holding the vial upside down, **tap the syringe gently** to let any air bubbles rise to the top.
- **Push the plunger rod slowly** until all air bubbles are gone.



- **Unscrew the vial adapter** with the vial.

Don't touch the syringe tip. If you touch the syringe tip germs from your fingers can be transferred.



Caution: The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector.

Some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave®/MicroClave®, InVision-Plus®, InVision-Plus CS®, Invision-Plus Junior®, Bionector®).

The use of these needleless connectors can damage the connector and affect administration.

To administer Novoeight® through incompatible needleless connectors, withdraw reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe.

If you have encountered any problems with attaching the pre-filled sodium chloride diluent syringe to any Luer-lock compatible device, please contact Novo Nordisk at (844) 303-4448.

5. Inject the mixed solution

Novoeight® is now ready to inject into your vein.

- Do not mix Novoeight® with any other intravenous infusions or medications.
- Inject the mixed solution slowly over 2 to 5 minutes as instructed by your doctor or nurse.

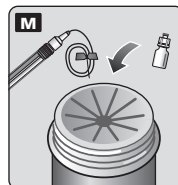
Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or subcutaneous port:

- Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and central venous access device in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 mL plastic syringe for withdrawal of the mixed solution and injection.
- If necessary, use 0.9% Sodium Chloride Injection, USP to flush the CVAD line before or after Novoeight® injection.

The peel-off label found on the Novoeight® vial can be used to record the lot number.

Disposal

- **After injection, safely dispose** of all unused Novoeight® solution, the syringe with the infusion set, the vial with the vial adapter, and other waste materials in an appropriate container for throwing away medical waste.
- Don't throw it out with the ordinary household trash.



Don't disassemble the vial and vial adapter before disposal.

Don't reuse the equipment.

Important information

Contact your healthcare provider or local hemophilia treatment center if you experience any problems.

For full Prescribing Information please read the other insert included in this package.

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Revised: 11/2016

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