P&T Summary

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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novo nordisk®

Section IA: Background on Hemophilia

Hemophilia: Disease State Overview

Hemophilia is a hereditary disorder that prevents blood from clotting normally, resulting in excessive, uncontrolled bleeding. The disease can be classified as mild, moderate, or severe depending on the level of factor deficiency.[1] As such, the age of diagnosis is tied to severity of disease, as symptoms will present at a younger age for patients with greater coagulant factor deficiency.[2] The median ages of diagnosis for patients with mild, moderate, and severe hemophilia are 36 months, 8 months, and 1 month, respectively.[2] Symptoms of hemophilia may include increased bruising, bleeding into muscles and joints, spontaneous bleeding with no clear cause, and prolonged bleeding after an injury.[1]

Pathophysiology

Coagulation is a critical, highly regulated process. When blood vessel walls are damaged, the surrounding cells will secrete procoagulant factors.[3] These proteins serve to activate platelets that go to the site of injury. Activated platelets serve as a scaffold for building a clot that prevents excessive blood loss, and they help to synthesize thrombin, a critical protein for clot formation.[3]

In hemophilia, there is a deficiency of 1 of 2 coagulation factors used to produce thrombin, resulting in decreased thrombin generation and clot formation. Deficiencies in factor VIII and factor IX lead to hemophilia type A and B, respectively.[1,4] In either case, the amplification of thrombin is suppressed, mitigating clot formation.[4] About 70% of patients with hemophilia inherited the condition.[5] Another 30% of patients, however, present without a family history of hemophilia; these patients develop hemophilia through spontaneous mutation.[4]

Epidemiology of Hemophilia in the United States

There are 2 main subtypes of hemophilia: hemophilia A, which is a deficiency of coagulation factor VIII, and hemophilia B, which is a deficiency of coagulation factor IX.[1] The incidence of hemophilia A is 1 in 5,000 male births, and the incidence of hemophilia B is 1 in 30,000 male births.[4] Hemophilia is seen predominantly in males, as it is inherited in an X-linked recessive fashion.[4] The Centers for Disease Control and Prevention estimates there are approximately [30,000] people with hemophilia in the United States.[6]

Morbidity and mortality are significant problems for patients with hemophilia.

In the past, patients with severe hemophilia had a median life expectancy of approximately 64 years.[7,8] Additionally, patients with a lack of comprehensive care services may also have a lower life expectancy.[9] Patients with uncontrolled hemophilia often suffer from pain due to bleeding into muscle tissue or joints that results in swelling and stiffness.[1] Bleeding in other sites like the head, throat, or gastrointestinal tract can become life-threatening.[1] Morbidity associated with bleeding into the joints is a major cause of concern for patients with hemophilia.[10] There is a tendency for joint bleeding to occur repeatedly in the same site, also known as the target joint.[4] The damage resulting from repeated bleeds in a target joint can result in progression to hemophilic arthropathy.[1]

Physical symptoms of hemophilia can have a large impact on patients.

Numerous physical symptoms can contribute to patients' ability to function normally. Bleeding into target joints represents the majority of bleeding episodes, and repeated bleeding can result in tissue damage, physical deformity, and significant chronic pain.[1,4] Progressive degeneration of muscle tissue and bones can lead to loss of mobility and range of motion.[1]

Recent data have shown that hemophilia has a significant negative impact on a person's well-being. The Hemophilia Utilization Group Study – Part Va (HUGS-Va), which observed only patients in the United States, found that overall physical abilities were significantly impaired as severity of hemophilia increased.[11]

Hemophilia is a managed chronic disease.

Advances in hemophilia management in recent decades have led to a near normal life expectancy in patients with hemophilia.[9,12] However, hemophilia still leads to a greater risk of complications later in life, as well as, age-related co-morbidities. In addition, aging patients treated before the date viral inactivation was introduced to the manufacture of injectable therapies for hemophilia (1985) have a high prevalence of hepatitis C infection, increasing their risk of liver failure.[13] In one study conducted between 1998 and 2011, 32% of hemophilia-related deaths were related to liver disease; HIV-related causes accounted for another 18.5% of deaths in this time period.[14]

Hemophilia places a substantial economic burden on health care payers, patients/caregivers, and society as a whole. There are many direct medical costs associated with hemophilia including hospitalization, outpatient visits, laboratory tests, and drug costs.[15]

Treatment Options

Hemorrhage in patients with hemophilia A can be treated by replacing factor VIII.[1] Factor VIII is available in several forms, including products purified from plasma and recombinant products.[1] Recombinant therapies have gained favor as the standard of care due to a lower risk of viral contamination.[16] The National Hemophilia Foundation's Medical and Scientific Advisory Council (NHF MASAC) recommends that recombinant products be considered as a first-line treatment option for patients with hemophilia A.[16] Additionally, there are alternative treatment options, including a bispecific antibody mimicking factor VIII that can be used as a prophylactic treatment in people with hemophilia A.[16]

For many patients, factor replacement is effective when used as needed for bleeding episodes. Alternatively, prophylactic administration of factor VIII can help to prevent bleeding episodes and joint damage associated with hemophilia.[1] Prophylaxis is important for patients with severe disease in order to help prevent joint bleeding.[1]

Section IB: Product Introduction

Novoeight®: A Third-Generation Recombinant Factor VIII Treatment

Novoeight® is a recombinant, B-domain truncated factor VIII indicated for treatment of adults and children with hemophilia A.[17] Novoeight® is purified through several steps, including immunoaffinity chromatography, anionic exchange chromatography, and gel filtration.[18] Two viral clearance steps, detergent treatment and filtration through a 20-nm pore, are also part of the purification process for Novoeight®.[17]

Vials of Novoeight® in lyophilized powder form can be stored for no longer than 12 months at room temperature up to 86°F (30°C) or for no longer than 3 months at up to 104°F (≤40°C).[17] Please see Prescribing Information for complete storage instructions.

Factor VIII inhibitors are antibodies produced by patients that can bind and counteract factor VIII, making treatment of bleeding episodes more challenging.[4] In one of the largest clinical trials of SHL rFVIII to date, there were no cases of confirmed inhibitors to factor VIII in 242 previously treated patients who switched to Novoeight®. The median annualized bleeding rate for all patients in the study was 3.67 bleeds per year.[17]

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.[17] 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.[17]

Section II:
Review of Prescribing Information for Novoeight®[17]

1 INDICATIONS AND USAGE

Novoeight®, Antihemophilic Factor (Recombinant), is a human antihemophilic factor (human blood coagulation factor VIII (FVIII)) indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to 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:

  Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 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 *[See Clinical Pharmacology (12.3)]*.

2.1 Dose (cont'd)

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 Table 1. Dose to maintain 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 On-demand Treatment and Control 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, intraabdominal 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. Consider 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, 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)

2.1 Dose (cont'd)

Routine Prophylaxis

A guide for dosing Novoeight® for routine prophylaxis is included below in Table 3.

Table 3: Dosing for Routine Prophylaxis

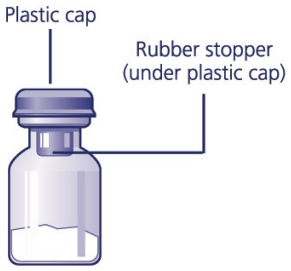
Patient Population	Factor VIII Dose Required (IU/kg)	Frequency of Doses
Adults and adolescents (≥12 years)	20-50	3 times weekly
	20-40	Every other day
Children (<12 years)	25-60	3 times weekly
	25-50	Every other day

2.2 Preparation and Reconstitution

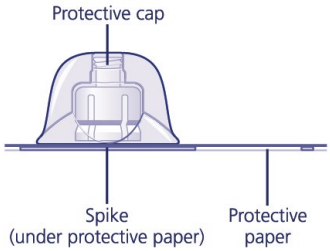
- Always wash hands and ensure that the area is clean before performing the procedures.
- Use aseptic technique during the reconstitution procedures.
- If the dose requires more than one vial of Novoeight® per injection, reconstitute each vial according to the following instructions:

Overview of Novoeight® Package

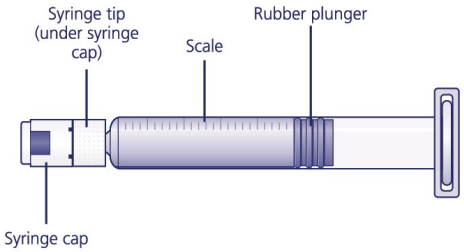
Vial with Novoeight® powder



Vial adapter



Pre-filled syringe with diluent



Plunger rod

novo nordisk®

Please see Important Safety Information on page 33.
Please click here for full Prescribing Information.

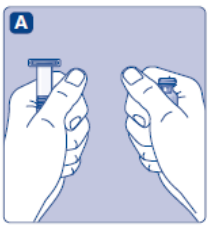
novoeight®
Antihemophilic Factor (Recombinant)

2.2 Preparation and Reconstitution (cont'd)

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

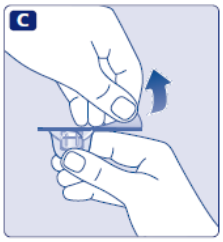
1. Bring the Novoeight® vial and the pre-filled diluent syringe to room temperature.



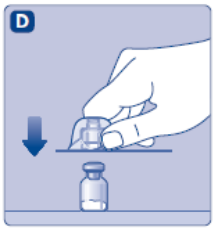
2. Remove the plastic cap from the Novoeight® vial.

3. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to dry prior to use.

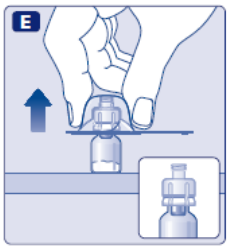
4. Remove the protective paper from the vial adapter. **Do not remove the vial adapter from the protective cap.**



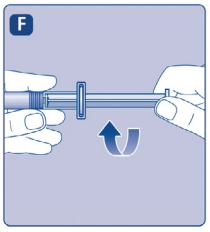
5. Place the vial on a flat and solid surface. While holding the protective cap, place the vial adapter over the Novoeight® vial and press down firmly on the protective cap until the vial adapter spike penetrates the rubber stopper.



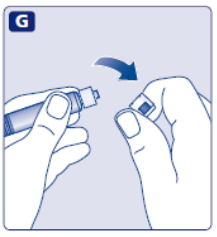
6. Carefully remove the protective cap from the vial adapter.



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.



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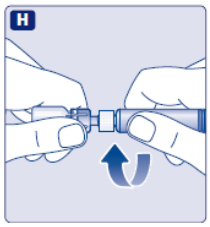
novoeight®
Antihemophilic Factor (Recombinant)

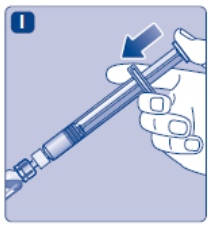
2.2 Preparation and Reconstitution (cont'd)

Reconstitution (cont'd)

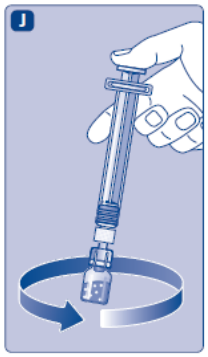
9. Connect the pre-filled diluent syringe to the vial adapter by turning it clockwise until it is secured.



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.



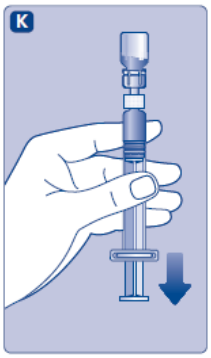
12. Use the Novoeight® solution immediately. If not, store the solution in the vial with the vial adapter and the syringe attached. Use Novoeight® within 4 hours after reconstitution when stored at <86°F (30°C) or within 2 hours when stored between 86°F (30°C) to 104°F (40°C).

2.3 Administration

For intravenous injection only.

- 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.

2.3 Administration (cont'd)



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. 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.

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.

3 DOSAGE FORMS AND STRENGTHS

Novoeight® is available as a white lyophilized powder in single-dose 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®. 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 *[see Adverse Reactions (6.1)]*. 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 observed in clinical trials (≥1%) were injection site reactions, 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®, 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).

6.1 Clinical Trials Experience (cont'd)

Table 4: Summary of Adverse Reactions (ARs) with a Frequency ≥ 1% in 301 Subjects

MedDRA System Organ class	Adverse Reactions	Frequency N (%)
General disorders and administration site conditions	Pyrexia	3 (1.0%)
	Injection site reaction	3 (1.0%)

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.

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.

6.2 Postmarketing Experience

Adverse reactions reported during post marketing period were similar in nature to those observed during clinical trials.

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®.

8.1 Pregnancy (cont'd)

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 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 in Tables 1 and 3. 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. *[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.

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

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 ≤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 5.

12.3 Pharmacokinetics (cont'd)

Table 5: Pharmacokinetics of Novoeight® in 20 adult and adolescent patients with hemophilia A[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)

[a]Dose: 50 IU/kg turoctocog alfa (single i.v. dose)

In a single dose PK assessment in adult patients with BMI ≥ 30 kg/m^2 in the extension trial *[See Clinical Studies (14)]*, the AUC was 59% higher and clearance was 33% lower in 6 subjects with BMI ≥ 30 kg/m^2 compared to subjects with normal BMI, see Table 6.

Table 6: Pharmacokinetics of Novoeight® in 6 adult patients with BMI ≥ 30 kg/m^2[a]

Parameters	Clotting Assay	Chromogenic Assay
	Mean (SD)	Mean (SD)
BMI (kg/m^2)	33.35 (2.367) Range 30.5 – 37.2	
Incremental Recovery (IU/mL)/(IU/kg)	0.024 (0.01)	0.035 (0.01)
AUC (IU*h/mL)	22.64 (5.74)	31.02 (9.78)
CL (mL/h/kg)	2.49 (0.77)	1.94 (0.95)
t½ (h)	12.80 (2.99)	12.40 (3.16)
Vss (mL/kg)	39.67 (10.03)	29.79 (7.87)
C_{max} (IU/mL)	1.49 (0.36)	2.03 (0.51)
MRT (h)	16.84 (4.78)	16.58 (4.26)

[a]Dose: 50 IU/kg turoctocog alfa (single i.v. dose)

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 7 for both age groups.

12.3 Pharmacokinetics (cont'd)

Table 7: 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.

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

Four multi-center, open-label, non-controlled trials have been conducted to evaluate the safety and efficacy of Novoeight® in the on-demand treatment and control of breakthrough bleeds, routine prophylaxis and perioperative management in patients with hemophilia A. Three of these trials were performed in PTPs (two trials and one extension trial) and the fourth in PUPs. The analysis included 297 exposed subjects: 175 previously treated adolescents or adult subjects from the age of 12 years (≥150 exposure days), 63 previously treated pediatric subjects below the age of 12 years (≥50 exposure days) and 59 PUPs below 6 years of age.

14 CLINICAL STUDIES (cont'd)

Immunocompetent patients with severe hemophilia A (factor VIII activity ≤1%) and no history of FVIII inhibitors were eligible for the trials. Subjects during routine prophylaxis and treatment of bleeds received Novoeight® at the dose levels described in Tables 1 and 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.

On-demand Treatment and Control of Bleeding Episodes

A total of 3153 bleeds in 260 subjects were treated with Novoeight®. The majority of the bleeds (90%) were of mild/moderate severity, 54% of the bleeds were spontaneous and 67% 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 3,153 bleeds, 2,809 (89%) were rated excellent or good in their response to treatment with Novoeight®, 274 (9%) were rated as moderate, 25 (0.8%) were rated as having no response and for 45 (1%) the response to treatment was unknown. A total of 2,794 (89%) of the bleeds were resolved with one or two injections of Novoeight®.

Of the 238 PTPs, 206 patients experienced 2,793 bleeds of which 2,492 (89%) were rated excellent or good in their response to treatment with Novoeight®, 244 (9%) were moderate, 23 (0.8%) were rated as having no response, and for 34 (1%) the response to treatment was unknown. Of the 2,793 reported bleeds observed in 206 of the patients, 2,504 (90%) of the bleeds were resolved with 1–2 injections of Novoeight®. The majority of the bleeds were of mild/moderate severity.

Of the 59 PUPs, 54 patients experienced 360 bleeds of which 317 (88%) were rated excellent or good in their response to treatment with Novoeight®, 30 (8%) were moderate, 2 (0.6%) were rated as having no response, and for 11 (3%) the response to treatment was unknown. Of the 360 reported bleeds observed in 54 of the patients, 290 (81%) of the bleeds were resolved with 1–2 injections of Novoeight®. The majority of the bleeds were of mild/moderate severity and the most frequent bleeds were subcutaneous.

Routine Prophylaxis

In the two trials, one trial including 150 adult/adolescent subjects (6 months duration) and the other trial including 63 pediatric subjects (4 months duration) received Novoeight® for routine prophylaxis (Table 8). These previously treated patients received prophylaxis treatment every other day or three times weekly at the dose levels described in Table 3.

14 CLINICAL STUDIES (cont'd)

Table 8: Annualized Bleeding Rate (ABR[a]) for previously treated patients from the two trials

	Small children 0 – <6 years	Older children 6 – <12 years	Adolescents 12 – <18 years	Adults ≥18 years	Total
N[b]	31	32	24	126	213
Median (IQR)	2.97 (6.30)	3.65 (8.93)	3.98 (6.21)	3.70 (9.02)	3.67 (8.70)
Mean (95%CI)	4.77 (3.07; 7.41)	5.93 (3.81; 9.22)	5.48 (3.29; 9.14)	6.69 (5.36; 8.36)	6.24 (5.25; 7.41)

a: The ABRs were estimated using a Poisson model allowing for overdispersion.
b: Patients dosed every other day or three times weekly
Abbreviations: N: number of patients; IQR: interquartile range defined as the difference between the 75th percentile and the 25th percentile; CI: confidence interval.

One hundred and eighty-eight (188) subjects from the two trials above continued into the extension trial (up to 6 years duration) (Table 9). Additionally, 18 subjects (7 subjects from an on-demand sub-trial and 11 subjects from a pharmacokinetic trial) were included in the extension trial. These previously treated patients received prophylaxis treatment every other day or three times weekly at the dose levels described in Table 3.

Table 9: Annualized Bleeding Rate (ABR[a]) for previously treated patients from the extension trial

	Small children 0 – <6 years	Older children 6 – <12 years	Adolescents 12 - <18 years	Adults ≥18 years	Total
N[b]	27	28	23	128	206
Median (IQR)	1.08 (2.83)	1.57 (3.82)	1.57 (2.34)	1.38 (2.96)	1.39 (2.94)
Mean (95%CI)	1.87 (1.14; 3.09)	2.90 (2.01; 4.17)	1.93 (1.33; 2.82)	2.61 (2.08; 3.28)	2.45 (2.07; 2.90)

a: The ABRs were estimated using a Poisson model allowing for overdispersion.
b: Patients dosed every other day or three times weekly
Abbreviations: N: number of patients; IQR: interquartile range defined as the difference between the 75th percentile and the 25th percentile; CI: confidence interval.

In the trial with previously untreated patients, 56 subjects below 6 years of age received Novoeight® for routine prophylaxis. The median annualized bleeding rate in the previously untreated patients was 2.9 (IQR 5.4) and the mean (95%CI) was 4.4 (3.3; 5.8).

14 CLINICAL STUDIES (cont'd)

In the trial with previously untreated patients, 56 subjects below 6 years of age received Novoeight® for routine prophylaxis. The median annualized bleeding rate in the previously untreated patients was 2.9 (IQR 5.4) and the mean (95%CI) was 4.4 (3.3; 5.8).

Perioperative Management

A total of 30 surgeries were performed in 25 previously treated subjects between 8 and 58 years of age, of which 26 were major surgeries (20 orthopaedic, 5 non-orthopaedic and a circumcision), and 4 were minor (2 dental, 1 circumcision and 1 insertion of port-a-cath).

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-dose 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	• Novoeight® in single-dose vial [NDC 0169-7829-11] • Pre-filled sodium chloride diluent in syringe, 4 mL [NDC 0169-7008-98] • Vial adapter
500 International Units	NDC 0169 7850 01	• Novoeight® in single-dose vial [NDC 0169-7851-11] • Pre-filled sodium chloride diluent in syringe, 4 mL [NDC 0169-7008-98] • Vial adapter
1000 International Units	NDC 0169 7810 01	• Novoeight® in single-dose vial [NDC 0169-7811-11] • Pre-filled sodium chloride diluent in syringe, 4 mL [NDC 0169-7008-98] • Vial adapter

16 HOW SUPPLIED/STORAGE AND HANDLING (cont'd)

Presentation (Nominal Product Strength)	Carton NDC Number	Components
1500 International Units	NDC 0169 7815 01	• Novoeight® in single-dose vial [NDC 0169-7855-11] • Pre-filled sodium chloride diluent in syringe, 4 mL [NDC 0169-7008-98] • Vial adapter
2000 International Units	NDC 0169 7820 01	• Novoeight® in single-dose vial [NDC 0169-7821-11] • Pre-filled sodium chloride diluent in syringe, 4 mL [NDC 0169-7008-98] • Vial adapter
3000 International Units	NDC 0169 7830 01	• Novoeight® in single-dose vial [NDC 0169-7831-11] • Pre-filled sodium chloride diluent in syringe, 4 mL [NDC 0169-7008-98] • Vial adapter

- 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 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.
- Clearly record the date when the product was removed from the refrigerator in the space provided on the outer carton. Do not return the product to the refrigerator. Do not freeze Novoeight®.
- 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.

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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.

Version: 8
License Number: 1261

For information contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536, USA
1-800-30-EIGHT

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

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.

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novoeight®
Antihemophilic Factor (Recombinant)

Patient Product Information (cont'd)

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.

Patient Product Information (cont'd)

How should I use Novoeight®? (cont'd)

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.

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novoeight®
Antihemophilic Factor (Recombinant)

Patient Product Information (cont'd)

What are the possible side effects of Novoeight®?

Common Side Effects Include:

- Inhibitors in patients who were not previously treated with Factor VIII products
- Swelling or itching at the location of injection
- 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.

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novoeight®
Antihemophilic Factor (Recombinant)

Patient Product Information (cont'd)

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° to 46°F [2°C to 8°C]) for up to 30 months or up to the expiration date. During the 30-month shelf life, the product 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.

If you choose to store Novoeight® at room temperature:

- Note the date that the product is removed from refrigeration on the box.
- Do not return the product to the refrigerator.
- Do not use after 12 months if stored up to 86°F (30°C) **or** after 3 months if stored up to 104°F (40°C) **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 Novoeight® immediately after it is mixed, it must be used within 4 hours 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.

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.

Please see Important Safety Information on page 33.
Please click here for full Prescribing Information.

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. Single-dose vial. Discard unused portion.

Content

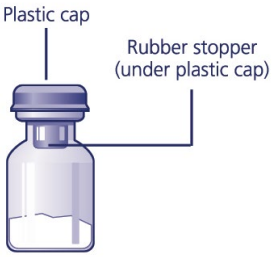
The package contains:

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

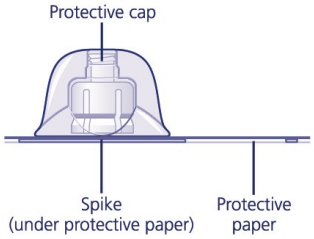
Instructions on how to use Novoeight® MixPro® (cont'd)

Overview

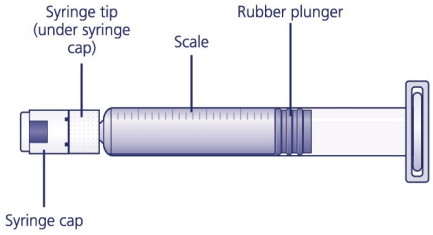
Vial with Novoeight® powder



Vial adapter

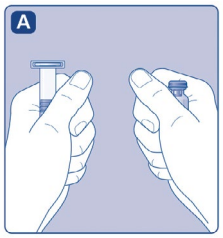


Pre-filled syringe with diluent

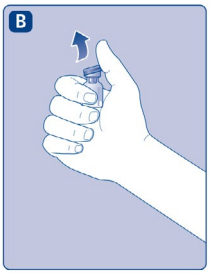


Plunger rod

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.

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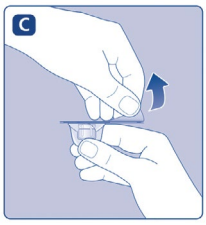
Instructions on how to use Novoeight® MixPro® (cont'd)

2. Attach the vial adapter

- **Remove the protective paper** from the vial adapter.

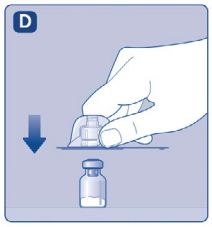
  Don't take the vial adapter out of the protective cap with your fingers. If you touch the spike on the vial adapter germs from your fingers can be transferred.

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



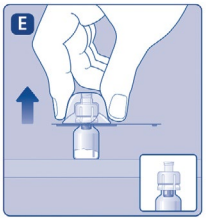
- **Place the vial on a flat and solid surface.**
- **Turn over the protective cap**, and snap the vial adapter onto the vial.

  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.

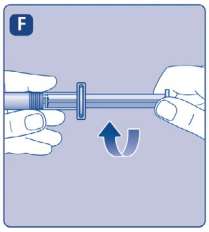
  Don't lift the vial adapter from the vial when removing the protective cap.



3. Attach the plunger rod and the syringe

- Grasp the plunger rod by the wide top end and take it out of the carton.

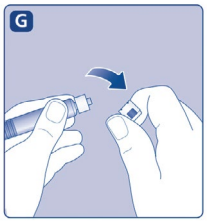
  Don't touch the sides or the thread of the plunger rod. If you touch the sides or the thread germs from your fingers can be transferred.
- **Immediately** connect the plunger rod to the syringe by turning it clockwise into the rubber plunger inside the pre-filled syringe until resistance is felt.



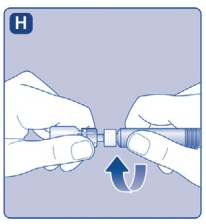
- **Remove the syringe cap** from the pre-filled syringe by bending it down until the perforation breaks.

  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.



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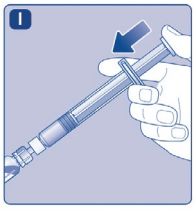
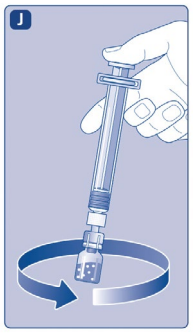
Antihemophilic Factor (Recombinant)

Instructions on how to use Novoeight® MixPro® (cont'd)

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.

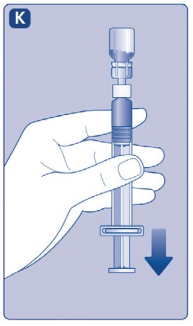
Novoeight® is recommended to be used immediately after it is mixed. This is because if left, the medicine may no longer be sterile and could cause infections.

If you cannot use the mixed Novoeight® solution immediately, it must be used within 4 hours 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.

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 steps **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.

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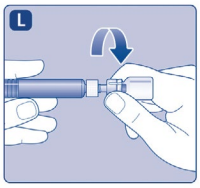
Antihemophilic Factor (Recombinant)

Instructions on how to use Novoeight® MixPro® (cont'd)

4. Mix the powder with the diluent (cont'd)



- **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.

Instructions on how to use Novoeight® MixPro® (cont'd)

5. Inject the mixed solution (cont'd)

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.

License No: 1261
Revised: 07/2020

For information about Novoeight® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536,
USA

Manufactured by:
Novo Nordisk A/S
DK-2880
Bagsvaerd, Denmark

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Section III: Distribution and Administration

Distribution of Novoeight®

Novoeight® is a specialty pharmaceutical product. Novoeight® can be accessed and distributed through specialty pharmacy distributors and hemophilia home care agencies.

Administration of Novoeight®

Novoeight® is self-administered by intravenous injection.[15] Patients may infuse Novoeight® at a hemophilia treatment center, at a healthcare provider's office, or at home.[15] Patients should not attempt to do self-infusion unless they are taught by their HCP or hemophilia center.[15]

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
- 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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