The NovoEight® Abbreviated Prescribing Information (aPI) is based on the EUSmPC as of November 2020 .Registration conditions differ internationally. Always refer to the full local SmPC before prescribing. NovoEight® is registered in the USA, EU and Japan

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 250 IU powder and solvent for solution for injection
NovoEight 500 IU powder and solvent for solution for injection
NovoEight 1000 IU powder and solvent for solution for injection
NovoEight 1500 IU powder and solvent for solution for injection
NovoEight 2000 IU powder and solvent for solution for injection
NovoEight 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoEight 250 IU powder and solvent for solution for injection.
Each powder vial contains nominally 250 IU human coagulation factor VIII (rDNA), turoctocog alfa.

After reconstitution NovoEight contains approximately 62.5 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

NovoEight 500 IU powder and solvent for solution for injection.
Each powder vial contains nominally 500 IU human coagulation factor VIII (rDNA), turoctocog alfa.

After reconstitution NovoEight contains approximately 125 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

NovoEight 1000 IU powder and solvent for solution for injection.
Each powder vial contains nominally 1000 IU human coagulation factor VIII (rDNA), turoctocog alfa.

After reconstitution NovoEight contains approximately 250 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

NovoEight 1500 IU powder and solvent for solution for injection.
Each powder vial contains nominally 1500 IU human coagulation factor VIII (rDNA), turoctocog alfa.

After reconstitution NovoEight contains approximately 375 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

NovoEight 2000 IU powder and solvent for solution for injection.
Each powder vial contains nominally 2000 IU human coagulation factor VIII (rDNA), turoctocog alfa.

After reconstitution NovoEight contains approximately 500 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

NovoEight 3000 IU powder and solvent for solution for injection.
Each powder vial contains nominally 3000 IU human coagulation factor VIII (rDNA), turoctocog alfa.

After reconstitution NovoEight contains approximately 750 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa.

The potency (IU) is determined using the European Pharmacopoeia (Ph. Eur) chromogenic assay. The specific activity of NovoEight is approximately 8,300 IU/mg protein.

Turoctocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 1,445 amino acids with an approximate molecular mass of 166 kDA. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells, and prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation.

Turoctocog alfa is a B-domain truncated recombinant human coagulation factor VIII (B-domain consists of 21 amino acids of the wild type B-domain) without any other modifications in the amino acid sequence.

Excipient with known effect
The medicinal product contains 30.5 mg sodium per reconstituted vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White or slightly yellow powder or friable mass.

Clear and colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

NovoEight can be used for all age groups.

4.2 Posology and method of administration

Treatment should be under the supervision of a doctor experienced in the treatment of haemophilia.

Treatment monitoring
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In a single dose pharmacokinetic study in adult patients the maximum exposure (C_{max}) and the total exposure (AUC) increased with increasing body mass index (BMI) indicating that dose adjustments may be required. An increase in dose may be required for underweight patients (BMI <18.5 kg/m^2) and a decrease in dose may be required for obese patients (BMI ≥30 kg/m^2), but there is insufficient data to recommend specific dose adjustments, see section 5.2.

In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

When using an *in vitro* thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Posology
The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal level human plasma) or in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml normal human plasma.

On-demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (IU/dl) x 0.5 (IU/kg per IU/dl).

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/Type of surgical procedure	FVIII level required (%) (IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours, at least 1 day, until the bleeding episode as indicated by pain is resolved or healing achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30–60	Repeat infusion every 12–24 hours for 3–4 days or more until pain and acute disability are resolved
Life threatening haemorrhages	60–100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery *Minor surgery including tooth extraction*	30–60	Every 24 hours, at least 1 day, until healing is achieved
Major surgery	80–100 (pre- and postoperative)	Repeat infusion every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl)

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A. The usual recommended doses are 20–40 IU of factor VIII per kg body weight every second day or 20–50 IU of factor VIII per kg body weight 3 times weekly. In adults and adolesents (>12 years) a less frequent

regimen (40-60 IU/kg every third day or twice weekly) may be applicable. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Surgery
There is limited experience of surgery in paediatric patients.

Elderly
There is no experience in patients >65 years.

Paediatric population
For long term prophylaxis against bleeding in patients below the age of 12, doses of 25–50 IU of factor VIII per kg body weight every second day or 25–60 IU of factor VIII per kg body weight 3 times weekly are recommended. For paediatric patients above the age of 12 the dose recommendations are the same as for adults.

Method of administration
Intravenous use.

The recommended infusion rate for NovoEight is 1–2 ml/min. The rate should be determined by the patient's comfort level.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to hamster proteins.

4.4 Special warnings and precautions for use

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Allergic type hypersensitivity reactions are possible with NovoEight. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.
In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observation and laboratory test. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate

dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Cardiovascular event
In patients with existing cardiovascular risk factors, substitiution therapy with FVIII may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

It is strongly recommended that every time that NovoEight is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

Excipient related considerations
The medicinal product contains 30.5 mg sodium per reconstituted vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with NovoEight. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

NovoEight has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Very rarely development of antibodies to hamster protein with related hypersensitivity reactions has been observed.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with NovoEight. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre is contacted.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Frequency of adverse drug reactions in clinical trials

System Organ Class	Frequency[a] in PTPs	Frequency[a] in PUPs	Adverse reaction
Blood and lymphatic system disorders	Uncommon[b]	Very common[b]	FVIII inhibition
Psychiatric disorders	Uncommon		Insomnia
Nervous system disorders	Uncommon		Headache, dizziness, burning sensation
Cardiac disorders	Uncommon		Sinus tachycardia, acute myocardial infarction
Vascular disorders	Uncommon		Hypertension, lymphoedema, hyperaemia
		Common	Flushing, Thrombophlebitis superficial
Skin and subcutaneous tissue disorders		Common	Rash, rash erythematous
	Uncommon		Rash, lichenoid keratosis, skin burning sensation
Musculoskeletal and connective tissue disorders	Uncommon		Musculoskeletal stiffness, arthropathy, pain in extremity, musculoskeletal pain
		Common	Haemarthrosis, Muscle haemorrhage
Respiratory, thoracic and mediastinal disorders		Common	Cough
General disorders and administration site conditions	Common		Injection site reactions[c]
		Common	Pyrexia, catheter site erythema
	Uncommon		Fatigue, feeling hot, oedema peripheral, pyrexia
Investigations	Common		Hepatic enzymes increased[d]
		Common	Anti factor VIII antibody positive
	Uncommon		Heart rate increased
Gastrointestinal disorders		Common	Vomiting
Injury, poisoning and procedural complications	Common		Incorrect dose administered
		Common	Infusion related reaction
	Uncommon		Contusion
Product issues		Common	Thrombosis in device

a Calculated based on total number of unique patients in all clinical trials (301), of which 242 were previously treated patients (PTPs) and 60 were previously untreated patients (PUPs).

b Frequency is based on studies with all FVIII products which included patients with severe haemophilia A.

c Injection site reactions include injection site erythema, injection site extravasation and injection site pruritus.

d Hepatic enzymes increased include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase and bilirubin.

Description of selected adverse reactions
During all clinical studies with NovoEight in previously treated patients, a total of 35 adverse reactions were reported in 23 of 242 patients exposed to NovoEight. The most frequently reported adverse reactions were injection site reactions, incorrect dose administered and hepatic enzymes increased. Of the 35 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in patients from 6 to ≤12 years of age, 1 event in 1 out of 24 patients (12 to <18 years of age) and 32 were reported in 21 out of 155 adults (≥18 years).

Paediatric population
In clinical trials involving 63 previously treated paediatric patients between 0 and 12 years of age and 24 adolescents between 12 and 18 years of age with severe haemophilia A no difference in the safety profile of NovoEight was observed between paediatric patients and adults.

In the trial with previously untreated patients, between 0 and 6 years of age, a total of 46 adverse reactions were reported in 33 of 60 patients exposed to NovoEight. The most frequently reported adverse reaction was Factor VIII inhibition, see section 4.4. High risk genetic mutations were identified in 92.3% of the overall and 93.8% of the high titre confirmed inhibitors. No other factors were significantly associated with inhibitor development.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No symptoms of overdose with recombinant coagulation factor VIII have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII, ATC code: B02BD02.

Mechanism of action
NovoEight contains turoctocog alfa, a human coagulation factor VIII (rDNA), with a truncated B-domain. This glycoprotein has the same structure as human factor VIII when activated, and post-translational modifications that are similar to those of the plasma-derived molecule. The tyrosine sulphation site present at Tyr1680 (native full length), which is important for the binding to von Willebrand factor, has been found to be fully sulphated in the turoctocog alfa molecule. When infused into a haemophilia patient, factor VIII binds to endogenous von Willebrand Factor in the patient's circulation. The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. Activated factor VIII acts as a co-factor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of bleeding tendencies.

Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

Clinical efficacy

Four multi-centre, open-labelled, non-controlled trials have been conducted to evaluate the safety and efficacy of NovoEight in the prevention and treatment of bleeds and during surgery in patients with severe haemophilia A (FVIII activity ≤1%). Three of these trials were performed in previously treated patients and the fourth in previously untreated patients. The trials included 298 exposed patients; 175 adolescents or adult patients without inhibitors from the age of 12 years (≥150 exposure days), 63 previously treated paediatric patients without inhibitors below 12 years of age (≥50 exposure days) and 60 previously untreated patients below 6 years of age.
188 out of 238 previously treated patients continued into the safety extension trial. Treatment with NovoEight was shown to be safe and had the intended haemostatic and preventive effect.
Of the 3,293 reported bleeds observed in 298 of the patients, 2,902 (88.1%) of the bleeds were resolved with 1-2 infusions of NovoEight.

Table 3 Consumption of NovoEight and haemostatic success rates in previously untreated patients (PUP) and previously treated patients (PTP)

	Younger children (0 – <6 years) PUP	Younger children (0 – <6 years) PTP	Older children (6 – <12 years) PTP	Adolescents (12 – <18 years) PTP	Adults (≥18 years) PTP	Total
Number of patients	60	31	32	24	151	298
Dose used for prevention per patient (IU/kg BW) Mean (SD) Min ; Max	45.2 (14.4) 4.5 ; 363.8	41.5 (8.1) 3.4 ; 196.3.	38.4 (9.4) 3.2 ; 62.5	28.5 (9.3) 17.4 ; 73.9	28.5 (8.3) 12.0 ; 97.4	32.8 (10.9) 3.2 ; 363.8
Dose used for treatment of bleed (IU/kg BW) Mean (SD) Min ; Max	43.6 (15.2) 11.9 ; 118.9	44.0 (12.6) 21.4 ; 193.8	40.4 (10.5) 24.0 ; 71.4	29.3 (10.3) 12.4 ; 76.8	35.0 (12.3) 6.4 ; 104.0	37.5 (13.4) 6.4 ; 193.8
Success rate[a] %	87.0%	92.2%	88.4%	85.1%	89.6%	88.9%

BW: Body weight, SD: Standard deviation
[a] Success is defined as either 'Excellent' or 'Good'.

Pre-authorisation clinical data were corroborated by a non-interventional, post-authorisation safety study conducted in order to provide additional documentation of the immunogenicity, and efficacy and safety of NovoEight in routine clinical practice. In total 68 previously treated patients (>150 EDs), of which 14 patients were <12 years and 54 patients were ≥12 years, received either on-demand (N=5) or prophylactic (N=63) treatment for a total of 87.8 patient years and 8967 EDs.

Surgery
A total of 30 surgeries were performed in 25 patients of which 26 were major surgeries and 4 were minor. Haemostasis was successful in all surgeries and no treatment failures were reported.

Data on Immune Tolerance Induction (ITI) has been collected in patients with haemophilia A who had developed inhibitors to factor VIII. During clinical trial in PUPs, 21 patients were treated with ITI and 18 (86%) patients completed ITI with a negative inhibitor test result.

5.2 Pharmacokinetic properties

All pharmacokinetic (PK) studies with NovoEight were conducted after i.v. administration of 50 IU/kg NovoEight in previously treated patients with severe haemophilia A (FVIII ≤1%). The analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

The assay performance of NovoEight in FVIII:C assays was evaluated and compared to a marketed full length recombinant FVIII product. The study showed that comparable and consistent results were obtained for both products and that NovoEight can be reliably measured in plasma without the need of a separate NovoEight standard.

The single dose pharmacokinetic parameters of NovoEight are listed in Table 4 for the one-stage clotting assay and in Table 5 for the chromogenic assay.

Table 4 Single-dose pharmacokinetic parameters of NovoEight (50 IU/kg) by age - one stage clotting assay - Mean (SD)

Parameter	0 − <6 years	6 − <12 years	≥12 years
	n=14	n=14	n=33
Incremental recovery (IU/dl)/(IU/kg)	1.8 (0.7)	2.0 (0.4)	2.2 (0.4)
AUC ((IU*h)/dl)	992 (411)	1109(374)	1526 (577)
CL (ml/h/kg)	6.21 (3.66)	5.02 (1.68)	3.63 (1.09)
$t_{½}$ (h)	7.65 (1.84)	8.02 (1.89)	11.00 (4.65)
V_{ss} (ml/kg)	56.68 (26.43)	46.82 (10.63)	47.40 (9.21)
C_{max} (IU/dl)	100 (58)	107 (35)	123 (41)
Mean residence time (h)	9.63 (2.50)	9.91 (2.57)	14.19 (5.08)

Abbreviations: AUC = area under the factor VIII activity time profile; CL = clearance; $t_{1/2}$ = terminal half-life; Vss = volume of distribution at steady-state; C_{max} = maximum factor VIII activity.

Table 5 Single-dose pharmacokinetic parameters of NovoEight (50 IU/kg) by age - chromogenic assay - Mean (SD)

Parameter	0 − <6 years	6 − <12 years	≥12 years
	n=14	n=14	n=33
Incremental recovery (IU/dl)/(IU/kg)	2.2 (0.6)	2.5 (0.6)	2.9 (0.6)
AUC ((IU*h)/dl)	1223 (436)	1437 (348)	1963 (773)
CL (ml/h/kg)	4.59 (1.73)	3.70 (1.00)	2.86 (0.94)
$t_{½}$ (h)	9.99 (1.71)	9.42 (1.52)	11.22 (6.86)
V_{ss} (ml/kg)	55.46 (23.53)	41.23 (6.00)	38.18 (10.24)
C_{max} (IU/dl)	112 (31)	125 (27)	163 (50)
Mean residence time (h)	12.06 (1.90)	11.61 (2.32)	14.54 (5.77)

Abbreviations: AUC = area under the factor VIII activity time profile; CL = clearance; $t_{1/2}$ = terminal half-life; Vss = volume of distribution at steady-state; C_{max} = maximum factor VIII activity.

The pharmacokinetic parameters were comparable between paediatric patients below 6 years of age and the paediatric patients from 6 to below 12 years of age. Some variation was observed in the pharmacokinetic parameters of NovoEight between paediatric and adult patients. The higher CL and the shorter $t_{½}$ seen in paediatric patients compared to adult patients with haemophilia A may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

A single dose pharmacokinetic trial (50 IU/kg) was performed in 35 haemophilia patients (≥18 years of age) in different BMI categories. The maximum exposure (C_{max}) and the total exposure (AUC) increase with increasing BMI indicating that dose adjustments may be required for underweight (BMI <18.5 kg/m^2) and obese patients (BMI ≥30 kg/m^2), see section 4.2.

Table 6 Single-dose pharmacokinetic parameters of NovoEight (50 IU/kg) by BMI classes[a] – One-stage clotting assay - Mean (SD)

PK parameter	Underweight N=5	Normal weight N=7	Overweight N=8	Obese class I N=7	Obese class II/III N=7

Incremental recovery (IU/dl)/(IU/kg)	1.7 (0.2)	2.0 (0.2)	2.4 (0.4)	2.3 (0.3)[b]	2.6 (0.3)
AUC ((IU*h)/dl)	1510 (360)	1920 (610)	1730 (610)	2030 (840)	2350 (590)
CL (ml/h/kg)	3.91 (0.94)	3.20 (1.00)	3.63 (1.24)	3.37 (1.79)	2.51 (0.63)
$t_{½}$ (h)	11.3 (2.0)	11.7 (3.5)	9.4 (2.9)	11.2 (3.5)	11.1 (2.7)
V_{ss} (ml/kg)	56.8 (5.4)	44.8 (6.5)	39.6 (6.0)	42.0 (9.0)	35.0 (4.6)
C_{max} (IU/dl)	100 (11)	121 (10)	144 (26)	140 (21)	161 (32)
Mean residence time (h)	15.1 (3.0)	15.3 (4.8)	11.9 (3.7)	14.4 (4.6)	14.6 (3.7)

[a] BMI groups: Underweight: BMI <18.5 kg/m^2, Normal weight: BMI 18.5-24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obese class I: BMI 30-34.9 kg/m^2, Obese class II/III: BMI ≥35 kg/m^2.
[b] Based on 6 patients only.

Table 7 Single-dose pharmacokinetic parameters of NovoEight (50 IU/kg) by BMI classes[a] – Chromogenic assay - Mean (SD)

PK parameter	Underweight N=5	Normal weight N=7	Overweight N=9	Obese class I N=7	Obese class II/III N=7
Incremental recovery (IU/dl)/(IU/kg)	2.2 (0.4)	2.9 (0.3)	3.0 (0.5)	3.2 (0.5)	3.5 (0.5)
AUC ((IU*h)/dl)	1860 (700)	2730 (860)	2310 (1020)	2780 (1210)	3050 (730)
CL (ml/h/kg)	3.28 (0.87)	2.25 (0.73)	2.84 (1.09)	2.58 (1.56)	1.94 (0.52)
$t_{½}$ (h)	11.7 (2.4)	11.5 (3.6)	9.7 (3.4)	10.4 (3.2)	10.5 (2.5)
V_{ss} (ml/kg)	49.1 (10.4)	31.2 (4.5)	31.6 (5.8)	28.9 (5.1)	25.7 (4.0)
C_{max} (IU/dl)	138 (29)	185 (24)	194 (31)	200 (33)	227 (32)
Mean residence time (h)	15.5 (3.2)	15.2 (4.9)	12.6 (4.8)	13.5 (4.6)	13.9 (3.7)

[a] BMI groups: Underweight: BMI <18.5 kg/m^2, Normal weight: BMI 18.5-24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obese class I: BMI 30-34.9 kg/m^2, Obese class II/III: BMI ≥35 kg/m^2.

5.3 Preclinical safety data

Non-clinical data reveal no special concern for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium chloride
L-histidine
Sucrose
Polysorbate 80
L-methionine
Calcium chloride dihydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

Solvent:
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial
30 months when stored in a refrigerator (2°C – 8°C).

During the shelf life, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months
  or
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months.

Once the product has been taken out of the refrigerator, the product must not be returned to the refrigerator.

Please record the beginning of storage and the storage temperature on the product carton.

After reconstitution:
Chemical and physical in-use stability have been demonstrated for:
- 24 hours stored at 2°C – 8°C
- 4 hours stored at 30°C, for product which has been kept for a single period no longer than 9 months at room temperature (≤30°C)
- 4 hours stored up to 40°C, for product which has been kept for a single period no longer than 3 months at above room temperature (30°C up to 40°C).

From a microbiological point of view, the medicinal product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than as stated above, unless reconstitution has taken place in controlled and validated aseptic conditions.

Any unused reconstituted product stored at room temperature (≤30°C) or up to 40°C for more than 4 hours should be discarded.

6.4 Special precautions for storage

Store in refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage at room temperature (≤30°C) or up to 40°C and storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack of NovoEight 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU powder and solvent for solution for injection contains:

– 1 glass vial (type I) with powder and chlorobutyl rubber stopper
– 1 sterile vial adapter for reconstitution
– 1 pre-filled syringe of 4 ml solvent with backstop (polypropylene), a rubber plunger (bromobutyl) and a syringe cap with a stopper (bromobutyl)
– 1 plunger rod (polypropylene).

6.6 Special precautions for disposal and other handling

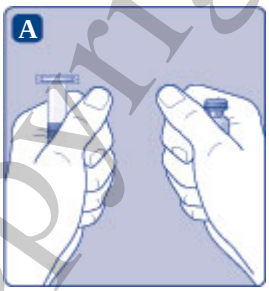
NovoEight is to be administered intravenously after reconstitution of the powder with the solvent supplied in the syringe. After reconstitution the solution appears as a clear or slightly opalescent solution. Do not use solutions that are cloudy or have deposits.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the NovoEight package.

Always use an aseptic technique.

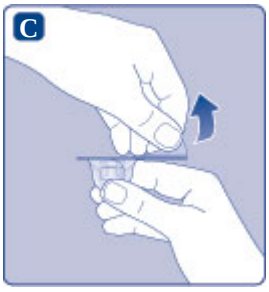
Reconstitution

A)
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. Do not use any other way to heat the vial and pre-filled syringe.



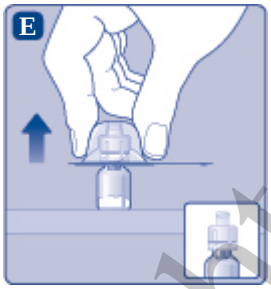
B)
Remove the plastic cap from the vial. If the plastic cap is loose or missing, do not use the vial. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to air dry for a few seconds before use.

C)
Remove the protective paper from the vial adapter. If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.
Do not take the vial adapter out of the protective cap with your fingers.

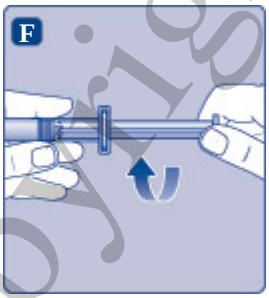


D)
Turn over the protective cap and snap the vial adapter onto the vial. Once attached do not remove the vial adapter from the vial.

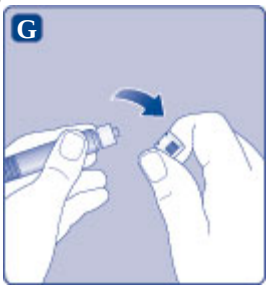
E)
Lightly squeeze the protective cap with your thumb and index finger as shown. Remove the protective cap from the vial adapter.



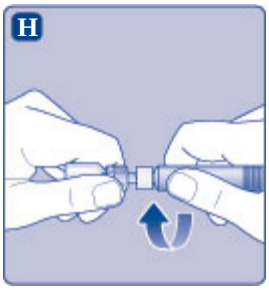
F)
Grasp the plunger rod by the wide top and immediately connect the plunger rod to the syringe by turning it clockwise into the plunger inside the pre-filled syringe until resistance is felt.



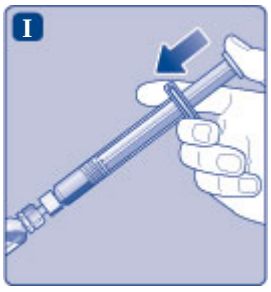
G)
Remove the syringe cap from the pre-filled syringe by bending it down until the perforation breaks. Do not touch the syringe tip under the syringe cap.



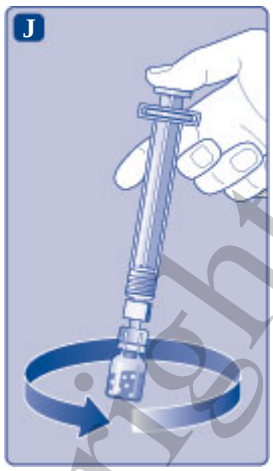
H)
Screw the pre-filled syringe securely onto the vial adapter until resistance is felt.



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



J)
Keep the plunger rod pressed down and swirl the vial gently until all the powder is dissolved. Do not shake the vial as this will cause foaming.

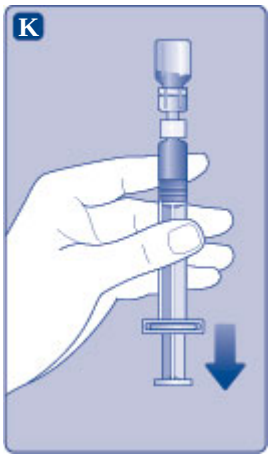


It is recommended to use NovoEight immediately after reconstitution. For storage conditions of the reconstituted medicinal product see section 6.3.

If a larger dose is needed, repeat steps A to J with additional vials, vial adapters and pre-filled syringes.

Administration of the reconstituted solution

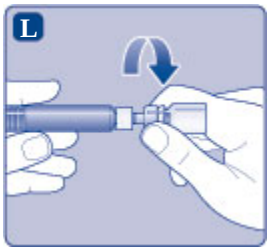
K)
Keep the plunger rod pushed completely in. Turn the syringe with the vial upside down. Stop pushing the plunger rod and let it move back on its own while the reconstituted solution fills the syringe. Pull the plunger rod slightly downwards to draw the reconstituted solution into the syringe.



In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted 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.

L)
Unscrew the vial adapter with the vial.



NovoEight is now ready for injection. Locate a suitable site and slowly inject NovoEight into the vein over a period of 2-5 minutes.

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 as instructed by your pharmacist.

Do not throw it out with the ordinary household waste.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

NovoEight 250 IU
EU/1/13/888/001

NovoEight 500 IU
EU/1/13/888/002

NovoEight 1000 IU
EU/1/13/888/003

NovoEight 1500 IU
EU/1/13/888/004

NovoEight 2000 IU
EU/1/13/888/005

NovoEight 3000 IU
EU/1/13/888/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 2013
Date of latest renewal: 30 July 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

BioReliance Ltd
Todd Campus, West of Scotland Science Park,
Glasgow, G20 0XA
United Kingdom

Novo Nordisk US Bio Production Inc.
9 Technology Drive
West Lebanon
NH 03784
USA

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSUR)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 250 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of NovoEight contains approximately 62.5 IU of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, hydrochloric acid
Solvent: Sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in pre-filled syringe, plunger rod and vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze

During storage, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months **or**
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months

Taken out of refrigerator: _____Stored at ≤30°C __ Stored at 30°C up to 40°C __

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/888/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoEight 250 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoEight 250 IU powder for solution for injection

turoctocog alfa

Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 500 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of NovoEight contains approximately 125 IU of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, hydrochloric acid
Solvent: Sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in pre-filled syringe, plunger rod and vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze

During storage, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months **or**
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months

Taken out of refrigerator: _____Stored at ≤30°C __ Stored at 30°C up to 40°C __

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/888/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoEight 500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoEight 500 IU powder for solution for injection

turoctocog alfa

Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 1000 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of NovoEight contains approximately 250 IU of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, hydrochloric acid
Solvent: Sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in pre-filled syringe, plunger rod and vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze

During storage, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months **or**
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months

Taken out of refrigerator: _____Stored at ≤30°C __ Stored at 30°C up to 40°C __

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/888/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoEight 1000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoEight 1000 IU powder for solution for injection

turoctocog alfa

Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1000 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 1500 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of NovoEight contains approximately 375 IU of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, hydrochloric acid
Solvent: Sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in pre-filled syringe, plunger rod and vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze

During storage, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months **or**
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months

Taken out of refrigerator: _____Stored at ≤30°C __ Stored at 30°C up to 40°C __

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/888/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoEight 1500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoEight 1500 IU powder for solution for injection

turoctocog alfa

Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1500 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 2000 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of NovoEight contains approximately 500 IU of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, hydrochloric acid
Solvent: Sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in pre-filled syringe, plunger rod and vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze

During storage, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months **or**
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months

Taken out of refrigerator: _____Stored at ≤30°C __ Stored at 30°C up to 40°C __

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/888/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoEight 2000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoEight 2000 IU powder for solution for injection

turoctocog alfa

Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2000 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoEight 3000 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of NovoEight contains approximately 750 IU of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide, hydrochloric acid
Solvent: Sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in pre-filled syringe, plunger rod and vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze

During storage, the product may be kept at:
- room temperature (≤ 30°C) for a single period no longer than 9 months **or**
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months

Taken out of refrigerator: _____Stored at ≤30°C __ Stored at 30°C up to 40°C __

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/888/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoEight 3000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoEight 3000 IU powder for solution for injection

turoctocog alfa

Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3000 IU

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for NovoEight

Sodium chloride 9 mg/ml

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 ml

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NovoEight 250 IU powder and solvent for solution for injection
NovoEight 500 IU powder and solvent for solution for injection
NovoEight 1000 IU powder and solvent for solution for injection
NovoEight 1500 IU powder and solvent for solution for injection
NovoEight 2000 IU powder and solvent for solution for injection
NovoEight 3000 IU powder and solvent for solution for injection

turoctocog alfa (human coagulation factor VIII (rDNA))

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor.
– This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
– If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoEight is and what it is used for

NovoEight contains the active substance turoctocog alfa, human coagulation factor VIII. Factor VIII is a protein naturally found in the blood that helps it to clot.

NovoEight is used to treat and prevent bleeding episodes in patients with haemophilia A (inborn factor VIII deficiency) and can be used for all age groups.

In patients with haemophilia A, factor VIII is missing or not working properly. NovoEight replaces this faulty or missing ‘factor VIII’ and helps blood to form clots at the site of bleeding.

2. What you need to know before you use NovoEight

Do not use NovoEight:
- if you are allergic to the active substance or to any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to hamster proteins.

Do not use NovoEight if either of the above applies to you. If you are not sure, talk to your doctor before using this medicine.

Warnings and precautions

Talk to your doctor before using NovoEight.

There is a rare chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to NovoEight. Early signs of allergic reactions are rash, hives, weals, generalised itching,

swelling of lips and tongue, difficulty in breathing, wheezing, tightness of the chest, general feeling of being unwell, and dizziness.

If any of these symptoms occur, stop the injection immediately and contact your doctor.

Talk to your doctor if you think that your bleed is not being controlled with the dose you receive, as there can be several reasons for this. Some people using this medicine can develop antibodies to factor VIII (also known as factor VIII inhibitors). Factor VIII inhibitors make NovoEight less effective in preventing or controlling bleeding. If this happens you may need a higher dose of NovoEight or a different medicine to control your bleed. Do not increase the total dose of NovoEight to control your bleed without talking to your doctor. You should tell your doctor if you have been previously treated with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again.

The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with NovoEight, tell your doctor immediately.

Other medicines and NovoEight
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think that you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
NovoEight has no influence on your ability to drive and use machines.

NovoEight contains sodium
This medicine contains 30.5 mg sodium (main component of cooking/table salt) per reconstituted vial. This is equivalent to 1.5% of the recommended maximum dietary intake of sodium for an adult.

Talk to your doctor if you are on a controlled sodium diet.

3. How to use NovoEight

Treatment with NovoEight will be started by a doctor who is experienced in the care of patients with haemophilia A. Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will calculate your dose for you. This will depend on your weight and what the medicine is being used for.

Prevention of bleeding
The usual dose of NovoEight is 20 to 50 international units (IU) per kg of body weight. The injection is given every 2 to 3 days. In some cases, especially in younger patients, more frequent injections or higher doses may be needed.

Treatment of bleeding
The dose of NovoEight is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

Use in children and adolescents
NovoEight can be used in children of all ages. In children (below the age of 12) higher doses or more frequent injections may be needed. Adolescents (above the age of 12) can use the same dose as adults.

How NovoEight is given
NovoEight is given as an injection into a vein. See 'Instructions on how to use NovoEight' for more information.

If you use more NovoEight than you should
If you use more NovoEight than you should, tell your doctor or go to a hospital straight away.

If you forget to use NovoEight
You should contact your doctor if you have missed a dose and do not know how to compensate for this.

If you stop using NovoEight
If you stop using NovoEight you may no longer be protected against bleeding or a current bleed may not stop. Do not stop using NovoEight without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may occur with this medicine.

If severe, sudden allergic reactions (anaphylactic reactions) occur (very rare), the injection must be stopped immediately. You must contact your doctor immediately if you have one of the following early symptoms:

- difficulty in breathing, shortness of breath or wheezing
- chest tightness
- swelling of the lips and tongue
- rash, hives, weals or generalised itching
- feeling dizzy or loss of consciousness
- low blood pressure (having pale and cold skin, fast heartbeat).

Severe symptoms, including difficulty in swallowing or breathing and red or swollen face or hands, require prompt emergency treatment.

If you have a severe allergic reaction, your doctor may change your medicine.

For children not previously treated with Factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with Factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 patients). If this happens to you or your child´s medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Common side effects (may affect up to 1 in 10 people)
- blood tests showing changes in the way the liver functions
- reactions (redness and itching) around the site where you injected the medicine.

Common side effects (may affect up to 1 in 10 people) in patients who have not previously treated with Factor VIII medicines
- blushing of the skin
- inflammation of vein
- bleeding into joint spaces
- bleeding in muscle tissue
- cough

- redness around the site where you placed catheter
- vomiting.

Uncommon side effects (may affect up to 1 in 100 people)
- feeling tired
- headache
- feeling dizzy
- difficulty sleeping (insomnia)
- fast heartbeat
- increased blood pressure
- rash
- fever
- feeling hot
- stiffness of muscles
- pain in muscles
- pain in legs and arms
- swelling of legs and feet
- joint disease
- bruising
- heart attack.

Side effects in children and adolescents
The side effects observed in children and adolescents are the same as observed in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NovoEight

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

Do not use this medicine after the expiry date, which is stated after 'EXP' on the carton and on the vial and the pre-filled syringe labels. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Before the NovoEight powder is reconstituted it may be kept at:

- room temperature (≤ 30°C) for a single period no longer than 9 months
  or
- above room temperature (30°C up to 40°C) for a single period no longer than 3 months.

Once the product has been taken out of the refrigerator, the product must not be returned to the refrigerator.

Please record the beginning of storage and the storage temperature on the product carton.

Once you have reconstituted NovoEight it should be used right away. If you cannot use the reconstituted NovoEight solution immediately, it should be used within:
- 24 hours stored at 2°C – 8°C

- 4 hours stored at ≤ 30°C, for product which has been kept for a single period no longer than 9 months at room temperature (≤30°C)
- 4 hours stored up to 40°C, for product which has been kept for a single period no longer than 3 months at above room temperature (30°C up to 40°C).

Store the reconstituted product in the vial. If not used straight away the medicine may no longer be sterile and could cause infection. Do not store the solution without your doctor's advice.

The powder in the vial appears as a white or slightly yellow powder. Do not use the powder if the colour has changed.

The reconstituted solution will be clear to slightly opalescent. Do not use this medicine if you notice that it is cloudy or contains visible particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoEight contains
- The active substance is turoctocog alfa (human coagulation factor VIII (rDNA)). Each vial of NovoEight contains nominally 250, 500, 1000, 1500, 2000 or 3000 IU turoctocog alfa.
- The other ingredients are L-histidine, sucrose, polysorbate 80, sodium chloride, L-methionine, calcium chloride dihydrate, sodium hydroxide and hydrochloric acid.
- The ingredients in the solvent are sodium chloride and water for injections.

After reconstitution with the supplied solvent (sodium chloride 9 mg/ml (0.9%) solution for injection), the prepared solution for injection contains 62.5, 125, 250, 375, 500 or 750 IU turoctocog alfa per ml, respectively, (based on the strength of turoctocog alfa, i.e. 250, 500, 1000, 1500, 2000 or 3000 IU).

What NovoEight looks like and contents of the pack
NovoEight is a powder and solvent for solution for injection. Each pack of NovoEight contains a vial with white or slightly yellow powder, a 4 ml pre-filled syringe with a clear colourless solution, a plunger rod and a vial adapter.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions on how to use NovoEight

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NOVOEIGHT.

NovoEight is supplied as a powder. Before injection (administration) it must be reconstituted with the solvent supplied in the syringe. The solvent is a sodium chloride 9 mg/ml (0.9%) solution. The reconstituted NovoEight must be injected into your vein (intravenous injection). The equipment in this package is designed to reconstitute and inject NovoEight.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the NovoEight package.

Do not 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 medicine 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.

Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it is expired. Use a new package instead. The expiry date is printed after 'EXP' on the outer carton, on the vial, on the vial adapter, and on the pre-filled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

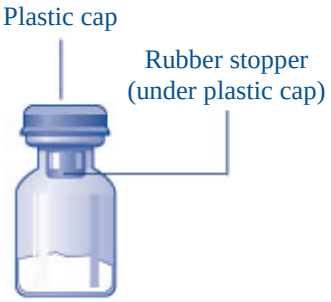
Contents

The package contains:

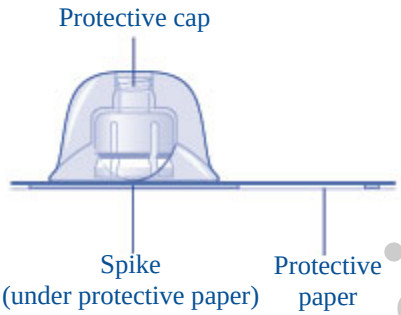
- 1 vial with NovoEight powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

Overview

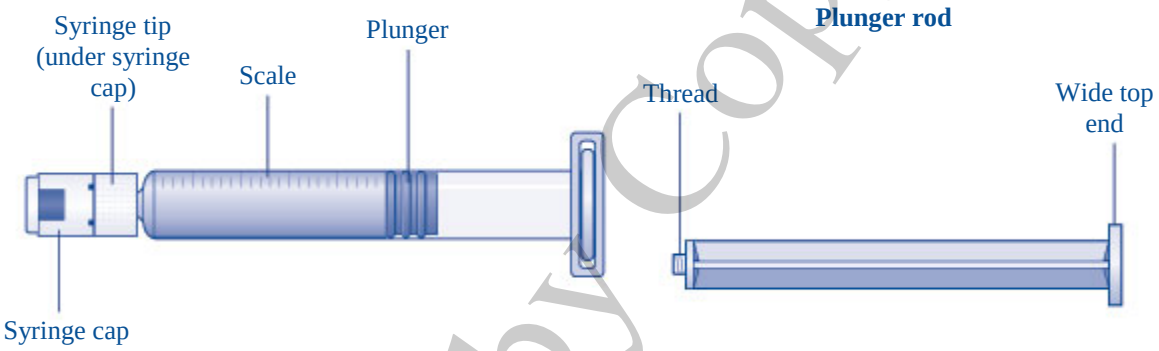
Vial with NovoEight powder



Vial adapter

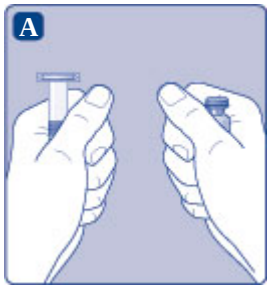


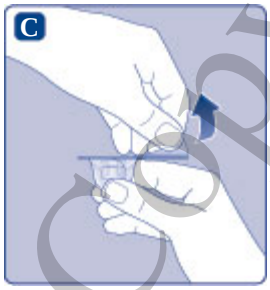
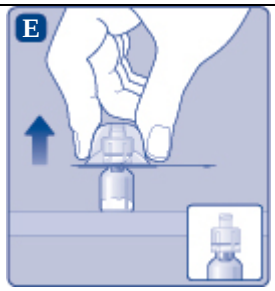
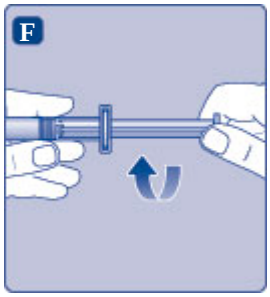
Pre-filled syringe with solvent

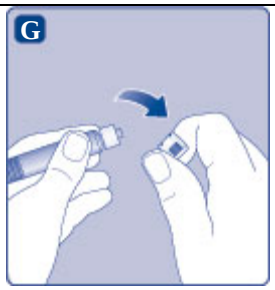
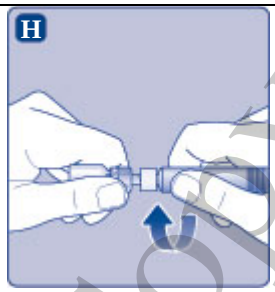
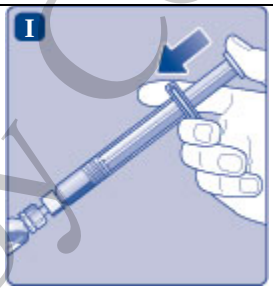


1. Prepare the vial and the syringe

- **Take out the number of NovoEight packages you need.**
- **Check the expiry date.**
- **Check the name, strength and colour** 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.
- **Do not use any other way to heat** the



vial and pre-filled syringe.	
• **Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, do not 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. • **Do not 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. **If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.** **Do not 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.	
• **Place the vial on a flat and solid surface.** • **Turn over the protective cap,** and snap the vial adapter onto the vial. **Once attached, do not 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. **Do not 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. **Do not 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	

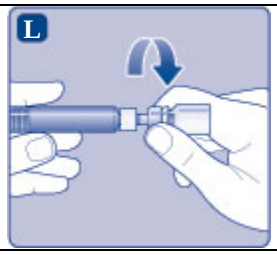
into the plunger inside the pre-filled syringe until resistance is felt.	
• **Remove the syringe cap** from the pre-filled syringe by bending it down until the perforation breaks. • **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers can be transferred. **If the syringe cap is loose or missing, do not use the pre-filled syringe.**	
• **Screw the pre-filled syringe securely** onto the vial adapter until resistance is felt.	
4. Reconstitute the powder with the solvent • **Hold the pre-filled syringe slightly tilted** with the vial pointing downwards. • **Push the plunger rod** to inject all the solvent into the vial.	
• **Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** • **Check the reconstituted solution.** It must be clear to slightly opalescent (slightly unclear). **If you notice visible particles or discolouration, do not use it.** Use a new package instead.	
NovoEight is recommended to be used immediately after it has been reconstituted. This is because if left, the medicine may no longer be sterile and could cause infections. **If you cannot use the reconstituted NovoEight solution immediately,** it should be used within 4 hours when stored at room temperature or up to 40°C and within 24 hours when stored at 2°C – 8°C. Store the reconstituted product in the vial. **Do not freeze reconstituted NovoEight solution or store it in syringes.** **Do not store the solution without your doctor's advice.** **Keep reconstituted 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 reconstituted solution fills the syringe.
- **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe.
- **In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted solution you withdraw, as instructed by your doctor or nurse.**

  If, at any point, there is too much air in the syringe, inject the air back into the vial.
- 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.
- **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers can be transferred.



5. Inject the reconstituted solution

NovoEight is now ready to be injected into your vein.

- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 2 to 5 minutes.
- Do not mix NovoEight with any other intravenous infusions or medicines.

Injecting NovoEight via needleless connectors for intravenous (IV) catheters

Caution: The pre-filled syringe is made of glass and is designed to be compatible with standard

luer-lock connections. Some needleless connectors with an internal spike are incompatible with the pre-filled syringe. This incompatibility may prevent administration of the medicine and/or result in damage to the needleless connector.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:
• Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
• Injecting into a CVAD may require using a sterile 10 ml plastic syringe for withdrawal of the reconstituted solution. This should be done right after step J.
• If the CVAD line needs to be flushed before or after NovoEight injection, use sodium chloride 9 mg/ml solution for injection.

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 as instructed by your pharmacist.

  Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.

Do not reuse the equipment.