SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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

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.

The potency (IU) is determined using the European Pharmacopoeia 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:
0.31 mmol sodium (7 mg) per ml of reconstituted solution.

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).

4.2 Posology and method of administration

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

Previously untreated patients
The safety and efficacy of NovoEight in previously untreated patients have not yet been established. No data are available.

Posology
The dosage 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 1International 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 some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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. 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. Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

Surgery
There is no experience in surgery of paediatric patients.

Older people
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 protein.

4.4 Special warnings and precautions for use

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 exposure to factor VIII, the risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

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.

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.

Excipient related considerations
After reconstitution this medicinal product contains 0.31 mmol sodium (7 mg) per ml of reconstituted solution. To be taken into consideration by patients on a controlled sodium diet.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with NovoEight.

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 breast-

feeding is not available. Therefore, factor VIII should be used during pregnancy and breast-feeding 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.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. 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); 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*	Adverse reaction
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Uncommon	Headache, dizziness
Cardiac disorders	Uncommon	Sinus tachycardia
Vascular disorders	Uncommon	Hypertension, lymphoedema
Hepatobiliary disorders	Common	Hepatic enzymes increased**
Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Uncommon	Musculoskeletal stiffness, arthropathy, pain in extremity, musculoskeletal pain
General disorders and administration site conditions	Common	Injection site reactions***
	Uncommon	Fatigue, feeling hot, oedema Peripheral, pyrexia
Investigations	Uncommon	Heart rate increased
Injury, poisoning and procedural complications	Uncommon	Contusion

* Calculated based on total number of unique patients in all clinical studies (214).
** Hepatic enzymes increased include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase and bilirubin.
*** Injection site reactions include injection site erythema, injection site extravasation and injection site pruritus.

Description of selected adverse reactions
During all clinical studies with NovoEight, a total of 30 adverse reactions were reported in 19 of 214 patients exposed to NovoEight. The most frequently reported adverse reactions were injection site reactions and hepatic enzymes increased. Of the 30 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in patients from 6 to 18 years of age and 28 were reported in 18 out of 127 adults.

Paediatric population
In clinical studies involving 63 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.

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.

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 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.

Clinical efficacy
Three 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 in previously treated patients with severe haemophilia A (FVIII activity ≤1%). The studies included 213 exposed patients; 150 adolescents or adult patients without inhibitors from the age of 12 years (≥150 exposure days) and 63 paediatric patients without inhibitors below 12 years of age (≥50 exposure days). 187 out of 213 patients continued in the safety extension trial. Treatment with NovoEight was shown to be safe and had the intended haemostatic and preventive effect. During an accumulated exposure of more than 54,000 days (corresponding to 342 patient years), no factor VIII inhibitor development was observed

in the phase 3a clinical trials in previously treated patients. Of the 1,377 reported bleeds observed in 177 of the 213 patients, 1,244 (90.3%) of the bleeds were resolved with 1-2 infusions of NovoEight.

Table 3 Consumption of turoctocog alfa and overall success rates

	Younger children (0 – <6 years)	Older children (6 – <12 years)	Adolescents (12 – <18 years)	Adults (≥18 years)	Total
Number of patients	31	32	24	126	213
Dose used for prevention per patient (IU/kg BW)					
Mean (SD)	40.1 (8.5)	36.6 (9.0)	27.0 (7.6)	26.9 (6.9)	30.3 (9.2)
Min ; Max	26.5 ; 57.3	24.9 ; 57.9	20.5 ; 46.9	20.0 ; 50.8	20.0 ; 57.9
Dose used for treatment of bleed (IU/kg BW)					
Mean (SD)	44.4 (17.9)	40.0 (10.4)	28.2 (10.2)	33.8 (11.9)	34.5 (12.6)
Min ; Max	25.9 ; 193.8	25.5 ; 65.5	12.4 ; 76.8	9.3 ; 104.0	9.3 ; 193.8
Success rate* %	92.9%	88.9%	79.7%	85.6%	85.9%

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

A total of 14 surgeries were performed in 14 patients of which 13 were major surgeries and 1 was minor. Haemostasis was successful in all surgeries and no treatment failures were reported.

5.2 Pharmacokinetic properties

All pharmacokinetic studies with turoctocog alfa were conducted 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.

In an international study involving 36 laboratories, 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 clotting assay and in Table 5 for the chromogenic assay.

Table 4 Single-dose pharmacokinetics of turoctocog alfa in patients with severe haemophilia A (FVIII ≤1%), clotting assay

Parameter	0 − <6 years	6 − <12 years	≥12 years
	n=14	n=14	n=33
	Mean (SD)	Mean (SD)	Mean (SD)
Incremental recovery (IU/ml)/(IU/kg)	0.018 (0.007)	0.020 (0.004)	0.022 (0.004)
AUC ((IU*h)/ml)	9.92 (4.11)	11.09 (3.74)	15.26 (5.77)
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/ml)	1.00 (0.58)	1.07 (0.35)	1.226 (0.41)
Mean residence time (h)	9.63 (2.50)	9.91 (2.57)	14.19 (5.08)

Table 5 Single-dose pharmacokinetics of turoctocog alfa in patients with severe haemophilia A (FVIII ≤1%), chromogenic assay

Parameter	0 − <6 years	6 − <12 years	≥12 years
	n=14	n=14	n=33
	Mean (SD)	Mean (SD)	Mean (SD)
Incremental recovery (IU/ml)/(IU/kg)	0.022 (0.006)	0.025 (0.006)	0.029 (0.006)
AUC ((IU*h)/ml)	12.23 (4.36)	14.37 (3.48)	19.63 (7.73)
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/ml)	1.12 (0.31)	1.25 (0.27)	1.63 (0.50)
Mean residence time (h)	12.06 (1.90)	11.61 (2.32)	14.54 (5.77)

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.

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
Hydrochloric acid

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:
30 months

During the shelf life, the product may be kept at room temperature (≤30°C) for a single period not exceeding 9 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 at room temperature on the product carton.
Keep the vial in the outer carton in order to protect from light.

After reconstitution:
Chemical and physical in-use stability have been demonstrated for 24 hours stored at 2°C – 8°C and 4 hours stored at room temperature (≤30°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 4 hours stored at room temperature (≤30°C) or 24 hours at 2°C – 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Any unused product stored at room temperature for more than 4 hours should be discarded.

6.4 Special precautions for storage

Store in refrigerator (2°C – 8°C). Do not freeze.

For storage at room temperature 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 powder and solvent for solution for injection contains:

- 1 glass vial (type I) with powder and chlorobutyl rubber stopper
- 1 sterile vial adaptor for reconstitution
- 1 prefilled syringe of 4 ml solvent with backstop (polypropylene), a rubber plunger (bromobutyl) and a tipcap 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.

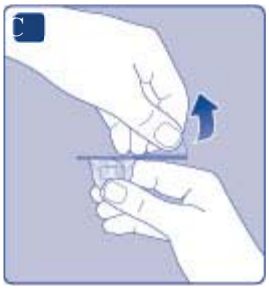
Always use an aseptic technique.

Reconstitution

A)
Take the vial, the vial adapter and the prefilled syringe out of the carton. Leave the plunger rod untouched in the carton. Bring the vial and the prefilled 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 prefilled syringe.

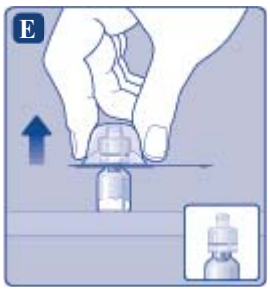
B)
Remove the plastic cap from the vial. If the plastic cap is loose or missing, do not use the vial. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to air dry for a few seconds before use.

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.

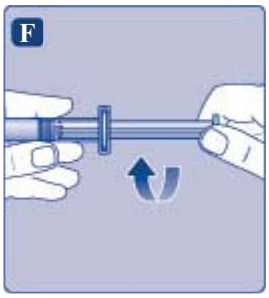


D)
Turn over the protective cap and snap the vial adapter onto the vial. Once attached do not remove the vial adapter from the vial.

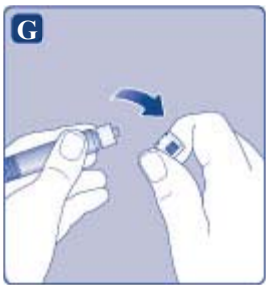
E)
Lightly squeeze the protective cap with your thumb and index finger as shown. Remove the protective cap from the vial adapter.



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 prefilled syringe until resistance is felt.



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



H)
Screw the prefilled syringe securely onto the vial adapter until resistance is felt.

I)
Hold the prefilled 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 prefilled syringes.

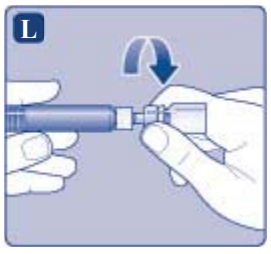
Administration of the reconstituted solution

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 Pharma Thailand Ltd., Bangkok, Thailand, 10500

8. MARKETING AUTHORISATION NUMBERS

NovoEight 250 IU
Registration number from the Thai FDA

NovoEight 500 IU
Registration number from the Thai FDA

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date approved in Thailand

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the Thai FDA