Professional Information

S4 NovoEight® 250 IU, 500 IU, 1 000 IU, 1 500 IU, 2 000 IU & 3 000 IU

Turoctocog alfa, Powder and solvent for solution for injection

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Scheduling status

S4

1. Name of the medicine

NovoEight® 250 IU powder and solvent for solution for injection

NovoEight® 500 IU powder and solvent for solution for injection

NovoEight® 1 000 IU powder and solvent for solution for injection

NovoEight® 1 500 IU powder and solvent for solution for injection

NovoEight® 2 000 IU powder and solvent for solution for injection

NovoEight® 3 000 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® 1 000 IU powder and solvent for solution for injection:

Each powder vial contains nominally 1 000 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® 1 500 IU powder and solvent for solution for injection:

Each powder vial contains nominally 1 500 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® 2 000 IU powder and solvent for solution for injection:

Each powder vial contains nominally 2 000 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® 3 000 IU powder and solvent for solution for injection:

Each powder vial contains nominally 3 000 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.

Excipients with known effect

NovoEight® contains 30,5 mg sodium per reconstituted vial.

Contains sugar (12 mg sucrose per vial).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection.

Powder: White or slightly yellow powder or friable mass.

Solvent: Clear and colourless solution for injection.

4. Clinical particulars

4.1 Therapeutic indications

Treatment, prophylaxis and peri-operative management 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.

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		

Degree of haemorrhage/Type of surgical procedure	**FVIII level required (%) (IU/dL)**	**Frequency of doses (hours)/Duration of therapy (days)**
Mild Mild haemorrhage, Early haemorrhage into muscles/joints Early haemorrhages in the oral cavity, 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.
Moderate Moderate haemorrhage, more extensive haemarthrosis, haemorrhage into muscles/joints, haemorrhages in the oral cavity or haematoma	30 – 60	Repeat injection every 12 – 24 hours for 3 – 4 days or more until pain and acute disability are resolved
Major Severe, life/limb threatening haemorrhage, gastro-intestinal bleeding,	60 – 100	Repeat injection every 8 to 24 hours until threat is resolved

Degree of haemorrhage/Type of surgical procedure	**FVIII level required (%) (IU/dL)**	**Frequency of doses (hours)/Duration of therapy (days)**
intracranial, intra-abdominal or intra-thoracic haemorrhages or fractures		
Surgery		
Minor surgery Including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved
Major surgery (intracranial, intra-abdominal, intrathoracic or joint replacement surgery)	80 – 100 (pre-and post-operative)	Repeat injection 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 2 – 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. Individual patients may vary in their response to factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives. 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 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.

Surgery

There is limited experience of major surgery in paediatric patients.

Elderly 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 injection rate for NovoEight® is 1 – 2 mL/min. The rate should be determined by the patient's comfort level.

For instructions on reconstitution of NovoEight® 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

Traceability

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

Hypersensitivity

Allergic type hypersensitivity reactions are possible with NovoEight®. NovoEight® 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 NovoEight® immediately and contact their doctor and/or seek emergency medical treatment. 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, the 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 inhibitors, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by doctors with experience in the care of haemophilia and factor VIII inhibitors.

Paediatric population

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

Excipient related considerations

NovoEight® 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 medicines and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

No animal reproductive studies have been conducted with NovoEight®.

Pregnancy

Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy is not available. Therefore, NovoEight® should only be used during pregnancy if clearly indicated.

Breastfeeding

Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during breastfeeding is not available. Therefore, NovoEight® should only be used during breastfeeding if clearly indicated.

Fertility

It is not known if NovoEight® can affect fertility.

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

During all clinical studies with NovoEight®, a total of 35 adverse reactions were reported in 23 of 242 previously treated 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).

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition may 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 reactions in clinical trials

System Organ Class	**Frequency* in PTPs**	**Frequency* in PUPs**	**Adverse reaction**
Blood and lymphatic system disorders		Very common	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, superficial thrombophlebitis
Skin and subcutaneous tissue disorders		Common	Rash, erythematous rash
	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	Common		Injection site reactions**

administration site conditions		Common	Pyrexia, catheter site erythema
	Uncommon		Fatigue, feeling hot, peripheral oedema, pyrexia
Investigations	Common		Increased hepatic enzymes***
		Common	Anti-factor VIII antibody positive
	Uncommon		Increased heart rate
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

* 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).

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

*** Increased hepatic enzymes includes alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase and bilirubin.

During an accumulated exposure of more than 130 000 EDs (854,9 patient years) factor VIII inhibitor development was not observed in 269 previously treated patients in the 3 clinical trials and

4 PK trials.

During an accumulated exposure of more than 10 000 EDs (115,4 patient years) in the clinical trial with previously untreated patients, factor VIII inhibitor development was observed in 26 of 58 (44,8 %) patients. Mean time to inhibitor development was 17,5 EDs. 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

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.

Description of selected adverse reactions in PUPs

A total of 46 probably related adverse reactions were reported in 33 of 60 patients exposed to NovoEight®. The most frequently reported adverse reaction was Factor VIII inhibition. Factor VIII inhibitor development was observed in 26 of 58 (44,8 %) previously untreated patients; 16 (27,6 %) were high titre and 10 (17,2 %) were low titre inhibitors.

Adverse reactions from post-marketing sources

No new significant information that affects the safety profile of NovoEight® was received from post-marketing sources. Overall, the distribution, pattern and type of ADRs received from post marketing sources are comparable to ADRs from clinical trials.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of NovoEight® is important. It allows continued monitoring of the benefit/risk balance of NovoEight®. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 8.1 Coagulants, Haemostatics

Pharmacotherapeutic group: Antihaemorrhagics, blood coagulation factor VIII, ATC code: B02BD02

Mechanism of action

NovoEight® contains human coagulation factor VIII (rDNA), turoctocog alfa, a glycoprotein that has the same structure as human factor VIII when activated, and post-translational modifications that are similar to those of the plasma-derived molecule. When injected 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

Clinical efficacy, with regards to prophylaxis and treatment of bleeds, was investigated and the prophylactic effect of NovoEight® was confirmed in children and adults.

An overall annualised bleeding rate during preventive treatment was 3,03 bleeds/patient/year. The annualised bleeding rate in less frequent (twice-weekly or every third day) preventive regimen in previously treated patients was 2,01 bleeds/patient/year.
The annualised bleeding rate in the three times a week or every other day preventive regimen in previously treated patients was 2,91 bleeds/patient/year.

A success rate for treatment of bleeds of 88,9 % was observed when pooling data from all trials. Excluding bleeds for which there was no reported outcome (N = 49) resulted in a success rate of 90,2 %.

A total of 2 902 (88,1 %) bleeds were resolved with 1 − 2 infusions of NovoEight®, indicating that the clinical efficacy of NovoEight® in treatment of bleeds is similar to that of other rFVIII products.

Haemostasis was successful in 30 (100 %) of the surgeries, indicating that NovoEight® has a haemostatic effect both during and after surgery.

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 (factor VIII ≤ 1 %). Plasma factor VIII activity was measured using both the one-stage clotting assay and the chromogenic assay.

The single dose pharmacokinetic parameters of NovoEight® are listed in Table 3 for the one stage clotting assay and Table 4 for the chromogenic assay.

Table 3 Single-dose pharmacokinetics 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)	1 109 (374)	1 526 (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; $t_{½}$ = terminal half-life; Vss = volume of distribution at steady state; C_{max} = maximum factor VIII activity.

Table 4 Single-dose pharmacokinetics 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)	1 223 (436)	1 437 (348)	1 963 (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; $t_{½}$ = terminal half-life; Vss = volume of distribution at steady state; C_{max} = maximum factor VIII activity.

There was a tendency towards lower factor VIII activity levels in younger children (0 − 5 years) and older children (6 − 11 years) than in adolescents and adults. In general, there was a trend of increasing incremental recovery and decreasing clearance (mL/h/kg) with age. 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 body mass index (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 5 Single-dose pharmacokinetics 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)	1 510 (360)	1 920 (610)	1 730 (610)	2 030 (840)	2 350 (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 6 Single-dose pharmacokinetics 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)	1 860 (700)	2 730 (860)	2 310 (1020)	2 780 (1210)	3 050 (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

Calcium chloride dihydrate

Hydrochloric acid (for pH adjustment)

L-histidine

L-methionine

Polysorbate 80

Sodium chloride

Sodium hydroxide (for pH adjustment)

Sucrose

Solvent

Sodium chloride

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

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 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 or below 30 °C, for product which has been kept for a single period no longer than 3 months at room temperature (≤ 30 °C).

From a microbiological point of view, the medicine 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) 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) and storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Each pack of NovoEight® 250 IU, 500 IU, 1 000 IU, 1 500 IU, 2 000 IU and 3 000 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).

Not all strengths may be marketed.

6.6 Special precautions for disposal and other handling

After reconstitution the solution appears as a clear or slightly opalescent solution.

An infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters will also be needed. These devices are not included in the NovoEight® package.

Always use an aseptic technique.

After injection, safely dispose of the syringe with the infusion set and the vial with the vial adapter.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Holder of certificate of registration

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton

Johannesburg, 2196

8. Registration numbers

NovoEight® 250 IU: 56/8.1/0458

NovoEight® 500 IU: 56/8.1/0459

NovoEight® 1 000 IU: 56/8.1/0460

NovoEight® 1 500 IU: 56/8.1/0461

NovoEight® 2 000 IU: 56/8.1/0462

NovoEight® 3 000 IU: 56/8.1/0463

9. Date of first authorisation/Renewal of the authorisation

06 February 2024/07 February 2029

10. Date of revision of the text

N/A

NovoEight® is a trademark owned by Novo Nordisk Health Care AG, Switzerland.

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