PRODUCT INFORMATION

NOVOEIGHT®
Turoctocog alfa (rch)
(recombinant human coagulation factor VIII; rFVIII)
250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU

Powder and pre-filled solvent syringe for solution for injection

NAME OF THE MEDICINE

Turoctocog alfa (rch)

CAS name: Blood-coagulation factor VIII (synthetic human turoctocog alfa heavy chain), compd. with blood-coagulation factor VIII (synthetic human turoctocog alfa light chain).

CAS Registry Number: 1192451-26-5

DESCRIPTION

NovoEight (turoctocog alfa; human coagulation factor VIII) is a purified protein for use in the clinical management of factor VIII deficiency (haemophilia A or classic haemophilia). Turoctocog alfa is produced by recombinant DNA technology in Chinese hamster ovary cells and is a third generation FVIII product prepared without the use of serum or other animal-derived components. The manufacturing method of NovoEight minimises the risk of transmission of viral diseases.

Turoctocog alfa has an approximate molecular mass of 166 kDa (calculated excluding post-translational modifications). The turoctocog alfa molecule is a 1445 amino acid polypeptide containing a heavy chain of 87 kDa and a light chain of 79 kDa held together by non-covalent interactions. In wild type factor VIII the heavy chain contains varying lengths of B-domain, which in turoctocog alfa is a truncated B-domain with 21 amino acid residues. Six potential sites for tyrosine sulfation have been shown to be sulfated in the turoctocog alfa molecule. The tyrosine sulfation site present at Tyr32 (in the light chain; Tyr1680 in native full length), which is important for the binding to von Willebrand factor, has been found to be fully sulfated in the turoctocog alfa molecule.

Each vial contains nominally 250, 500, 1000, 1500, 2000 or 3000 international units (IU) turoctocog alfa (rch) (human coagulation factor VIII). One ml of NovoEight contains approximately 62.5-750 IU of turoctocog alfa (rch) (human coagulation factor VIII) after reconstitution. The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of NovoEight is 8337 IU/mg protein.

NovoEight powder for solution for injection contains the following excipients: sodium chloride, histidine, sucrose, polysorbate 80, methionine, calcium chloride, sodium hydroxide (for pH-adjustment) and hydrochloric acid (for pH-adjustment). NovoEight solvent contains sodium chloride and water for injections.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII. ATC code: Not yet assigned.

Mechanism of action

NovoEight contains 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 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.

Pharmacokinetics

All pharmacokinetic studies with NovoEight were conducted in previously treated patients (subjects) with severe haemophilia A (FVIII $\leq$ 1%) and without inhibitors to FVIII. The analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

A multi-centre, randomised and blinded field study of simulated post-injection plasma samples has been conducted to evaluate activity and assay performance and variability of NovoEight in *in-vitro* spiked plasma from subjects with haemophilia A at different clinical laboratories with the methodology and reagents routinely used in the laboratories. A total of 36 laboratories participated in the study; 33 laboratories used the one-stage clotting assay, 5 used the chromogenic assay, and 2 laboratories used both assays. Comparable and consistent estimates of target value were observed for NovoEight among the participating laboratories.

The pharmacokinetic parameters derived from an open-label sequential trial comparing the pharmacokinetics and safety of NovoEight and comparator drug in 23 previously treated patients (subjects) $\geq$ 12 years of age are listed in Table 1.

Table 1 Single-dose pharmacokinetics of NovoEight in 20* adult and adolescent subjects with severe haemophilia A (FVIII ≤ 1%)

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Inc. recovery (IU/ml)/(IU/kg)	0.020 (0.002)	0.028 (0.006)
AUC ((IU*h)/ml)	14.22 (3.75)	18.70 (5.08)
CL (ml/h/kg)	3.74 (0.95)	2.87 (0.80)
$t_{½}$ (h)	10.83 (4.95)	10.04 (3.59)
V_{ss} (ml/kg)	53.43 (10.88)	44.31 (28.17)
C_{max} (IU/ml)	1.07 (0.16)	1.54 (0.29)
MRT (h)	15.43 (6.36)	16.40 (10.14)

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

*Full analysis set adjusted for dose and product strength and excluding outliers; N=20

Abbreviations: Inc. recovery = incremental recovery; AUC = area under the plasma concentration-time curve; CL= clearance; $t_{½}$ = plasma elimination half-life; V_{ss} = steady date volume of distribution; C_{max} = peak plasma concentration; MRT = mean residence time

Pharmacokinetic data from single-dose administrations of NovoEight in 14 paediatric subjects below 6 years of age and in 14 paediatric subjects from 6 to below 12 years of age are listed in tables 2 and 3.

Table 2 Single-dose pharmacokinetics of NovoEight in children with haemophilia A (1 − < 6 years)

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Inc. recovery (IU/ml)/(IU/kg)	0.018 (0.007)	0.022 (0.006)
AUC ((IU*h)/ml)	9.89 (4.14)	12.21 (4.38)
CL (ml/h/kg)	6.26 (3.73)	4.60 (1.75)
$t_{½}$ (h)	7.65 (1.84)	9.99 (1.71)
V_{ss} (ml/kg)	57.30 (26.75)	55.79 (23.71)
C_{max} (IU/ml)	1.00 (0.58)	1.12 (0.31)
MRT (h)	9.65 (2.46)	12.09 (1.88)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N = 14

Table 3 Single-dose pharmacokinetics of NovoEight in children with haemophilia A (6 − < 12 years)

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Inc. recovery (IU/ml)/(IU/kg)	0.020 (0.004)	0.025 (0.006)
AUC ((IU*h)/ml)	11.09 (3.73)	14.36 (3.48)
CL (ml/h/kg)	5.02 (1.67)	3.70 (1.00)
$t_{½}$ (h)	8.02 (1.89)	9.42 (1.52)
V_{ss} (ml/kg)	46.82 (10.62)	41.23 (6.00)
C_{max} (IU/ml)	1.07 (0.35)	1.25 (0.27)
MRT (h)	9.91 (2.57)	11.61 (2.32)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N = 14

The pharmacokinetic parameters were comparable between paediatric subjects below 6 years of age and the paediatric subjects from 6 to below 12 years of age. Some variation was observed in the pharmacokinetic parameters of NovoEight between paediatric and adult

subjects. The higher CL and the shorter $t_{½}$[1] seen in paediatric subjects compared to adults with haemophilia A may be due in part to the known higher plasma volume per kilogram body weight in younger subjects.

CLINICAL TRIALS

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 subjects; 150 adolescents or adult subjects without inhibitors from the age of 12 years (≥150 exposure days) and 63 paediatric subjects without inhibitors below the age of 12 years of age (≥50 exposure days). 187 out of the 213 subjects continued in the safety extension trial.

Treatment with NovoEight was shown to be safe and had the intended haemostatic and preventative potential. No factor VIII inhibitor development was observed in any of the phase 3a clinical trials. A total of 991 bleeds were reported in 158 out of the 213 subjects. Traumatic bleeds were more frequent among paediatric subjects whereas spontaneous bleeds were more frequent among adolescents and adults. The vast majority of the bleeds were of mild/moderate severity and most frequently localised in articular joints. An overall assessment of efficacy was performed by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using a 4-point scale of excellent, good, moderate, or none. If the haemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the haemostatic response was rated as moderate or none, the treatment was considered a failure. The overall success rate for treatment of bleeds when pooling all trials was 84.6%. Of these 991 bleeds, 838 (84.6%) were rated excellent or good in their response to treatment with NovoEight, 111 (11.2%) were moderate, 17 (1.7%) was rated as having no response, and for 25 (2.5%) the response to treatment was unknown. Of the 991 reported bleeds, 898 (90.6%) of the bleeds were resolved with 1-2 injections of NovoEight.

Table 4 Success rate for haemostatic response by site of bleed

Site of bleed	Bleeds	Success rate (%) [a]
Joint	717	84.4%
Subcutaneous	41	87.8%
Muscular	70	85.7%
Gastrointestinal	5	60.0%
Mucosal	10	90.0%
Haemarthrosis + other sites	19	78.9%
Other	104	86.5%
Site not reported	25	80.0%
Total	991	84.6%

[a] Success rate: Number of 'Excellent' or 'Good' haemostatic responses/number of bleeds

[1] 29% and 26% lower $t_{1/2}$ for children 1-<6 yrs and 6-12 yrs, respectively, versus adolescents+adults ($t_{1/2}$ = 7.65 h and 8.02 h resp. versus 10.83 h).

The estimated annualised bleeding rate when pooled for all trials was 4.89 bleeds/subject/year whilst on treatment for prevention of bleeds.

Table 5 Annualised and Monthly Bleeding Rate

	Pooled trials	**Pivotal trial**	**Paediatric trial**	**Extension trial[a]**
Monthly Bleeding Rate	0.41	0.54	0.44	0.30
Annualised Bleeding Rate	4.89[b]	6.50	5.33	3.54

[a] Extension part of pivotal trial and paediatric trial

[b] Total duration of preventative treatment: 202.6 patient years

The 3543 and 3568 phase 3 clinical trials included surgery sub-trials. Subjects needing to undergo a major or minor surgical procedure requiring at least 7 days' of daily factor VIII treatment, including the day of surgery, participated in these sub-trials. A total of 11 surgeries were performed in 11 subjects of which 9 were major surgeries and 2 were minor. Apart from 1 adolescent, all of the subjects undergoing surgery were adults. Haemostasis was successful in all surgeries and no treatment failures were reported.

Table 6 Surgical procedures

Description of surgery	**Type**	**Haemostatic response [a]**	**Exposure Days [b]**
Left knee replacement	Major	Excellent	27
Arthroscopy and synovectomy, partial meniscectomy	Major	Good	154
Surgical extraction of tooth 48 and radix of tooth 12	Minor	Excellent	141
Right knee synovectomy with extirpation of ostheosynthetic graft	Major	Good	83
Circumcision	Minor	Excellent	106
Left total hip arthroplasty	Major	Excellent	38
Right ankle synovectomy	Major	Excellent	16
Right ankle synovectomy	Major	Excellent	9
Right ankle synovectomy	Major	Excellent	65
Arthroscopy of left ankle	Major	Excellent	421
Left hip arthroprosthesis, reduction finger fracture	Major	Good	437

a Haemostatic response during surgery

b Exposure days since first exposure to NovoEight at the time of surgery

INDICATIONS

NovoEight is indicated for the treatment and prophylaxis of bleeding episodes in patients with haemophilia A, including control and prevention of bleeding in surgical settings.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Known allergic reaction to hamster protein.

PRECAUTIONS

General

Hypersensitivity

As with any intravenous protein product, 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 NovoEight immediately and contact their physician 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 anaphylactic shock, the current medical standards for treatment of anaphylaxis should be followed.

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 Nijmegen modified Bethesda assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, the risk being highest within the first 20 exposure days. On rare occasions inhibitors may develop after the first 100 exposure days.

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 plasma levels of factor VIII activity 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.

No factor VIII inhibitor development was observed during the phase 3a clinical trial programme with NovoEight. The programme included 213 previously exposed subjects; 150 adolescents or adult subjects without inhibitors from the age of 12 years (≥150 previous exposure days) and 63 paediatric subjects without inhibitors aged 1 - < 12 years of age (≥50 previous exposure days).

There were no studies of NovoEight in subjects with inhibitors.

Previously untreated patients

There is no experience in previously untreated patients.

Effects on fertility

Animal reproduction studies have not been conducted with recombinant factor VIII products, including NovoEight.

Use in pregnancy

Pregnancy category: B2

Animal reproduction studies have not been conducted with recombinant factor VIII products, including NovoEight. 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.

Use in lactation

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 lactation if clearly indicated.

Paediatric use

There is no experience in children younger than 1 year of age and limited experience in children under 2 years (N=2). In clinical studies involving 31 children aged 1 − < 6 years, 32 children aged 6 to < 12 years, and 24 adolescents aged 12 to 18 years, with severe haemophilia A, no difference in the safety profile of NovoEight was observed between paediatric subjects and adults.

Use in the elderly

There is no experience in elderly patients (> 60 years of age).

Genotoxicity

Genotoxicity studies have not been performed with NovoEight since FVIII is an endogenous protein.

Carcinogenicity

No carcinogenicity studies have been conducted with NovoEight since FVIII is an endogenous protein.

Effect on laboratory tests

No significant effects on laboratory tests have been observed.

Incompatibilities

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

Effects on ability to drive and use machines

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

Advice when travelling

Patients should be advised to ensure they have adequate supplies of NovoEight prior to travelling. Patients should consult their healthcare professional prior to travelling to obtain appropriate guidance on the clinical management of their condition.

INTERACTION WITH OTHER MEDICINES

No interaction studies have been performed with NovoEight. No interactions of recombinant factor VIII products with other medicines are known.

ADVERSE EFFECTS

During all clinical studies, a total of 503 adverse events were reported in 154 of 214 subjects exposed to NovoEight. Of the 503 adverse events, 337 events were reported in 98 subjects ≥18 years, 66 events in 19 adolescents between 12 and 17 years, 46 events in 18 children between 6 and 11 years, and 54 events were reported in 19 children < 6 years.

Table 7 Summary of adverse events with an incidence of ≥ 5% in the total safety population

MedDRA System Organ Class	MedDRA Preferred Term	Number of Events	Number of Subjects	% of evaluable Subjects
Nervous system disorders	Headache	34	22	10.3
Infections and infestations	Nasopharyngitis	30	22	10.3
	Upper respiratory tract infection	13	11	5.1
Injury, poisoning and procedural complications	Incorrect dose administered	26	19	8.9
Musculoskeletal and connective tissue disorders	Arthralgia	15	13	6.1
General disorders and administration site conditions	Pyrexia	15	13	6.1
Gastrointestinal disorders	Toothache	12	11	5.1

Paediatric population

In clinical studies involving 63 paediatric subjects aged 1 to <12 years of age and 24 adolescents aged 12 to 18 years of age with severe haemophilia A, no difference in the safety profile of NovoEight was observed between paediatric subjects and adults.

DOSAGE AND ADMINISTRATION

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

NovoEight is suitable for use in both children and adults.

Dosage

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 dose of factor VIII is expressed in international units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal level human plasma) or in IU (relative to an international standard for factor VIII in plasma).

One 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 dosage of factor VIII is based on the empirical finding that 1 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 (IU) = body weight (kg) x desired factor VIII rise (% or IU/dl) x 0.5 (IU/kg per IU/dl)

The dose and frequency of administration should be adjusted to achieve clinical effectiveness in the individual case.

In 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 9 Guide for dosing in bleeding episodes and surgery

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

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.

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 patients under 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. In comparison to adults, children may have shorter half-life and lower recovery of factor VIII. This should be taken into account when dosing or following factor VIII levels in the paediatric population. Because clearance (based on per kg body weight) has been demonstrated to be higher in the paediatric population, larger or more frequent dosing based on per kg body weight may be needed in this population. For details, see 'Pharmacokinetics.'

Method of administration

NovoEight should be administered via the intravenous route. For instructions on reconstitution of the medicinal product before administration, see Consumer Medicine Information.

OVERDOSAGE

No symptoms of overdose have been reported in the clinical trial programme for NovoEight. For information on the management of overdose, contact the Poison Information Centre on 131 126 (Australia).

PRESENTATIONS AND STORAGE CONDITIONS

NovoEight is supplied as a white or slightly yellow lyophilised powder to be reconstituted with solvent. The solvent is clear and colourless. The reconstituted solution has a pH of approximately 6.5 to 7.5.

Each pack of NovoEight 250-3000 IU powder and solvent for solution for injection contains:

- Glass vial (type I) with powder and chlorobutyl rubber stopper
- Sterile vial adaptor for reconstitution
- 4.3 ml of solvent in prefilled syringe with backstop (polypropylene), a rubber plunger (bromobutyl) and a tipcap with a stopper (bromobutyl)
- Plunger rod (polypropylene)

The complete composition of NovoEight after reconstitution for 250 – 3000 IU/vial:

Contents	**Per vial***	**Function**
Turoctocog alfa (rFVIII)	250/500/1000/1500/2000/ 3000 IU	Active pharmaceutical ingredient
Sodium chloride	18 mg/ml	Stabiliser
Histidine	1.5 mg/ml	Buffering agent
Sucrose	3 mg/ml	Bulking agent
Polysorbate 80	0.1 mg/ml	Surfactant
Methionine	0.055 mg/ml	Antioxidant
Calcium chloride	0.25 mg/ml	Stabiliser
Sodium hydroxide	QS	pH adjustment
Hydrochloric acid	QS	pH adjustment

*plus overage

Contents	**Per prefilled syringe**	**Function**
Sterile water for injection	4.3 ml	Solvent
Sodium chloride	0.9 %	

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

During the shelf life, the product may be kept at room temperature ≤ 30°C for a single period not exceeding 6 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.

For storage conditions of the reconstituted medicinal product, see ’Shelf life.

Shelf life

Unopened:
2 years

After reconstitution:
Do not use reconstituted NovoEight exhibiting particulates or discoloration. NovoEight contains no antimicrobial preservative and is intended for use in one patient on one occasion only.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution. If the reconstituted product is not used immediately it should be used within 4 hours when stored at room temperature (≤ 30°C), and within 24 hours when stored at 2°C - 8°C. Store the reconstituted product in the vial. Any unused product stored at room temperature for more than 4 hours should be discarded.

NAME AND ADDRESS OF THE SPONSOR

Novo Nordisk Pharmaceuticals Pty. Ltd.
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POISON SCHEDULE OF THE MEDICINE

Unscheduled.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

8 January 2014