ANNEX I

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

Esperoct 500 IU powder and solvent for solution for injection
Esperoct 1000 IU powder and solvent for solution for injection
Esperoct 1500 IU powder and solvent for solution for injection
Esperoct 2000 IU powder and solvent for solution for injection
Esperoct 3000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Esperoct 500 IU powder and solvent for solution for injection
Each powder vial contains nominally 500 IU turoctocog alfa pegol*.
After reconstitution, 1 mL of solution contains approximately 125 IU turoctocog alfa pegol.

Esperoct 1000 IU powder and solvent for solution for injection
Each powder vial contains nominally 1000 IU turoctocog alfa pegol*.
After reconstitution, 1 mL of solution contains approximately 250 IU turoctocog alfa pegol.

Esperoct 1500 IU powder and solvent for solution for injection
Each powder vial contains nominally 1500 IU turoctocog alfa pegol*.
After reconstitution, 1 mL of solution contains approximately 375 IU turoctocog alfa pegol.

Esperoct 2000 IU powder and solvent for solution for injection
Each powder vial contains nominally 2000 IU turoctocog alfa pegol*.
After reconstitution, 1 mL of solution contains approximately 500 IU turoctocog alfa pegol.

Esperoct 3000 IU powder and solvent for solution for injection
Each powder vial contains nominally 3000 IU turoctocog alfa pegol*.
After reconstitution, 1 mL of solution contains approximately 750 IU turoctocog alfa pegol.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of turoctocog alfa pegol is approximately 9500 IU/mg protein.

The active substance turoctocog alfa pegol is a covalent conjugate of the protein turoctocog alfa* with a 40 kDa polyethylene-glycol (PEG).

*Human factor VIII, produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line, and no additives of human or animal origin are used in the cell culture, purification, conjugation or formulation of Esperoct.

Excipient with known effect

Each reconstituted vial contains 30.5 mg of sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The solvent is clear and colourless.

pH: 6.9.

Osmolality: 590 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).

4.2 Posology and method of administration

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

Previously untreated patients

The safety and efficacy of Esperoct in previously untreated patients have not yet been established.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII activity levels is advised to guide adjustments of the dosing regimen of Esperoct, if needed. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and incremental recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, monitoring of the factor VIII substitution therapy by measurement of plasma factor VIII activity is necessary.

The factor VIII activity of Esperoct can be measured using the conventional factor VIII assays, the chromogenic assay and the one-stage assay.
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.
When using a one-stage clotting assay some silica based reagents should be avoided as they cause underestimation. 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, dosing interval and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. The number of units of factor VIII administered is expressed in International Units (IU), which is related to the current WHO concentrate standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal human plasma level) or in International Units per dL (relative to the current 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 of human plasma.

On demand treatment and treatment of bleeding episodes

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 (IU) = 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.

Guidance for the dosing of Esperoct for the on-demand treatment and treatment of bleeding episodes is provided in table 1. Plasma factor VIII activity levels should be maintained at or above the described plasma levels (in IU per dL or % of normal). For treatment of bleeds a maximum single dose of Esperoct at 75 IU/kg and a maximum total dose of 200 IU/kg/24 hours may be administered.

Table 1 Guidance for treatment of bleeding episodes with Esperoct

Degree of haemorrhage	**Factor VIII level required (IU/dL or % of normal)**[a]	**Frequency of doses (hours)**	**Duration of therapy**
Mild Early haemarthrosis, mild muscle bleeding or mild oral bleeding	20-40	12-24	Until the bleeding is resolved
Moderate More extensive haemarthrosis, muscle bleeding, haematoma	30-60	12-24	Until the bleeding is resolved
Severe or life-threatening haemorrhages	60-100	8-24	Until the threat is resolved

[a] The required dose is determined using the following formula:
Required units (IU) = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL).

Perioperative management

The dose level and dosing intervals for surgery depend on the procedure and local practice. A maximum single dose of Esperoct at 75 IU/kg and a maximum total dose of 200 IU/kg/24 hours may be administered.
The frequency of doses and duration of therapy should always be individually adjusted based on individual clinical response.

Table 2 includes general recommendation for dosing of Esperoct for perioperative management. Consideration should be given to maintain a factor VIII activity at or above the target range.

Table 2 Guidance for dosing of Esperoct for perioperative management

Type of surgical procedure	**Factor VIII level required (%) (IU/dL)**[a]	**Frequency of doses (hours)**	**Duration of therapy**
Minor surgery Including tooth extraction	30-60	Within one hour before surgery	Single dose or repeat injection every 24 hours for at least 1 day until healing is achieved

		Repeat after 24 hours if necessary	
Major surgery	80-100 (pre- and post-operative)	Within one hour before surgery to achieve factor VIII activity within the target range Repeat every 8 to 24 hours to maintain factor VIII activity within the target range	Repeat injection every 8 to 24 hours as necessary until adequate wound healing is achieved Consider to continue therapy for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL)

[a] The required dose is determined using the following formula:
Required units (IU) = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL).

Prophylaxis
The recommended dose is 50 IU of Esperoct per kg body weight every 4 days.

Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency.

Paediatric population
The dose in adolescents (12 years and above) is the same as for adults.
In children below 12 years long-term safety has not been established.

Method of administration

Esperoct is for intravenous use.

Esperoct should be administered by intravenous injection (over approximately 2 minutes) after reconstitution of the powder with 4 mL supplied solvent (sodium chloride 9 mg/mL (0.9%) solution for injection).

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

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 Esperoct. 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 immediately discontinue the use of the medicinal product 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 pro-coagulant 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 observations and laboratory tests. 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 events

In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk.

Catheter-related complications

If a central venous access device (CVAD) is required, the 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 adolescents (12-18 years).

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 2.0 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) with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. 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 lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

Esperoct 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 Esperoct. 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 frequencies of adverse reactions as observed in 270 unique subjects across five prospective, multi-centre clinical studies in previously treated patients (PTPs) with severe haemophilia A (<1% endogenous factor VIII activity) and no history of inhibitors are listed in table 3. The categories of adverse reactions presented in table 3 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).

Table 3 Frequency of adverse reactions in clinical trials for PTPs*

MedDRA System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)**
Immune system disorders	Hypersensitivity	Uncommon
Skin and subcutaneous tissue disorders	Rash Erythema Pruritus	Common
General disorders and administration sites conditions	Injection site reactions***	Common

* PTPs: Previously-treated patients.
** Frequency is based on studies with all factor VIII products which included patients with severe haemophilia A.
*** Preferred terms included in injection site reactions: Injection site reaction, Vessel puncture site haematoma, Infusion site reaction, Injection site erythema, Injection site rash, Vessel puncture site pain, and Injection site swelling.

Description of selected adverse reactions

Factor VIII inhibitors
One confirmed case of factor VIII inhibitor occurred in an 18 year-old previously treated patient on prophylactic treatment with Esperoct. The patient had a factor VIII gene intron 22 inversion and was at a high risk of developing factor VIII inhibitors.
There is no indication of an increased risk of factor VIII inhibitor development with treatment of Esperoct as compared to other factor VIII products.

Anti-drug antibodies
There was one case of persistent anti-drug antibodies concomitant with the confirmed case of factor VIII inhibitors (see *Factor VIII inhibitors)*. Three patients had transiently positive test results for anti-drug antibodies after administration of Esperoct but no correlation with adverse events could be established.

Anti-PEG antibodies

Thirty-two patients had pre-existing anti-PEG antibodies before administration of Esperoct. Twenty of the 32 patients were negative for anti-PEG antibodies post administration of Esperoct. Eleven patients developed transient low titre anti-PEG antibodies. No correlation with adverse events could be established.

Paediatric population

No difference in the safety profile was observed between previously treated adolescents (12-18 years) and adult patients.

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: antihemorrhagics, blood coagulation factor VIII, ATC code: B02BD02.

Mechanism of action

Turoctocog alfa pegol is a purified recombinant human factor VIII (rFVIII) product with a 40 kDa polyethylene-glycol (PEG) conjugated to the protein. The PEG is attached to the O-linked glycan in the truncated B-domain of rFVIII (turoctocog alfa). The mechanism of action of turoctocog alfa pegol is based on the replacement of the deficient or absent factor VIII in patients with haemophilia A. When turoctocog alfa pegol is activated by thrombin at the site of injury, the B-domain containing the PEG moiety and the a3-region are cleaved off, thus generating activated recombinant factor VIII (rFVIIIa) which is similar in structure to native factor VIIIa.
The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When injected into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor 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 results of accidental or surgical trauma. By factor VIII replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Clinical efficacy during prophylaxis and treatment of bleeding episodes

The clinical efficacy of Esperoct for prophylaxis and treatment of bleeds was investigated in five prospective, multi-centre clinical studies in 270 previously treated patients (PTPs) with severe haemophilia A.

Prophylaxis in adults/adolescents

The efficacy of Esperoct for prophylaxis and treatment of bleeds was evaluated in an open-label, non-controlled trial in adolescents and adult patients with severe haemophilia A ages 12 years and above. The prophylactic effect of Esperoct was demonstrated with a dosing at 50 IU per kg body weight every 4 days or every 3–4 days (twice weekly) in 175 patients. The median annualised bleeding rate (ABR) in adults and adolescents receiving Esperoct was 1.18 (Interquartile range IQR: 0.00;4.25), whereas the spontaneous ABR was 0.00 (IQR: 0.00;1.82), traumatic ABR was 0.00 (IQR: 0.00;1.74) and joint ABR was 0.85 (IQR: 0.00;2.84). When including imputations, (replacing missing data for withdrawn patients with a substituted value) the estimated mean ABR for all bleeds was 3.70 (95% CI: 2.94;4.66). Of the 175 adults/adolescents on prophylaxis, 70 (40%) did not have any bleeds. The mean annual consumption for prophylaxis was 4641 IU/kg.

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

Adults/adolescents who had a low bleeding rate of 0-2 bleeding episodes during the last 6 months and had obtained at least 50 doses of Esperoct had the option of being randomised to prophylaxis treatment every 7 days (75 IU/kg every 7 days) or every 4 days (50 IU/kg every 4 days). A total of 55 of the 120 eligible patients chose to be randomised (17 to the every 4 days dosing and 38 to the 75 IU every 7 days). The ABR for randomised patients was 1.77 (0.59; 5.32) for treatment every 4 days and 3.57 (2.13; 6.00) for once weekly prophylaxis. Nine of these patients reverted back to prophylaxis every 4 days during the randomised study phase. Overall, including all extensions parts, 31 of 61 patients on every 7 days prophylaxis switched back to every 4 days treatment.

Prophylaxis in children (below 12 years)

The use of Esperoct in children below 12 years is not indicated (see section 4.2 for information on paediatric use).
The efficacy and safety of Esperoct for prophylaxis treatment of bleeds were evaluated in an open-label, single-arm, non-controlled trial in 68 children below 12 years with severe haemophilia A. The prophylactic effect of Esperoct was demonstrated with a dosing at 60 IU per kg body weight (50-75 IU/kg) twice weekly. The median and estimated mean annualised bleeding rate in children below 12 years receiving Esperoct twice weekly was 1.95 and 2.13 (95% CI: 1.48;3.06), whereas the spontaneous ABR was 0.00 and 0.58 (95% CI: 0.24;1.40), traumatic ABR was 0.00 and 1.52 (95% CI: 1.07;2.17) and joint ABR was 0.00 and 1.03 (95% CI: 0.59;1.81), respectively. Of the 68 children below 12 years on prophylaxis, 29 (42.6%) did not have any bleeds.
The mean annual consumption for prophylaxis was 6475 IU/kg.

Clinical efficacy of Esperoct in treatment of bleeding episodes and during on-demand treatment

The efficacy of Esperoct in the treatment of bleeding episodes was demonstrated in all age groups. The vast majority of bleeds treated with Esperoct were of mild/moderate severity.
The overall success rate for the treatment of bleeds was 87.7% and 94.4% of all bleeds treated with 1-2 injections.

In 12 patients above 18 years of age, 1,126 bleedings were treated among patients receiving on-demand treatment with an average treatment dose of 38.1 IU/kg with a mean annual consumption of 1457 IU/kg. Of the total 1,126 bleeds, 86.9% were effectively treated with 1 injection and 96.8% were effectively treated with 1-2 injections of Esperoct.

Clinical efficacy of Esperoct during major surgery

Esperoct was effective in maintaining haemostasis during major surgery with a success rate of 95.6% in all major surgeries performed (43 out of 45 had the effect rated as ‘excellent‘ or ‘good‘).

5.2 Pharmacokinetic properties

In total, 129 single-dose pharmacokinetic (PK) profiles of Esperoct were evaluated in 86 patients (including 24 paediatric patients of 0 to below 12 years).

All pharmacokinetic studies with Esperoct were conducted in previously treated patients with severe haemophilia A (factor VIII <1%). Patients received a single dose of 50 IU/kg, and blood samples were collected prior to dosing and at multiple time points up to 96 hours after dosing.

The half-life of Esperoct was 1.6 fold longer compared to unmodified factor VIII products in adults.

Pharmacokinetic parameters

A total of 108 single dose pharmacokinetic profiles at 50 IU/kg Esperoct were evaluated in 69 patients. The single dose pharmacokinetic parameters are comparable between young children (0 to below 6 years) and older children (6 to below 12 years), and between adolescents (12 to17 years) and adults (18 years and above).
As expected incremental recovery appeared to be lower while body weight adjusted clearance appeared to be higher in children compared to adults and adolescents. In general, there was a trend of increasing incremental recovery and decreasing clearance (mL/h/kg) with age. This corresponds to a higher volume of distribution per kilo body weight in children compared to adults (table 4).
The single dose pharmacokinetic parameters determined after 28 weeks of prophylactic treatment with Esperoct were consistent with the initial pharmacokinetic parameters.

Single-dose pharmacokinetic parameters of Esperoct are listed in table 4. The use of Esperoct in children below 12 years is not indicated.

Table 4 Single-dose pharmacokinetic parameters of Esperoct 50 IU/kg in children, adolescents and adults by age using the chromogenic assay (geometric mean [CV%])

PK Parameter N=No. of patients	0 to below 6 years N=13	6 to below 12 years N=11	12 to below18 years N=3	18 years and above N=42
Number of profiles	13	11	5	79
IR (IU/dL) per (IU/kg)[a]	1.80 (29)	1.99 (25)	2.79 (12)	2.63 (22)
Maximum factor VIII activity (IU/dL)[a]	101.2 (28)	119.6 (25)	133.2 (9)	134.4 (23)
$t_{1/2}$ (hours)	13.6 (20)	14.2 (26)	15.8 (43)	19.9 (34)
AUC_{inf} (IU*hour/dL)	2147 (47)	2503 (42)	3100 (44)	3686 (35)
CL (mL/hour/kg)	2.6 (45)	2.4 (40)	1.5 (43)	1.4 (32)
Vss (mL/kg)	44.2 (34)	41.2 (25)	33.4 (10)	37.7 (27)
MRT (hours)	17.0 (22)	17.3 (31)	21.7 (45)	25.2 (29)[b]

Abbreviations: AUC = area under the factor VIII activity time profile; $t_{1/2}$ = terminal half-life; MRT = mean residence time; CL = clearance; Vss = volume of distribution at steady–state; IR = Incremental recovery.
[a] Incremental recovery and factor VIII were assessed 30 min post-dosing for patients 12 years and above and 60 min post-dosing (first sample) for children below12 years.
[b] Calculation based on 67 profiles.

The mean trough plasma factor VIII activity levels at steady–state during prophylactic treatment with Esperoct dosed with 50 IU/kg every 4 days is 3.0 IU/dL (95% CI: 2.6;3.4) in patients 12 years and above.

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 or reconstituted with injection solutions other than the provided sodium chloride solvent.

The reconstituted product should not be administered in the same tubing or container with other medicinal products.

6.3 Shelf life

Unopened vial (before reconstitution):

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 12 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 stored outside of the refrigerator, the product must not be returned for storage in the refrigerator.

Record the beginning of storage outside refrigerator and the storage temperature in the space provided on the carton.

After reconstitution

Chemical and physical in-use stability have been demonstrated for:
- 24 hours when stored in a refrigerator (2°C - 8°C) or
- 4 hours at ≤30°C or

- 1 hour between >30°C and 40°C, only if the product was stored above room temperature (>30°C up to 40°C) before reconstitution for no longer than 3 months.

From a microbiological point of view, the 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 users and would normally not be recommended for longer than as stated above, unless reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution should be stored in the vial.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package 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 Esperoct contains:
– 1 glass vial (type I) with powder closed with a chlorobutyl rubber stopper, an aluminium seal with a plastic snap-off cap
– 1 sterile vial adapter for reconstitution
– 1 pre-filled syringe of 4 mL solvent with backstop (polypropylene), a rubber plunger (bromobutyl) and a rubber tip cap (bromobutyl)
– 1 plunger rod (polypropylene).

6.6 Special precautions for disposal and other handling

Esperoct 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 and colourless liquid free of visible particles. The reconstituted medicinal product should be inspected visually for particulate matter and discolouration prior to administration. The solution should be clear and colourless. Do not use solutions that are cloudy or have deposits.

For instructions on reconstitution of the medicinal product before administration, see the package leaflet.

The rate of administration should be determined by the patient's comfort level over approximately 2 minutes.

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

Always use an aseptic technique.

Disposal

After the injection, safely dispose of the syringe with the infusion set and the vial with the vial adapter. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1374/001
EU/1/19/1374/002
EU/1/19/1374/003
EU/1/19/1374/004
EU/1/19/1374/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2019

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

Name and address of the manufacturer of the biological active substance

Novo Nordisk US Bio Production Inc.
9 Technology Drive
West Lebanon
New Hampshire
03784
United States

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 (PSURs)**

The requirements for submission of PSURs 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.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date

Post-authorisation safety study (PASS): In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a post-authorisation safety study according to an agreed protocol.	31/12/2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Esperoct 500 IU powder and solvent for solution for injection

turoctocog alfa Pegol
(recombinant coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 500 IU turoctocog alfa pegol (approx. 125 IU/mL 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 a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

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 the shelf life, the product may be stored
- at room temperature (≤30°C) for a single period no longer than 12 months **or**
- above room temperature (>30°C - 40°C) for a single period no longer than 3 months

Date removed from refrigerator: _____ Stored at ≤30°C ☐ or >30°C - 40°C ☐

Store in the original package 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 NUMBER

EU/1/19/1374/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Esperoct 500

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(S) OF ADMINISTRATION

Esperoct 500 IU powder for solution for injection
turoctocog alfa Pegol
IV

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

Esperoct 1000 IU powder and solvent for solution for injection

turoctocog alfa Pegol
(recombinant coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 1000 IU turoctocog alfa pegol (approx. 250 IU/mL 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 a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

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 the shelf life, the product may be stored
- at room temperature (≤30°C) for a single period no longer than 12 months **or**
- above room temperature (>30°C - 40°C) for a single period no longer than 3 months

Date removed from refrigerator:_____Stored at ≤30°C ☐ or >30°C - 40°C ☐

Store in the original package 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 NUMBER

EU/1/19/1374/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Esperoct 1000

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(S) OF ADMINISTRATION

Esperoct 1000 IU powder for solution for injection
turoctocog alfa Pegol
IV

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

Esperoct 1500 IU powder and solvent for solution for injection

turoctocog alfa Pegol
(recombinant coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 1500 IU turoctocog alfa pegol (approx. 375 IU/mL 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 a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

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 the shelf life, the product may be stored
- at room temperature (≤30°C) for a single period no longer than 12 months **or**
- above room temperature (>30°C - 40°C) for a single period no longer than 3 months

Date removed from refrigerator: _____ Stored at ≤30°C ☐ or >30°C - 40°C ☐

Store in the original package 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/1/19/1374/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Esperoct 1500

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(S) OF ADMINISTRATION

Esperoct 1500 IU powder for solution for injection
turoctocog alfa Pegol
IV

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

Esperoct 2000 IU powder and solvent for solution for injection

turoctocog alfa Pegol
(recombinant coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 2000 IU turoctocog alfa pegol (approx. 500 IU/mL 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 a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

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 the shelf life, the product may be stored
- at room temperature (≤30°C) for a single period no longer than 12 months **or**
- above room temperature (>30°C - 40°C) for a single period no longer than 3 months

Date removed from refrigerator: _____ Stored at ≤30°C ☐ or >30°C - 40°C ☐

Store in the original package 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/1/19/1374/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Esperoct 2000

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(S) OF ADMINISTRATION

Esperoct 2000 IU powder for solution for injection
turoctocog alfa Pegol
IV

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

Esperoct 3000 IU powder and solvent for solution for injection

turoctocog alfa Pegol
(recombinant coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 3000 IU turoctocog alfa pegol (approx. 750 IU/mL 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 a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

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 the shelf life, the product may be stored
- at room temperature (≤30°C) for a single period no longer than 12 months **or**
- above room temperature (>30°C - 40°C) for a single period no longer than 3 months

Date removed from refrigerator: _____ Stored at ≤30°C ☐ or >30°C - 40°C ☐

Store in the original package 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/1/19/1374/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Esperoct 3000

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(S) OF ADMINISTRATION

Esperoct 3000 IU powder for solution for injection
turoctocog alfa Pegol
IV

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(S) OF ADMINISTRATION

Solvent for Esperoct

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

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

turoctocog alfa pegol (pegylated human coagulation factor VIII (rDNA))

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 Esperoct is and what it is used for

What Esperoct is
Esperoct contains the active substance turoctocog alfa pegol and is a long-acting recombinant coagulation factor VIII product. Factor VIII is a protein found in the blood that helps to prevent and stop bleeding.

What Esperoct is used for
Esperoct is used to treat and prevent bleeding in people 12 years and above with haemophilia A (inborn factor VIII deficiency).

In people with haemophilia A, factor VIII is missing or does not work properly. Esperoct 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 Esperoct

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

Warnings and precautions

Previous use of factor VIII medicine
Tell your doctor if you have used factor VIII medicines before, especially if you developed inhibitors (antibodies) against the medicine, since there might be a risk that it happens again.

Allergic reactions
There is a risk that you may experience a severe and sudden allergic reaction (e.g. anaphylactic reaction) to Esperoct.

Stop the injection and contact your doctor or an emergency unit immediately if you have early signs of allergic reactions. These early signs may include rash, hives, weals, itching on large areas of skin, redness and/or swelling of lips, tongue, face or hands, difficulty in swallowing or breathing, wheezing, tightness of the chest, pale and cold skin, fast heartbeat, or dizziness, headache, nausea and vomiting.

Development of 'FVIII inhibitors' (antibodies)
Inhibitors (antibodies) can develop during the treatment with all factor VIII medicines
- These inhibitors, especially at high levels, stop the treatment working properly
- You will be monitored carefully for development of these inhibitors
- If your bleeding is not being controlled with Esperoct, tell your doctor immediately
- Do not increase the total dose of Esperoct to control your bleed without talking to your doctor.

Catheter-related problems
If you have a catheter where medicines can be injected into your blood (central venous access device), you may develop infections or blood clots at the site of the catheter.

Heart disease
Talk to your doctor or pharmacist if you have heart disease or you are at risk of heart disease.

Children
Esperoct can not be used in children below 12 years of age.

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

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

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

Esperoct 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 daily dietary intake of sodium for an adult.

3. How to use Esperoct

Treatment with Esperoct will be started by a doctor who is experienced in the care of people with haemophilia A.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure about how to use Esperoct.

How Esperoct is given

Esperoct is given as an injection into a vein (intravenously), see “Instructions on how to use Esperoct” for more information.

How much to use
Your doctor will calculate your dose for you. This will depend on your body weight and whether it is used to prevent or to treat a bleeding.

To prevent bleeding
Adults and adolescents (12 years of age and above): The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Your doctor may choose another dose or how often the injections should be given, based on your need.

To treat bleeding
The dose of Esperoct 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. If you experience that the effect of Esperoct is insufficient, talk to your doctor.

Use in children and adolescents
Adolescents (12 years of age and above) can use the same dose as adults.

If you use more Esperoct than you should
If you use more Esperoct than you should, contact your doctor straight away.

If you have to significantly increase your usage of Esperoct to stop a bleed, talk to your doctor immediately. For further information, see “Development of ‘FVIII inhibitors’ (antibodies)” in section 2.

If you forget to use Esperoct
If you forget a dose, inject the missed dose as soon as you remember. Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor. If you are in doubt, contact your doctor.

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

Allergic reactions (hypersensitivity)
Stop the injection immediately if you develop severe and sudden allergic reactions (anaphylactic reactions). You must contact your doctor or an emergency unit immediately if you have signs of an allergic reaction such as:
- difficulty in swallowing or breathing
- wheezing
- chest tightness
- redness and/or swelling of the lips, tongue, face or hands
- rash, hives, weals or itching
- pale and cold skin, fast heartbeat, or dizziness (low blood pressure)
- headache, nausea or vomiting.

Development of ‘FVIII inhibitors’ (antibodies)
If you have previously received more than 150 days of treatment with factor VIII, inhibitors (antibodies) may develop (may affect up to 1 in 100 people). If this happens, your medicine may stop

working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately. See “Development of ‘FVIII inhibitors’ (antibodies)” in section 2.

The following side effects have been observed with Esperoct

Common side effects (may affect up to 1 in 10 people)
- skin reactions where the injection is given
- itching (pruritus)
- redness of skin (erythema)
- rash.

Uncommon side effects (may affect up to 1 in 100 people)
- allergic reactions (hypersensitivity). These may become severe and could be life-threatening, see “Allergic reactions (hypersensitivity)” above for more information
- factor VIII inhibitors (antibodies) in patients previously treated with factor VIII.

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 Esperoct

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, on the vial, and on the pre-filled syringe labels. The expiry date refers to the last day of that month.

Before reconstitution (before the powder is mixed with the solvent):
Store in a refrigerator (2°C - 8°C). Esperoct can be kept
- at room temperature (≤30°C) for a single period for up to 12 months within the shelf life of the product **or**
- above room temperature (>30°C up to 40°C) for a single period for up to 3 months within the shelf life of the product.

When you start to store Esperoct outside the refrigerator, record the date and the storage temperature in the space provided on the carton.
Once you have taken the product out of the refrigerator for storage you must not store it again in the refrigerator.Do not freeze. Store in the original package in order to protect from light.

After reconstitution (after the powder has been mixed with the solvent):
Once you have reconstituted Esperoct, it should be used immediately. If you cannot use the reconstituted solution immediately, it should be used within
- 24 hours when stored in a refrigerator (2°C - 8°C) **or**
- 4 hours at ≤30°C **or**
- 1 hour between >30°C and 40°C, only if the product was stored above room temperature (>30°C up to 40°C) before reconstitution for no longer than 3 months.

The powder in the vial appears as a white to off-white powder. Do not use the powder if the colour has changed.

The reconstituted solution must be clear and colourless. Do not use the reconstituted solution if you notice any particles or discolouration.

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 Esperoct contains

- The active substance is turoctocog alfa pegol (pegylated human coagulation factor VIII (rDNA)). Each vial of Esperoct contains nominally 500, 1000, 1500, 2000 or 3000 IU turoctocog alfa pegol.
- 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 9 mg/mL (0.9%) solution for injection 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 125, 250, 375, 500 or 750 IU turoctocog alfa pegol per mL, respectively (based on the strength of turoctocog alfa pegol, i.e. 500, 1000, 1500, 2000 or 3000 IU).

What Esperoct looks like and contents of the pack
Esperoct is available in packs containing 500 IU, 1000 IU, 1500 IU, 2000 IU, or 3000 IU. Each pack of Esperoct contains a vial with white to off-white powder, a 4 mL pre-filled syringe with a clear colourless solvent, 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 01/2020

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 Esperoct

Read these instructions carefully before using Esperoct.

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

You will also need:
- an infusion set (butterfly needle with tubing)
- sterile alcohol swabs
- gauze pads and plasters.

These items are not included in the Esperoct 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 a vein, it is important to **use a clean and germ- free (aseptic) technique.** An incorrect technique can introduce germs that can infect your 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 has expired. Use a new package instead. The expiry date is printed 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.

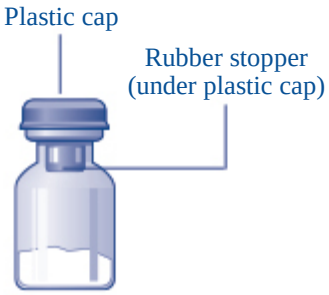
The equipment is for single use only.

Contents

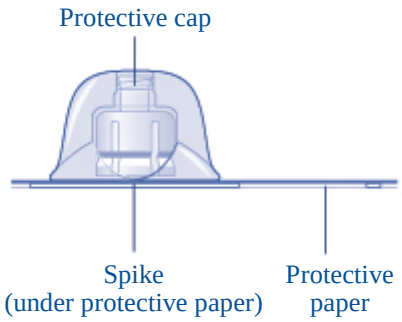
The package contains:
- 1 vial with Esperoct powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

Overview

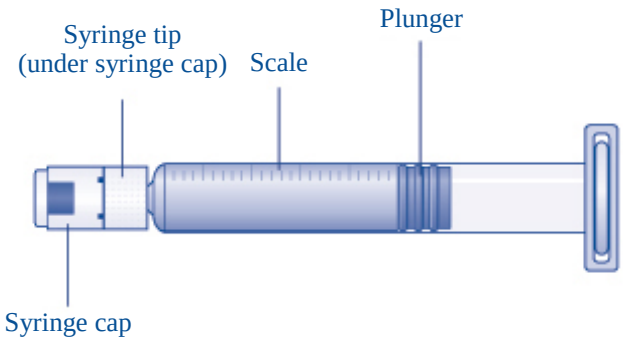
Vial with Esperoct powder



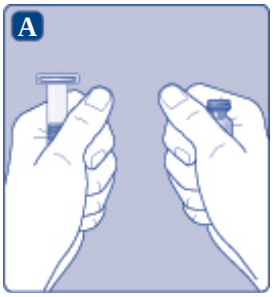
Vial adapter

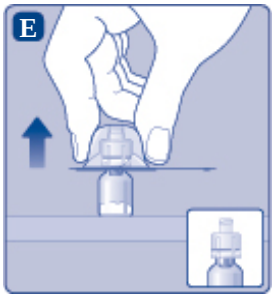
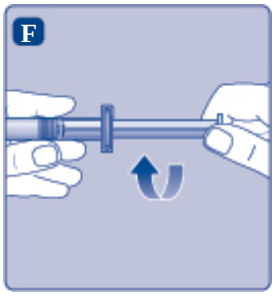
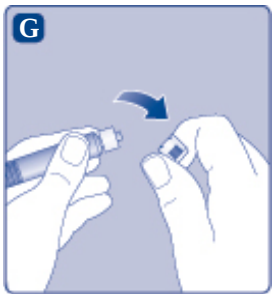
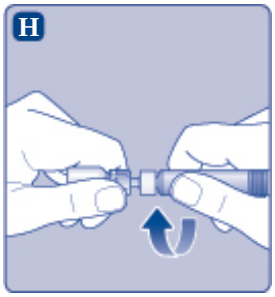


Pre-filled syringe with solvent



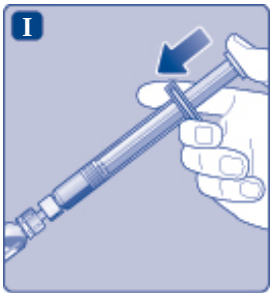
Plunger rod

1. Prepare the vial and the syringe • **Take out the number of Esperoct 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 let them 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, see figure **A**. **Do not use any other way to warm** 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.	

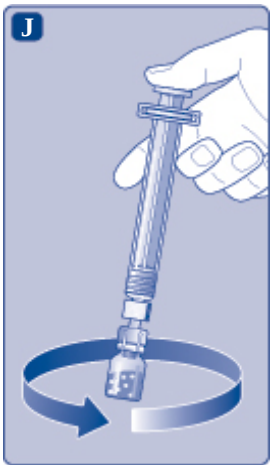
4. Reconstitute the powder with the solvent

- **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 and colourless and no particles should be visible. **If you notice particles or discolouration, do not use it.** Use a new package instead.



Esperoct is recommended to be used immediately after it has been reconstituted.

If you cannot use the reconstituted Esperoct solution immediately, it should be used within:
- 24 hours when stored in a refrigerator (2°C – 8°C) or
- 4 hours (≤30°C) or
- 1 hour between >30C and 40°C, only if the product was stored above room temperature (>30°C up to 40°C) before reconstitution for no longer than 3 months.

Store the reconstituted product in the vial.

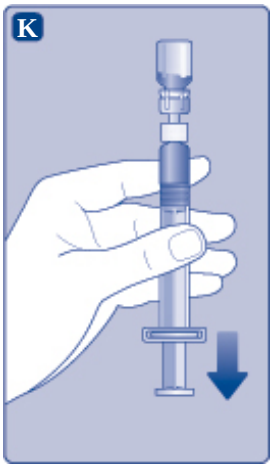
Do not freeze the reconstituted solution or store it in syringes.

Keep the reconstituted 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.

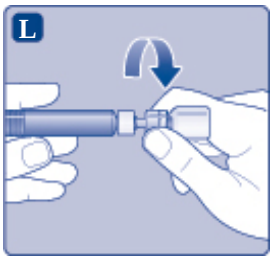
- **Keep the plunger rod pushed completely in.**
- **Turn the syringe with the vial** upside down.
- **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe.
- **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe.
- **If you do not need to use all of the reconstituted medicine from the vial,** use the scale on the syringe to withdraw the dose you need, as instructed by your doctor or nurse.

  If, at any point, there is 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

Esperoct is now ready to be injected into your vein.
- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over approximately 2 minutes.

Do not mix Esperoct with any other intravenous injections or medicines.

Injecting Esperoct 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 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 the injection of Esperoct, use sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

- **After injection, safely dispose** of all unused Esperoct 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.