▼ 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

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 alfapegol.

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 with haemophilia A (congenital factor VIII disorder).

4.2 Posology and method of administration

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

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	At least 1 day, until the bleeding is resolved

Moderate More extensive haemarthrosis, muscle bleeding, haematoma	30-60	12-24	3– 4 days or more, 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 Repeat after 24 hours if necessary	Single dose or repeat injection every 24 hours for at least 1 day until healing is achieved
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
Adults and adolescents (age 12 and over): The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. After this, the dosage schedule can be adjusted to 50 IU/kg every 3 – 4 days or 75 IU/kg every 7 days.

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

Children (under 12): One dose of 65 IU (50 – 75 IU) Esperoct® per kg body weight is administered twice a week

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.

Cases of (low-titre) returning inhibitors have been observed following the transition from one factor VIII product to another in previously treated patients with an exposure duration of over 100 days and a history of inhibitor formation. Therefore, it is advisable to monitor all patients carefully for the presence of inhibitors following a change of product.

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.

Decreased factor VIII activity in previously treated patients

From post marketing reports, a decreased factor VIII activity in the absence of detectable factor VIII inhibitors has been reported in previously treated patients. The decreased factor VIII activity was observed at time of switching to Esperoct and may, in some cases, have been associated with anti-PEG antibodies.

Appropriate determination of factor VIII activity upon switching should be considered.
See section 4.8 for additional information.

Treatment response in previously untreated patients (PUPs)
Decreased factor VIII incremental recovery (IR) has been observed in some previously untreated patients (PUPs), without detectable factor VIII inhibitors. Reduced factor VIII IR occurred after few exposures to Esperoct® and was generally transient. In all patients (PUPs without detectable factor VIII inhibitors), decreased IR was observed respectively together with increasing anti-PEG IgG titers. Monitoring of PUPs, including monitoring of factor VIII activity after administration, is recommended.

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 children.

Excipient-related considerations

The medicinal product contains 30.5 mg sodium per reconstituted vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2.0 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 or negligible 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 adverse event categories listed in Tables 3 and 4 correspond to the MedDRA System Organ Classification (SOC and Preferred Term Level):
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/1,000)
"very rare" (<1/10,000)
"not known" (cannot be estimated from the available data)

Previously treated patients
The frequencies of adverse reactions that occurred in 270 individual, previously treated patients (PTPs) with severe hemophilia A (<1% endogenous factor VIII activity) and without a history of inhibitors in five prospective, multicenter clinical studies are listed in Table 3.

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

MeDRA system organ class	**Adverse reaction**	**Frequency***
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon***
General disorders and administration site conditions	Reactions at the injection site**	Common
Immune system disorders	Hypersensitivity	Uncommon
Skin and subcutaneous tissue disorders	Skin rash Erythema Pruritus	Common
Investigations	Decrease in coagulation factor VIII	Not known****

* PTPs: Previously treated patients.
** "Reactions at the injection site" include: Injection site reaction, vessel puncture site hematoma, infusion site reaction, injection site erythema, injection site rash, vessel puncture site pain, and injection site swelling.
*** Frequency based on studies with all FVIII products, including in patients with severe hemophilia A.
**** Based on post-marketing reports.

Previously untreated patients
The frequency of adverse reactions observed in 81 individual subjects is shown in Table 4.

Table 4 Frequency of adverse reactions in clinical trials in PUPs*

System organ class	**Adverse reaction**	**Frequency**
Blood and lymphatic system disorders	Factor VIII inhibition**	Very common
General disorders and administration site conditions	Reactions at the injection site***	Common
Immune system disorders	Hypersensitivity	Common

Skin and subcutaneous tissue disorders	Skin rash	Common
	Erythema	Common

* PUPs: Previously untreated patients
** Includes patients with confirmed factor VIII inhibitor in population of at-risk patients (with at least 10 exposure days)
*** The preferred term "injection site reactions" includes: Injection site swelling and vessel puncture site hematoma

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
During the clinical trial programme, 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.
From post-marketing reporting, occurrence of anti-PEG-antibodies has also been observed at time of switching to Esperoct. In some patients anti-PEG antibodies may have been associated with lower than expected level of FVIII activity.

Paediatric population

No difference in the safety profile was observed between previously treated children and 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.

4.9 Overdose

In clinical trials with Esperoct, no overdose of Esperoct was reported at doses of up to 114 IU/kg. No clinical symptoms associated with overdoses of Esperoct 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. The haemostatic effect was confirmed in adults/adolescents and in children.

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)

In total, 68 children under 12 years of age received prophylactic treatment with Esperoct, with a dose of 65 IU per kg body weight (50 – 75 IU/kg) twice weekly. The prophylactic effect of Esperoct was demonstrated in all children under 12 with a median annualised bleeding rate of 1.95 (IQR: 0.00; 2.79), while the annualised spontaneous bleeding rate was 0.00 (IQR: 0.00; 0.00), the annualised traumatic

bleeding rate was 0.00 (IQR: 0.00; 2.03) and the annualised joint bleeding rate was 0.00 (IQR: 0.00; 1.95). In 29 (42.6%) of the 68 paediatric patients, no bleeding occurred during prophylactic treatment with Esperoct at a dose of 65 IU/kg (50 – 75 IU/kg).
Ten out of 13 patients with 17 target joints at baseline had no bleeding in 14 of their target joints during the 12-month treatment phase. If the data from the extension phase of the trial with the mean exposure of 3.4 years are included, the median annualised bleeding rate is 0.98 (IQR: 0.27; 1.44).

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.
The plasma samples were examined for factor VIII activity by means of chromogenic and one-stage coagulation tests. The pharmacokinetic parameters resulting from both tests were comparable.

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.

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. For patients under 12, who received 60 IU/kg (50 – 75 IU/kg) twice weekly, the mean steady-state factor VIII plasma activity level before administration during prophylactic treatment was 1.5 IU/dl (95% CI: 1.2; 1.9).

Predicted duration of factor VIII activity over 5%
Steady-state factor VIII activity profiles were simulated using a single compartment model with first order elimination kinetics with PK parameters for clearance (CL) and volume of distribution (Vss) at steady state. Pharmacokinetic predictions showed that patients who received treatment every 3 – 4 days mostly (72 – 95% of the time) demonstrate a factor VIII activity of over 5% (e.g. equivalent to minor haemophilia). According to predictions, patients who receive 75 IU/kg every 7 days should achieve over 5% for 57% of the time.

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.

In a toxicity study, Esperoct was repeatedly administered to immunodeficient rats (50 – 1,200 IU/kg/4 days for 52 weeks). No treatment related histopathological changes or adverse findings occurred. In tests using PEG-specific immunohistochemical staining, no PEG was discovered in brain tissue (including in the choroid plexus).

No effects on safety pharmacology endpoints (cardiovascular, renal, respiratory and central functions) were observed in male cynomolgus monkeys that were given up to 2,500 IU/kg/3 days of Esperoct.

Long-term studies in animals to evaluate the carcinogenic potential of Esperoct, and studies to determine the effects of Esperoct on genotoxicity, fertility, development and reproduction have not been performed. A review of the carcinogenic potential of Esperoct was conducted, and no carcinogenic risk was detected.

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):

36 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
- 2 hours 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

Manufacturer
1. Novo Nordisk A/S, Gentofte, Denmark
2. Novo Nordisk A/S, Kalundborg, Denmark

Importer
Novo Nordisk Pharma (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

Esperoct 500 IU : 1C 15070/65 (NBC)
Esperoct 1000 IU : 1C 15071/65 (NBC)

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 28 April 2022

10. DATE OF REVISION OF THE TEXT

24 January 2024