PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ESPEROCT®

Antihemophilic Factor VIII (Recombinant, B-Domain Truncated), PEGylated

turoctocog alfa pegol

Lyophilized Powder for Solution

500, 1000, 1500, 2000 and 3000 IU/vial

Intravenous injection

Blood Coagulation Factor VIII

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ESPEROCT® (Antihemophilic Factor VIII (Recombinant, B-Domain Truncated), PEGylated) is indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding.

ESPEROCT® is not indicated for the treatment of von Willebrand disease.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ESPEROCT® in previously treated pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use [see WARNINGS AND PRECAUTIONS/ Special Populations/Pediatrics (7.1.3) and CLINICAL TRIALS (14.2)].

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

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of ESPEROCT® did not include sufficient numbers of subjects age 65 and over to determine whether or not they respond differently than younger subjects.

2 CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient (including hamster protein), or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging (5.0).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.
- The dose, dosing interval and duration of the substitution therapy depend on the severity of the FVIII deficiency, on the location and extent of the bleeding, on the targeted FVIII activity level and the patient's clinical condition.
- Patients may vary in their pharmacokinetic (e.g., half-life*, in vivo* recovery) and clinical response. The dose and the frequency of ESPEROCT® should be based on the individual clinical response.
- In the case of major surgical interventions in particular, monitoring of the FVIII substitution therapy by measurement of plasma FVIII activity is necessary. If monitoring of FVIII activity is performed, use a chromogenic or one-stage clotting assay appropriate for use with ESPEROCT® [see WARNINGS AND PRECAUTIONS/ Monitoring and Laboratory Tests

(7.0)].

- The number of units of FVIII administered is expressed in International Units (IU), which is related to the current WHO concentrate standard for FVIII products. The activity of FVIII in plasma is expressed either as percentage (relative to normal human plasma level) or in IU per dL (relative to the current International Standard for FVIII in plasma).
- One IU of FVIII activity corresponds to the quantity of FVIII in one mL of normal human plasma.
- The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII activity by 2 IU/dL.
- ESPEROCT® may be dosed to achieve a specific target FVIII activity level for on-demand treatment/control of bleeding episodes or perioperative management [see Table 1-1 and Table 1-2]. To achieve a specific target FVIII activity level, use the following formula:

$$\underset{(IU)}{Dosage\ Required} = \underset{(kg)}{Body\ Weight} \times \underset{(IU/dL\ or\ \%\ normal)}{Desired\ FVIII\ Increase} \times \underset{}{0.5\ (IU/kg\ per\ IU/dL)}$$

3.2 Recommended Dose and Dosage Adjustment

Routine prophylaxis with ESPEROCT®

Adults and adolescents (12 years and above): The recommended starting dose is 50 IU of ESPEROCT® per kg body weight every 4 days.

Children (below 12 years): A dose of 60 IU/kg (50–75 IU) of ESPEROCT® per kg body weight administered twice weekly.

The dose regimens may be individually adjusted to less or more frequent dosing based on bleeding episodes.

On-demand Treatment and Control of Bleeding Episodes

Guidance for dosing of ESPEROCT® for the on-demand treatment and control of bleeding episodes is provided in Table 1-1.

Maintain plasma FVIII activity level at or above the described plasma levels (in IU per dL or % of normal).

The frequency of doses and duration of therapy should always be individually adjusted for optimal clinical effectiveness.

The expected *in vivo* increase in FVIII level expressed as IU per dL (or % of normal) is estimated using the following formula:

$$Estimated\ Increment\ of\ FVIII\ (IU/dL\ or\ \%\ of\ normal) = \frac{Total\ Dose\ (IU)}{Body\ Weight\ (kg)} \times 2\ (IU/dL\ \ per\ IU/kg)$$

Table 1-1: Dosing for Treatment and Control of Bleeding Episodes

Type of Bleeding	Desired Peak FVIII Level (IU/dL or % of normal)[1]	Dose (IU/kg)[2]	Frequency of Doses	
			Age Group	Repeat Dose
Minor Early hemarthrosis, mild muscle bleeding, or oral bleeding	20–40	40	≥ 12 years	One dose should be sufficient
		65	< 12 years	
Moderate More extensive hemarthrosis, muscle bleeding, or hematoma	30–60	40	≥ 12 years	An additional dose may be administered after 24 hours
		65	< 12 years	
Major Life- or limb-threatening hemorrhages, gastro-intestinal bleeding, intracranial, intraabdominal or intrathoracic bleeding, fractures	60–100	50	≥ 12 years	Additional dose(s) may be administered approximately every 24 hours
		65	< 12 years	

[1] As suggested by the World Federation of Hemophilia
[2] Dosage proposal based on clinical trial data with ESPEROCT®

Perioperative Management
The dose level and dosing intervals for surgery depend on the procedure and local practice. The frequency of doses and duration of therapy should always be individually adjusted based on individual clinical response.

Table 1-2 includes general recommendation for dosing of ESPEROCT® for perioperative management. Consideration should be given to maintain a FVIII activity at or above the target range.

Table 1-2: Dosing for Perioperative Management

Type of Surgery	Target FVIII Level (IU/dL or % of normal)[1]	Pre-operative Dose (IU/kg)[2]	Frequency of Doses	
			Age Group	Repeat Dose
Minor Including tooth extraction	30–60	50	≥ 12 years	Additional dose(s) can be administered after 24 hours if necessary
		65	< 12 years	
Major Intracranial, intra-abdominal, intrathoracic, or joint replacement surgery	80–100	50	≥ 12 years	Additional doses can be administered approximately every 24 hours for the first week and then approximately every 48
		65	< 12 years	

				hours until wound healing has occurred

[1] As suggested by the World Federation of Hemophilia
[2] Dosage proposal based on clinical trial data with ESPEROCT®

3.3 Administration

- ESPEROCT® should be administered by intravenous injection (over approximately 2 minutes) after reconstitution of the lyophilised powder with 4 mL 0.9% sodium chloride solvent (provided).
- Do not administer reconstituted ESPEROCT® in the same tubing or container with other medications.
- In case of self-administration or administration by a caregiver, appropriate training is required.

Injecting ESPEROCT® via needleless connectors for intravenous (IV) catheters

The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.

Caution: The MixPro® prefilled solvent 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 prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Follow the instructions for use that come with the needleless connector. Administration through a needleless connector may require withdrawal of the reconstituted solution into a standard 10 mL sterile luer-lock plastic syringe.

If you have encountered any problems with attaching the prefilled solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

For detailed instructions on how to administer ESPEROCT® refer to the PATIENT MEDICATION INFORMATION section of the Product Monograph.

3.4 Reconstitution

Table 1-3: Reconstitution

Vial Size	Volume of Solvent to be Added to Vial	Approximate Concentration After Reconstitution
500 IU/vial	4 mL	125 IU/mL
1000 IU/vial	4 mL	250 IU/mL
1500 IU/vial	4 mL	375 IU/mL
2000 IU/vial	4 mL	500 IU/mL
3000 IU/vial	4 mL	750 IU/mL

- ESPEROCT® should be used immediately after it has been reconstituted.
- ESPEROCT® should not be mixed or reconstituted with injection solutions other than the provided sodium chloride solvent.
- If you cannot use the reconstituted ESPEROCT® solution immediately, it should be kept in the vial, with the vial adapter and the syringe still attached, at room temperature below 30°C for no longer than 4 hours, or refrigerated at 2°C - 8°C for no longer than 24 hours.
- Do not freeze reconstituted ESPEROCT® solution or store it in syringes. Keep reconstituted ESPEROCT® solution out of direct light.
- After reconstitution, the solution should be clear and colourless. Do not use solutions that are cloudy or have deposits.

3.5 Missed Dose

Patients who forget a dose should be advised to inject the missed dose immediately and to continue treatment at regular intervals as required. Patients should not inject a double dose to make up for a forgotten dose.

4 OVERDOSAGE

Overdose of ESPEROCT® up to 114 IU/kg has been reported in clinical trials using ESPEROCT®. No clinical symptoms associated with overdoses of ESPEROCT® have been reported.

For management of a suspected drug overdose, contact your hemophilia treatment centre or your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1-4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intravenous injection	Lyophilized powder for solution: 500, 1000, 1500, 2000 and 3000 IU/vial	Powder Calcium chloride dihydrate, L-histidine, L-methionine, polysorbate 80, sodium chloride, sucrose Solvent Sodium chloride, water for injections

ESPEROCT® is supplied as a white to off-white lyophilized powder in a single-use vial.

The solvent for reconstitution of ESPEROCT® is 0.9% sodium chloride solution and is supplied as a clear colorless solution in a prefilled syringe.

The ESPEROCT® package contains 1 vial of ESPEROCT® and 1 MixPro® prefilled solvent syringe with sterile vial adapter, which serves as a needleless reconstitution system.

Each ESPEROCT® package contains:

- 1 glass vial (type I) with ESPEROCT® powder and chlorobutyl rubber stopper and a snap-off cap made of aluminium and plastic
- 1 sterile vial adapter (with 25 micrometer filter) for reconstitution
- 1 prefilled syringe containing 4 mL of solvent with a backstop (polypropylene), a rubber plunger (bromobutyl), and a rubber tip cap (bromobutyl). Further a luer lock (polycarbonate) and a plastic sleeve (polypropylene)
- 1 plunger rod (polypropylene)

The rubber stopper, rubber tip cap and rubber plunger have not been made with natural rubber latex.

After reconstitution, ESPEROCT® contains the following non-medicinal ingredients:

Contents	Quantity per mL in the withdrawal volume	Function
Sodium chloride	18 mg/mL	Stabiliser
L-Histidine	1.5 mg/mL	Buffer
Sucrose	3 mg/mL	Stabiliser
Polysorbate 80	0.1 mg/mL	Surfactant
L-Methionine	0.055 mg/mL	Antioxidant
Calcium chloride dihydrate	0.25 mg/mL	Stabiliser

6 DESCRIPTION

Recombinant human FVIII is produced in Chinese Hamster Ovary (CHO) cells and contains 21 amino acids of the endogenous B-domain. ESPEROCT® is a purified recombinant human FVIII product with a 40 kDa polyethylene-glycol (PEG) conjugated to the O-linked glycan in the truncated B-domain. When ESPEROCT® 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 FVIII (FVIIIa) which is similar in structure to native FVIIIa.

The protein part of ESPEROCT® is a polypeptide with a molecular mass of 166 kDa. It contains a heavy chain of 87 kDa and a light chain of 79 kDa held together by non-covalent interactions. The molecular mass of ESPEROCT® is 216 kDa including post-translational modifications and PEG moiety.

The recombinant FVIII protein is purified by a series of chromatographic steps, including an affinity chromatography step using a monoclonal antibody, expressed in CHO cells, to selectively isolate recombinant FVIII from the cell culture medium. The conjugation of the PEG-group is performed by an enzymatic reaction during the purification of ESPEROCT®. The production process includes two dedicated, validated viral clearance steps, namely a detergent treatment step for inactivation and a 20 nm filtration step for removal of viruses.

No additives of human or animal origin are used in the cell culture, purification, conjugation, or formulation of ESPEROCT®.

7 WARNINGS AND PRECAUTIONS

Immune

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 ESPEROCT® and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of anaphylactic shock, standard medical treatment for anaphylactic shock should be implemented.

Inhibitors
The formation of neutralizing antibodies (inhibitors) to FVIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) using the modified Bethesda assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to FVIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre, posing less of a risk of insufficient clinical response than high titre inhibitors.

Monitoring and Laboratory Tests
In general, all patients treated with coagulation FVIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate FVIII replacement therapy, then testing for the presence of FVIII inhibitors should be performed. In patients with high levels of inhibitor, FVIII 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 hemophilia and FVIII inhibitors.

During the course of treatment, appropriate determination of FVIII activity levels is advised to guide adjustments of the dosing regimen of ESPEROCT®, if needed. Individual patients may vary in their response to FVIII, demonstrating different half-lives and incremental recoveries. In the case of major surgical interventions in particular, monitoring of the FVIII substitution therapy by measurement of plasma FVIII activity is necessary.

FVIII activity levels can be monitored with a validated test (one-stage clotting or chromogenic assays). FVIII activity levels can be affected by the type of activated partial thromboplastin time (aPTT) reagent used in the one-stage clotting assay. Some silica-based aPTT reagents can underestimate the activity of ESPEROCT® by approximately 50%. If an appropriate one-stage clotting or chromogenic assay is not available locally, then use of a reference laboratory is recommended.

Peri-Operative Considerations
ESPEROCT® is indicated in the perioperative management of patients with hemophilia A. Careful monitoring of replacement therapy is necessary in cases of major surgery or life-threatening bleeding episodes. Data on surgery are not available for children < 12 years of age.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with ESPEROCT®. Given the rare occurrence of hemophilia A in women, experience regarding the use of ESPEROCT® during pregnancy is not available. Therefore, the benefit of using ESPEROCT® during pregnancy must be assessed against the risk for the mother and baby and the product should be used only if clearly needed.

7.1.2 Breast-feeding

Theoretical considerations would indicate that FVIII products could be present in human breast milk, but based on the rare occurrence of hemophilia A in women, experience regarding the use of FVIII products during breastfeeding is not available. Therefore, ESPEROCT® should only be used during breastfeeding if clearly indicated.

7.1.3 Pediatrics

Safety and efficacy were evaluated in 93 previously treated pediatric patients <18 years of age, who received at least one dose of ESPEROCT®; all received routine prophylaxis [see CLINICAL TRIALS (14.2)]. Thirty-four (34) of these subjects (36.6%) were 1 to <6 years of age; 34 subjects (36.6%) were 6 to <12 years of age; and 25 subjects (27%) were 12 to <18 years of age.

The safety profile of ESPEROCT® was comparable between previously treated pediatric subjects and adult subjects.

7.1.4 Geriatrics

Clinical studies of ESPEROCT® did not include sufficient numbers of subjects age 65 and over to determine whether or not they respond differently than younger subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions (incidence ≥1%) in clinical trials were rash, erythema, pruritus, and injection site reactions.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from

clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Previously treated patients:

The safety of ESPEROCT® has been evaluated in 270 unique subjects (202 adults/adolescents and 68 children) across five prospective, multi-centre clinical studies in previously treated patients (PTPs) with severe hemophilia A (<1% endogenous FVIII activity) and no history of inhibitors. As many patients participated in more than one trial, the sum of patients in the individual trials is higher than the total number of unique patients. All patients received at least one dose of ESPEROCT®. A previously treated patient was defined as a subject with a history of at least 150 exposure days to other FVIII products (adolescents/adult subjects) or 50 exposure days to other FVIII products (children below 6 years). Total exposure to ESPEROCT® was 80,425 exposure days corresponding to 889 patient years of treatment.

During the clinical trial program in previously treated patients, adverse reactions occurred at a rate of 0.10 events per patient year of exposure. The most frequently reported adverse reactions were rash (5.2%), injection site reaction (2.6%), erythema (1.9%), and pruritus (1.5%).

Table 1-5: Frequencies of adverse drug reactions in clinical trials in previously treated patients

System Organ Class	Preferred term	Frequency (%)	Frequency#
Blood and lymphatic system disorders	Factor VIII inhibition****	1/235*** (0.4%)	Uncommon
General disorders and administration site conditions	Injection site reaction**	7/270 (2.6%)	Common
Immune system disorders	Hypersensitivity	2/270 (0.7%)	Uncommon
Skin and subcutaneous tissue disorders	Rash	14/270 (5.2%)	Common
Skin and subcutaneous tissue disorders	Erythema	5/270 (1.9%)	Common
Skin and subcutaneous tissue disorders	Pruritus	4/270 (1.5%)	Common

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).
** Preferred terms included in injection site reactions: Injection site reaction, Vessel puncture site hematoma, Infusion site reaction, Injection site erythema, Injection site rash, Vessel puncture site pain, and Injection site swelling.
*** The number of patients at risk (denominator) is patients who have a minimum of 50 exposure days to ESPEROCT® or who have confirmed inhibitory antibodies against FVIII regardless of the number of exposure days.
****The confirmed FVIII inhibitor patient was identified by an initial inhibitor test result of ≥ 0.6 Bethesda units (BU) confirmed in a second sample taken no more than 2 weeks later.

The safety profile of ESPEROCT® was comparable between previously treated pediatric patients and adults.

Immunogenicity: Subjects were monitored for neutralizing and non-neutralizing antibodies to FVIII, PEG, and CHO host cell protein (HCP). One previously treated subject developed confirmed neutralizing antibodies to FVIII (13.5 Bethesda Units), and three additional subjects developed transient non-neutralizing antibodies to FVIII. Pre-existing anti-PEG antibodies were detected in 32 subjects of whom 20 had no anti-PEG antibodies at the end of the trials. Eleven patients developed anti-PEG antibodies of whom 9 were transient anti-PEG antibodies and two remained positive. The anti-PEG antibodies had no clinical significance. Nine subjects developed anti-CHO HCP antibodies with no clinical consequence.

The detection of antibodies is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Previously untreated patients:
The safety and efficacy of ESPEROCT® in previously untreated patients have not yet been established.

8.3 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.1 Overview

No interaction studies have been performed, and no interactions of ESPEROCT® with other medicinal products have been reported.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

When injected into a hemophilia patient, FVIII binds to endogenous von Willebrand factor (VWF), which stabilizes FVIII during circulation. At the site of injury, FVIII is activated and released from VWF. FVIII is activated by thrombin and acts as a co-factor for activated FIX (FIXa) on the surface of the activated platelets where the FVIIIa/FIXa complex converts FX to activated FX (FXa). FXa then leads to the generation of thrombin and to the formation of a stable hemostatic plug.

ESPEROCT®, a glycoPEGylated form of recombinant anti-hemophilic FVIII temporarily replaces the missing coagulation FVIII needed for effective hemostasis in congenital hemophilia A patients. The FVIII in ESPEROCT® is conjugated to a 40-kDa polyethylene glycol molecule, which slows down its removal from the blood circulation, prolonging its half-life compared to the non-pegylated molecule.

10.2 Pharmacodynamics

The administration of ESPEROCT® increases plasma levels of FVIII and can temporarily correct the coagulation defect in the hemophilia A patients, as reflected by a decrease in activated partial thromboplastin time (aPTT).

10.3 Pharmacokinetics

In total, 129 single-dose pharmacokinetic (PK) profiles of ESPEROCT® were evaluated in 86 patients (including 24 pediatric patients < 12 years).

All pharmacokinetic studies with ESPEROCT® were conducted in previously treated patients with severe hemophilia A (FVIII <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 was 19 hours for ESPEROCT® and 12 hours for unmodified FVIII products in adults, using the chromogenic assay.

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 (< 6 years) and older children (6 to <12 years), and between adolescents (12 to <18 years) and adults (≥18 years).

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 kg body weight in children compared to adults (Table 1-6).

Table 1-6: Single-dose pharmacokinetic parameters of ESPEROCT® 50 IU/kg, by age, using the chromogenic assay (geometric mean [CV%])

PK Parameter	<6 years	6 - <12 years	12 - <18 years	≥18 years
Number of patients	**N=13**	**N=11**	**N=3**	**N=42**
Number of profiles	13	11	5	79
IR (IU/dL per IU/kg)[a]	1.80 (29)	1.99 (25)[c]	2.79 (12)	2.63 (22)
Maximum FVIII 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 FVIII activity time profile; $t_{1/2}$ = terminal half-life; MRT = mean residence time; CL = clearance; Vss = volume of distribution; IR = Incremental recovery
[a] Incremental recovery and FVIII activity were assessed 30 min post-dosing for patients ≥ 12 years and 60 min post-dosing (first sample) for children < 12 years.
[b] Calculation based on 67 profiles.

Observed pre-dose (trough) and post-dose (peak) plasma FVIII activity levels at steady state during prophylactic treatment with ESPEROCT® are presented in Table 1-7.

Table 1-7: Steady-state trough and peak plasma FVIII activity by age and dose regimen of ESPEROCT® based on the chromogenic assay (geometric mean [95% CI])

	60 IU/kg twice weekly (50–75 IU/kg)**		50 IU/kg Every 4 days*	
	<6 years	6 - <12 years	12 -<18 years	≥18 years
# of patients	31	34	23	143
Mean trough IU/dL (95% CI) min, max*	1.2 (0.8;1.6)	2.0 (1.5;2.7)	2.7 (1.8;4.0)	3.0 (2.6;3.5)
Mean peak IU/dL (95% CI) min, max*	125.0 (118.7;131.6)	143.3 (136.8;150.2)	125.1 (116,0;135.0)	137.9 (133.9;142.2)

* Data included in analysis: NN7088-3859 main phase until 36 weeks at 50 IU/kg Q4D. Only measurements collected at steady-state for the given prophylaxis treatment are included in the analyses.
**Data included in analysis: NN7088-3885 interim 1 - main phase 60 IU/kg (50-75 IU/kg) twice weekly. Only measurements collected at steady state for the given prophylaxis treatment are included in the analyses. Measurements are included if within time window of prophylaxis treatment interval +/- 2 days, (i.e. 1.5–5.5 days for twice weekly, 2–6 days for Q4D) and if at least twice the prophylaxis treatment interval after last treatment of bleed.

Predicted Time of Factor VIII Activity Above 5 %

Steady-state FVIII activity profiles were predicted using a one-compartment model with first-order elimination with PK parameters of clearance (CL) and volume of distribution (Vss).

Pharmacokinetic predictions showed that patients dosed every 3-4 days in all age groups were above 5% FVIII activity (i.e. in the range of mild hemophilia) for the majority of time (72-95% of time).

11 STORAGE, STABILITY AND DISPOSAL

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

Store in the original package in order to protect from light.

ESPEROCT® vials can be stored in the refrigerator (2°C - 8°C) up to the expiration date stated on the label. During the shelf-life, ESPEROCT® may also be stored at room temperature (up to 30°C) for a single period not exceeding 12 months. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Record the beginning of storage at room temperature on the product carton.

Do not use ESPEROCT® after the end of the 12 month period at room temperature storage, or after the expiration date stated on the carton, whichever occurs earlier.

After reconstitution:
The reconstituted product should be used immediately.

Chemical and physical in-use stability have been demonstrated for 24 hours when stored in a refrigerator (2°C – 8°C) and 4 hours when stored at room temperature (up to 30°C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be recommended for longer than 4 hours stored at room temperature (up to 30°C) or 24 hours in a refrigerator (2°C – 8°C), unless reconstitution has taken place in controlled and validated aseptic conditions.

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.

12 SPECIAL HANDLING INSTRUCTIONS

After 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Antihemophilic Factor VIII (Recombinant, B-Domain Truncated), PEGylated

Chemical name: turoctocog alfa pegol

Molecular formula: $C_{7480}H_{11381}N_{1999}O_{2177}S_{62}$

Molecular mass: 166 kDa (excluding post-translational modifications and PEG moiety)

Structural formula:

Figure 1: Theoretical amino acid sequence of turoctocog alfa pegol with disulphide bridges indicated

Physicochemical properties:

Appearance, colour, physical state	The purified turoctocog alfa pegol drug substance appears as a clear and colourless solution
Solubility	The physical appearance of turoctocog alfa pegol drug substance (tested in concentration range 0.2-6 mg/ml) is a solution
Aqueous pH-solubility profile	Precipitation is observed between pH 2 and 4. Aggregation and degradation can be detected at pH lower than 5 and above pH 9
pI value	As turoctocog alfa pegol is a mixture of different glycoforms, it does not possess a distinct pI value

Product Characteristics

Antihemophilic Factor VIII (Recombinant, B-Domain Truncated), PEGylated, or turoctocog alfa pegol, is a recombinant human FVIII product with a specific glycoPEGylation on the O-linked glycan (primarily on Ser750 in the 21 amino acid B-domain). Turoctocog alfa pegol is produced by enzymatic glycoPEGylation of turoctocog alfa intermediate (truncated recombinant human FVIII containing 21 amino acids of the native B-domain). The size of the polyethylene glycol (PEG) attached to the O-linked glycan is 40kDa. When turoctocog alfa pegol is activated by thrombin, the B-domain containing the PEG moiety and the a3-region are cleaved off, thus generating activated rFVIII which is similar in structure to native FVIIIa.

The post-translational modifications of turoctocog alfa intermediate include disulphide bridges, tyrosine sulphations and glycosylations. Six potential tyrosine sulphation sites are present and all have been confirmed. Two N-linked glycosylations are present in the light chain and two N-linked glycosylations are present in the heavy chain. The N-linked glycan structures are mainly high mannose or complex type structures and the majority of the complex, bi-antennary structures are sialylated. Two O-linked glycosylation sites (Thr5 and Thr6) are present in the light chain and one O-linked glycosylation site (Ser750) is present in the B-domain.

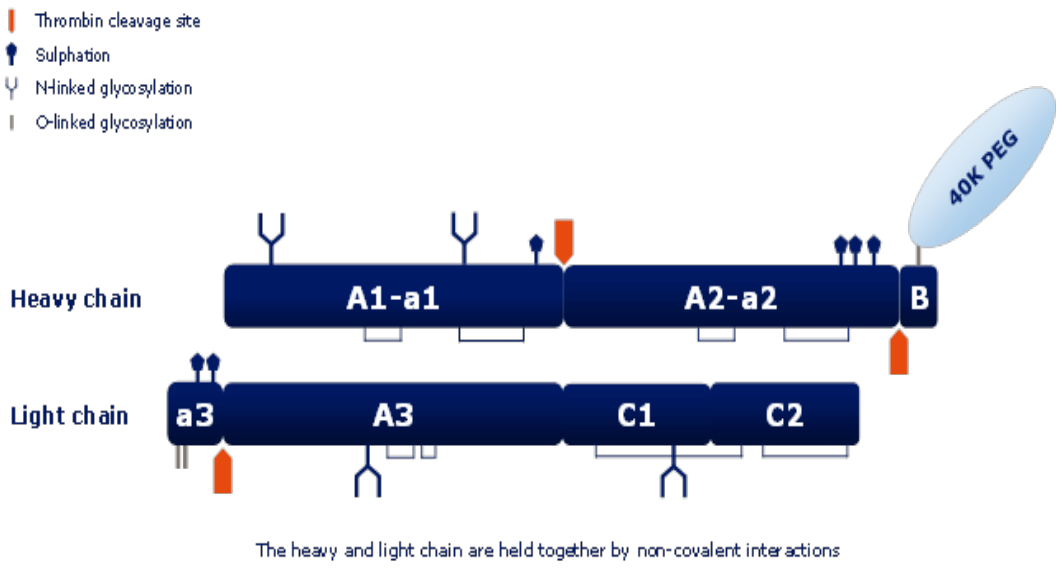


Figure 2: Structure of turoctocog alfa pegol with post-translational modifications, disulphide bridges and PEG moiety indicated

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 2-1: Summary of patient demographics for clinical trials in hemophilia A

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Trial 3859 Pivotal trial Main phase (complete)	A multi-centre, open-label, non-controlled trial evaluating the safety, efficacy and PK in prophylaxis and treatment of bleeds in previously treated adolescent and adult patients. Treatment groups: on-demand and prophylaxis (non-randomized).	 <u>Prophylaxis</u> 50 IU/kg Q3−4D <u>On-demand</u> 20–75 IU/kg	Total = 186+ 175 12	Mean= 31.1 years Range= 12−66 years	Male
Trial 3859 Pivotal trial Extension part 1 (complete)	Treatment groups: on-demand and 50 IU/kg Q3−4D prophylaxis (non-randomized); 75 IU/kg Q7D and 50 IU/kg Q4D prophylaxis (randomized 2:1)	 Patients not eligible for randomization Eligible patients who continued on 50 IU/kg Q3-4D <u>Prophylaxis (randomized)</u> 50 IU/kg Q4D 75 IU/kg Q7D <u>On-demand</u> 20–75 IU/kg	Total = 150 23 65 17 38 7		
Trial 3885 Pediatric trial Main phase (complete)	A multi-centre, open-label, single-arm, non-controlled trial to assess safety, efficacy and PK in previously treated children <12 years of age.	<u>Prophylaxis</u> ~60 IU/kg (50−75) twice weekly* <u>Treatment of bleeds</u> 20–75 IU/kg	68	Mean= 6.0 years Range= 1-11 years	Male
Trial 3860 Surgery trial (On-going)	A multi-centre, open-label, single-arm, non-controlled trial evaluating the efficacy and safety during surgical procedures in previously treated adolescent and adult patients ≥12 years old.	<u>Pre-surgery period</u> Pre-operative dose aiming for a FVIII activity level of 80−100%. <u>Post-operative period</u> Days 1−6: At the investigator's discretion, aiming for a FVIII activity level above 50% considering WFH guidelines. Days 7−14: At the investigator's discretion.	34#	Mean= 40.8 years Range= 15−69 years	Male

Q4D: every fourth day dosing; Q3−4D: patients starting dose was every fourth day, subsequently patients could switch to twice weekly*; Q7D: every seventh day dosing
+One patient switched from on-demand to prophylaxis during the pivotal part of the main phase.
Of the total 34 patients who were exposed to trial product, 33 patients had 45 surgeries in the trial.

The efficacy of ESPEROCT® has been evaluated in three multinational, open-label, non-controlled trials in male subjects with severe hemophilia A (<1% endogenous FVIII activity). All subjects were previously treated, which was defined as having received other FVIII products for ≥150 exposure days for adolescents and adults, and ≥50 exposure days for pediatric subjects. The key exclusion criteria across trials included known or suspected hypersensitivity to trial or related products and known history of FVIII inhibitors or current inhibitor ≥0.6 BU.

The efficacy evaluation included 254 subjects in the following trials:

- Adult/adolescent trial (Trial 3859): This trial included 186 subjects, 161 adults (18 to 65 years old) and 25 adolescents (12 to <18 years old); it consisted of a Main Phase and two Extension Phases. During the Main Phase, 175 subjects received the prophylaxis regimen which consisted of 50 IU every 3-4 days (Q3-4D), while 12 adults chose to be treated on-demand. All subjects received at least one dose of ESPEROCT® and are evaluable for safety and efficacy. A total of 165 subjects (91%) completed the Main Phase of this trial.
    - Extension 1: This extension compared two dose regimens: 75 IU/kg every 7 days (Q7D) and 50 IU/kg Q4D. The randomization was open to subjects who received 50 doses of ESPEROCT® and who experienced 2 or fewer bleeds during the last 6 months in the Main Phase. Of the 150 subjects who continued into Extension 1, 55 subjects chose to be randomized (2:1) to 75 IU/kg Q7D (38 subjects) and 50 IU/kg Q4D (17 subjects). Of the remaining 95 subjects, 7 were treated on-demand, 23 were not eligible to be randomized, and 65 eligible subjects chose to continue on 50 IU/kg Q3-4D. A total of 139 subjects (93%) completed Extension 1.

- Pediatric trial (Trial 3885): This trial included 68 subjects who were evenly divided with 34 in each age group, <6 and 6–<12 years of age. All subjects received the same prophylaxis regimen of approximately 60 IU/kg (50–75 IU/kg) twice weekly. A total of 63 subjects (93%) completed the Main Phase.

- Surgery trial (Trial 3860): In the surgery trial, 33 previously treated adolescents/adults underwent 45 major surgeries. The dose level of ESPEROCT® was chosen so that FVIII activity at least as recommended by World Federation of Hemophilia (WFH) guidelines was targeted. All subjects returned to the adult/adolescent trial after the surgery trial assessments were completed.

14.2 Study Results

Routine Prophylaxis in Adults / Adolescents

The efficacy of ESPEROCT® in routine prophylaxis was demonstrated for the adolescent/ adult population (see Table 2-2). During the Main Phase of the adult/adolescent trial, 186 subjects had at least 50 EDs. The estimated median annualized bleeding rate (ABR) in adults and adolescents treated every 3-4 days was 1.18 (IQR: 0.00:4.25).

Table 2-2: Efficacy in adult/adolescent prophylaxis, median ABR by age, treatment regimen, and bleed type

	Prophylaxis (50 IU/kg Q3-4D)			On-demand
Age Range	**12–<18 years**	**≥18 years**	**≥12 years**	**≥18 years**
# of patients	25	150	175	12
Mean treatment duration (years)	0.85	0.81	0.82	1.33
All bleeds (%) # of subjects without bleeds (%) Median ABR (IQR)	 6 (24%) 2.22 (0.87;4.73)	 64 (43%) 1.17 (0.00;3.71)	 70 (40%) 1.18 (0.00;4.25)	 0 30.87 (18.64;38.51)
Spontaneous bleeds # of subjects without bleeds (%) Median ABR (IQR)	 14 (56%) 0.00 (0.00;1.47)	 85 (57%) 0.00 (0.00;1.85)	 99 (57%) 0.00 (0.00;1.82)	 0 19.35 (12.07;31.04)
Traumatic bleeds # of subjects without bleeds (%) Median ABR (IQR)	 9 (36%) 1.33 (0.00;2.58)	 93 (62%) 0.0 (0.00;1.42)	 102 (58%) 0.00 (0.00;1.74)	 2 4.32 (0.77;9.93)
Joint bleeds # of subjects without bleeds (%) Median ABR (IQR)	 9 (36%) 1.22 (0.00;2.84)	 76 (51%) 0.00 (0.00;2.84)	 85 (49%) 0.85 (0.00;2.84)	 0 19.35 (4.48;28.76)

Routine Prophylaxis in Children <12 Years of Age

Overall, 68 children below 12 years received prophylactic treatment with ESPEROCT® at 60 IU/kg (50–75 IU/kg) twice weekly. The prophylactic effect of ESPEROCT® was demonstrated with an estimated median ABR rate of 1.95 (IQR: 0.00; 2.79) (see Table 2-3). Of the 68 children, 29 (42.6%) did not experience any bleeding episodes during the Main Phase of the trial. Of the 13 subjects with 17 documented target joints at baseline, 10 subjects (77%) and 14 target joints (82%) did not have any bleeds during the Main phase of the trial.

Table 2-3: Efficacy in pediatric prophylaxis, median ABR by age and bleed type

	Prophylaxis Regimen 60 IU/kg (50–75 IU/kg) Twice Weekly (every 3–4 days)		
Age Range	**< 6 years**	**6 –< 12 years**	**< 12 years**
# of patients	**N=34**	**N=34**	**N=68**
Mean treatment duration (years)	0.46	0.51	0.48
All bleeds # of subjects without bleeds (%) Median ABR (IQR)	 15 (44%) 1.94 (0.00;2.08)	 14 (41%) 1.97 (0.00;3.91)	 29 (43%) 1.95 (0.00;2.79)
Spontaneous bleeds # of subjects without bleeds (%) Median AsBR (IQR)	 28 (82%) 0.00 (0.00;0.00)	 27 (79%) 0.00 (0.00; 0.00)	 55 (81%) 0.00 (0.00; 0.00)
Traumatic bleeds # of subjects without bleeds (%) Median AtBR (IQR)	 19 (56%) 0.00 (0.00; 2.03)	 17 (50%) 0.88 (0.00;2.04)	 36 (53%) 0.00 (0.00;2.03)
Joint bleeds # of subjects without bleeds (%) Median AjBR (IQR)	 27 (79%) 0.00 (0.00;0.00)	 22 (65%) 0.00 (0.00;2.00)	 49 (72%) 0.00 (0.00;1.95)

On-demand Treatment and Control of Bleeding Episodes

The overall success rate (95% CI) for treatment of bleeds when pooling data from completed non-surgical trials was 84.7% (CI 81.3 ; 87.6). Of the 1506 bleeds, 1314 (87.3%) were rated excellent or good in their response to ESPEROCT®, 167 (11.1%) were moderate, 6 (0.4%) were rated as having no improvement, and for 19 (1.3%) the response to treatment was missing.

Doses used for treatment of bleeding episodes depended on age, treatment regimen and the severity of the bleed.

Of the 1407 mild and moderate bleeding episodes in all subjects in the adolescent/adult study, the median dose used was 42 IU/kg. For subjects who were on the on-demand arm the median initial dose was 28 IU/kg and 88.4% of the bleeds were treated successfully with a single dose. In subjects receiving routine prophylaxis, the median initial dose was 52 IU/kg, and 76.4% of the bleeds were successfully treated with a single dose. Of the 15 severe bleeds, 12 (80%) required more than one dose with a total median dose of 111 IU/kg.

In the pediatric study, 70 mild/moderate bleeds in children < 12 years old receiving routine prophylaxis were treated with a median initial dose of 64 IU/kg per injection, with 63% treated with a single injection. When needed, additional median doses of 62 IU/kg were used at approximately 24 hour intervals. The median total dose was 70 IU/kg per bleed.

The median dose to treat a bleeding episode was 51.9 IU/kg across all age groups; 94% of the bleeds were resolved with 1-2 injections of ESPEROCT® and 81% were resolved with 1 injection. There was no difference in the response to treatment across age groups (see Table 2-4).

Table 2-4: Summary of efficacy in control of bleeding episodes by age

Age range		< 6 years	6–< 12 years	12–<18 years	≥ 18 years	Total
# of patients		**N=34**	**N=34**	**N=25**	**N=161**	**N=254**
# of bleeds		30	40	112	1324	1506
Dose used for treatment of bleed from start to stop (IU/kg per bleed) median (Min;Max)		71.2 (63;124)	69.3 (50; 296)	53.0 (21;1575)	50.9 (17;489)	51.9 (17;1575)
# of injections	1 – 2	23 (76.7%)	33 (82.5%)	99 (88.4%)	1265 (95.5%)	1420 (94.3%)
	> 2	7 (23.3%)	7 (17.5%)	13 (11.6%)	59 (4.5%)	155 (5.7%)
Response to first treatment	Excellent/ Good	24 (80.0%)	31 (77.5%)	84 (75.0%)	1175 (88.7%)	1314 (87.3%)
	Moderate	4 (13.3%)	7 (17.5%)	20 (17.9%)	136 (10.3%)	167 (11.1%)

Definition of Hemostatic Response:
Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within approximately 8 hours after a single injection.
Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but possibly requiring more than one injection for complete resolution.
Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection, but usually requiring more than one injection.

There were 1,506 bleeds reported in 171 of 254 subjects across the clinical trials, and the most common bleed types were joint (65.2%), muscle (14.5%), and subcutaneous (8.9%). Of the 982 joint bleeds 87.9% were successfully treated, while 219 muscular bleeds and 134 subcutaneous bleeds had successful hemostatic responses of 80.8% and 97.0%, respectively.

Perioperative Management

The hemostatic efficacy was evaluated in 45 major surgeries performed in 33 patients. The exposure during surgery comprised of a total of 979 exposure days of ESPEROCT® corresponding to a total of 6.4 exposure years.

The hemostatic effect of ESPEROCT® was rated as ‘excellent’ and ‘good’ in 43 out of 45 major surgeries (95.6 %), while the effect was rated as ‘moderate’ in 2 surgeries (4.4 %). No surgeries had an outcome rated as ‘none’ or ‘missing’.

The median pre-operative dose for adults and adolescents undergoing major surgeries was 52 IU/kg, and the median total dose was 702 IU/kg. During post-operative days 1-6, the median dose was 32 IU/kg at approximately 24 hour intervals. During post-operative days 7-14, the median dose was 36 IU/kg at approximately 28 hour intervals. The number of doses and duration of treatment varied by procedure.

Table 2-5: Summary of hemostatic response during major surgery

Description of surgery	Hemostatic response			
	Number of surgeries	Excellent/ Good	Moderate	None
Orthopedic surgeries				
Joint replacement	15	14 (93.3%)	1 (6.7%)	0
Arthroscopic interventions	9	9 (100.0%)	0	0
Other orthopedic interventions	17	16 (94.1%)	1 (5.9%)	0
Non-orthopedic surgery	4	4 (100%)	0	0

The hemostatic effect was assessed by the investigator post-operatively and rated as:
Excellent: Better than expected/predicted in this type of procedure.
Good: As expected in this type of procedure.
Moderate: Less than optimal for the type of procedure but hemostatic response maintained without change of treatment regimen.
None: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required.

15 NON-CLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and impairment of fertility studies in animals have not been performed.

ESPEROCT® was administered in a repeat-dose toxicity study in immunodeficient rats (50–1200 IU/kg/4d for 52 weeks). No treatment related histopathological changes or adverse findings were observed. PEG was not detected in brain tissue (including choroid plexus) by a PEG specific immuno-histochemical staining.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ESPEROCT®
Antihemophilic Factor FVIII (Recombinant, B-Domain Truncated), PEGylated

Read this carefully before you start taking ESPEROCT® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ESPEROCT®.

What is ESPEROCT® used for?
ESPEROCT® 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.

ESPEROCT® is used to treat and prevent bleeding in people with hemophilia A.

How does ESPEROCT® work?
In people with hemophilia 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.

What are the ingredients in ESPEROCT®?
Medicinal ingredients: Antihemophilic Factor VIII (Recombinant, B-Domain Truncated), PEGylated

Non-medicinal ingredients: Calcium chloride dihydrate, L-Histidine, L-Methionine, polysorbate 80, sodium chloride, sucrose

ESPEROCT® comes in the following dosage forms:
ESPEROCT® is available in single-dose vials that contain nominally 500, 1000, 1500, 2000 or 3000 International Units (IU). After reconstitution with the supplied solvent (0.9% sodium chloride solution for injection), the prepared solution for injection will have the following concentration:

Vial Size	Approximate concentration after reconstitution
500 IU	125 IU/mL
1000 IU	250 IU/mL
1500 IU	375 IU/mL
2000 IU	500 IU/mL
3000 IU	750 IU/mL

Each pack of ESPEROCT® contains a vial with white to off-white powder, a 4 mL prefilled syringe with a clear colourless solvent, a plunger rod, and a vial adapter.

Do not use ESPEROCT® if:
You are allergic to the medicinal ingredient, or to any ingredient in the formulation (including hamster protein), or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional

before you take ESPEROCT®. Talk about any health conditions or problems you may have, including if you:

- Are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or herbal medicines.
- 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.

Other warnings you should know about:

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 (hypersensitivity)
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 (see Serious Side Effects table).

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 from 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.

ESPEROCT® contains sodium
This medicine contains 72 mg of sodium chloride (18 mg/mL) after it has been reconstituted. Talk to your doctor if you are on a controlled sodium diet.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ESPEROCT®:
There are no known interactions of ESPEROCT® with other medicinal products.

How to take ESPEROCT®:
Treatment with ESPEROCT® will be started by a doctor who is experienced in the care of people with hemophilia 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®.

ESPEROCT® is given as an injection into a vein (intravenously). Please refer to the end of this insert for instructions on how to prepare and administer ESPEROCT®.

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.

Usual dose:

Prevention of bleeding

- **Adults and adolescents** (children 12 years of age and above): The recommended starting dose is 50 IU of ESPEROCT® per kg body weight every 4 days.

- **Children** (below 12 years of age): The recommended starting dose is 50–75 IU of ESPEROCT® per kg of body weight. This is given twice weekly.

Treatment of bleeding
The dose of ESPEROCT® is calculated based on your body weight, the severity of your hemophilia A, and the location of the bleeding. If you experience that the effect of ESPEROCT® is insufficient, talk to your doctor.

Use in children and adolescents
ESPEROCT® can be used in children of all ages. In children (below 12 years of age) higher doses or more regular injections may be needed. Adolescents (children 12 years of age and above) can use the same dose as adults.

Overdose:

If you think you have taken too much ESPEROCT®, contact your healthcare professional, your hemophilia treatment centre or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
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.

Stopping Treatment:
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.

What are possible side effects from using ESPEROCT®?

These are not all the possible side effects you may feel when taking ESPEROCT®. If you experience any side effects not listed here, contact your healthcare professional.

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 Serious Side Effects table).
- Factor VIII inhibitors (antibodies) in patients previously treated with Factor VIII.

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.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Lack of effect: Bleeding does not stop after taking ESPEROCT®		✓	
Allergic reaction: Difficulty in swallowing or breathing; shortness of breath or wheezing; chest tightness; redness and/or swelling of the lips, tongue, face or hands; rash, hives, weals or generalized itching; pale and cold skin, fast heartbeat, or dizziness (low blood pressure)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, on the vial, and on the prefilled syringe labels. The expiry date refers to the last day of that month.

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

Prior to reconstitution

Before mixing the powder in the vial with the solvent:

Store in the original package in order to protect from light. Do not freeze.

ESPEROCT® vials can be stored in the refrigerator (2°C – 8°C) up to the expiration date, or at room temperature (up to 30°C) for a single period not exceeding 12 months.

If you choose to store ESPEROCT® at room temperature:
- Note the date that the product is removed from refrigeration on the carton.
- Do not use after 12 months from this date or the expiration date listed on the carton, whichever occurs earlier.
- Do not return the product to the refrigerator after it has been stored at room temperature.

After reconstitution

After the powder is 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 4 hours when stored at room temperature (up to 30°C) and within 24 hours when stored in a refrigerator (2°C – 8°C). Store the reconstituted product in the vial.

Keep reconstituted ESPEROCT® solution out of direct light.

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

If you want more information about ESPEROCT®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.novonordisk.ca, or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

Last Revised: July 4, 2019

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 0.9% sodium chloride solution. The reconstituted ESPEROCT® must be injected into your vein (intravenous [i.v.] 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 prefilled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

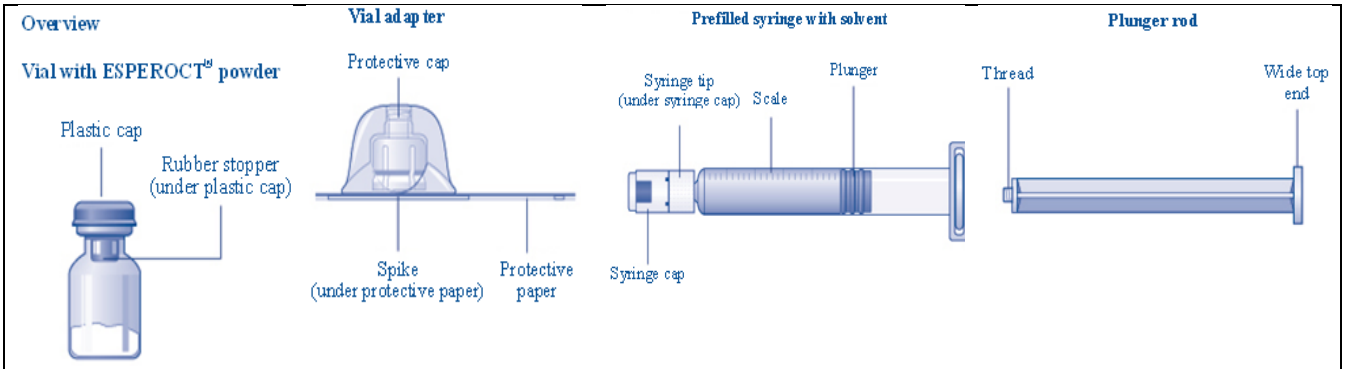
Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

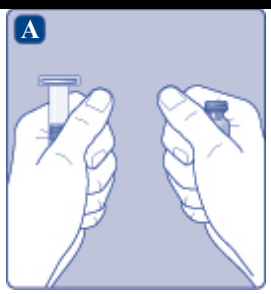
Contents

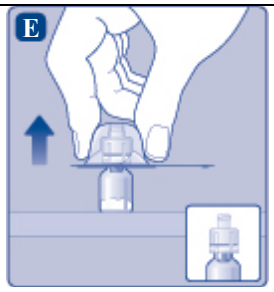
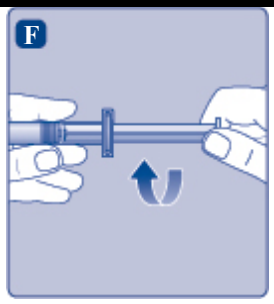
The package contains:
- 1 vial with ESPEROCT® powder
- 1 vial adapter
- 1 prefilled syringe with solvent
- 1 plunger rod (placed under the syringe)

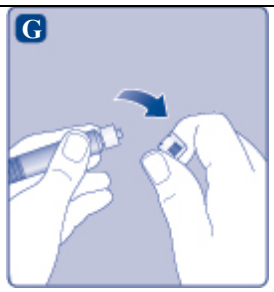
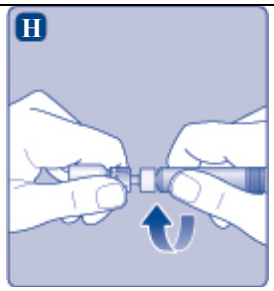
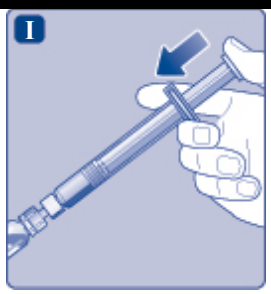
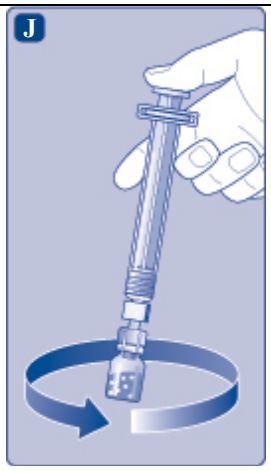
The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.



1. Prepare the Vial and Syringe

Step A		**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 prefilled syringe out of the carton. **Leave the plunger rod untouched in the carton.** **Bring the vial and the prefilled syringe to room temperature.** You can do this by holding them in your hands until they feel as warm as your hands. **Do not use any other way to warm** the vial and prefilled syringe.
Step B		**Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, do not use the vial.** **Wipe the rubber stopper 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		
Step C		**Remove the protective paper from the vial adapter.** **If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.** **Do not take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter, germs from your fingers can be transferred.
Step D		**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.**
Step E		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		
Step F		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 prefilled syringe until resistance is felt.

Step G		**Remove the syringe cap** from the prefilled syringe by bending it down until the perforation breaks. **Do not touch the syringe tip under the syringe cap.** 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 prefilled syringe.**
Step H		**Screw the prefilled syringe securely** onto the vial adapter until resistance is felt.
4. Reconstitute the Powder with the Solvent		
Step I		**Hold the prefilled syringe slightly tilted** with the vial pointing downwards. **Push the plunger rod** to inject all the solvent into the vial.
Step J		**Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** **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.

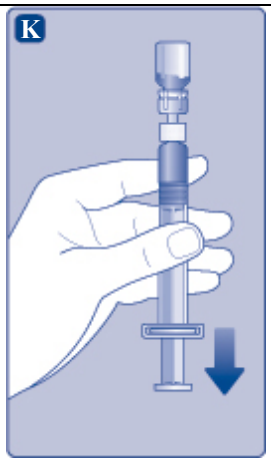
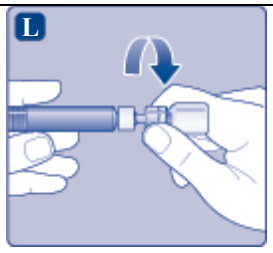
ESPEROCT® is recommended to be used immediately after it has been reconstituted.

If you cannot use the reconstituted ESPEROCT® solution immediately, it should be used within 4 hours when stored at room temperature (up to 30°C) and within 24 hours when stored in a refrigerator (at 2°C – 8°C). Store the reconstituted product in the vial.

Do not freeze reconstituted ESPEROCT® solution or store it in syringes.

Keep reconstituted ESPEROCT® solution out of direct light.

If your dose requires more than one vial, repeat step **A** to **J** with additional vials, vial adapters and prefilled syringes until you have reached your required dose.

Step K		**Keep the plunger rod pushed completely in.** **Turn the syringe with the vial** upside down. **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe. **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe. **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.
Step L		**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 medications.

Injecting ESPEROCT® via needleless connectors for intravenous (IV) catheters

Caution: The MixPro® prefilled solvent 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 prefilled syringe. This incompatibility may prevent administration of the drug 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 0.9% Sodium Chloride solution for injection.

If you have encountered any problems with attaching the prefilled solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

6. Disposal

Step M		**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 healthcare provider. Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.

Do not reuse the equipment.