▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ESPEROCT® (turoctocog alfa pegol) powder for injection with solvent

1 NAME OF THE MEDICINE

Turoctocog alfa pegol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Turoctocog alfa pegol is a human factor VIII produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells, covalently conjugated to a 40 kDa polyethylene glycol (PEG).

Each vial contains 500 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU turoctocog alfa pegol according to the declaration.

After reconstitution of the solution, each 1 mL ESPEROCT contains approximately 125 IU, 250 IU, 375 IU, 500 IU or 750 IU turoctocog alfa pegol, respectively.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ESPEROCT is 9500 IU/mg protein on average.

Excipient with known effect

This medicine contains 30.5 mg sodium per reconstituted vial (see Section 4.4 Special warnings and precautions for use).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white. The solvent is clear and colourless.

After reconstitution the solution appears as a clear and colourless liquid, free from visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ESPEROCT, is a long-acting recombinant Factor VIII concentrate indicated for use in previously treated patients with haemophilia A for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Peri-operative management of bleeding (surgical prophylaxis)

ESPEROCT does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Previously untreated patients

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

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide adjustment of the dosing regimen of ESPEROCT. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is necessary.

The factor VIII activity of ESPEROCT can be reliably measured in conventional factor VIII assays such as the one-stage coagulation test and chromogenic assay.

Silica based reagents (e.g. aPTT-SP, STA-PTT, Triniclot) should not be used with the one-stage coagulation assay as they cause underestimation. This is particularly important when changing laboratories or changing the reagents used in the test.

Dosage

The dose, dosing interval and duration of substitution therapy depend on the severity of the factor VIII deficiency, the location and extent of bleeding, the targeted factor VIII activity level and the patient's clinical condition. The quantity of factor VIII administered is expressed in International Units (IU), in accordance with the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as

percentage (relative to normal human plasma) or in International Units per decilitre (IU/dL) (relative to the current international standard for factor VIII in 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) × desired factor VIII rise (%) (IU/dL) × 0.5 (IU/kg per IU/dL)

Patients may differ in terms of pharmacokinetic response (e.g. half-life, *in vivo* recovery) and clinical response. The dosage and frequency of ESPEROCT administration should be based on the individual clinical response.

Guidance for the dosage of ESPEROCT during on-demand treatment and treatment of bleeding episodes can be found in Table 1. Care must be taken to ensure that factor VIII activity is maintained accordingly or based on the stated plasma levels (in IU/dL or as a percentage of the standard). The frequency of administration and duration of treatment must be adapted on a case-by-case basis in order to achieve optimum clinical efficacy.

Table 1 Dosing guide for treatment of bleeding episodes with ESPEROCT

Degree of bleeding	**Factor VIII level required (IU/dL or % of the standard)[a]**	**Frequency of doses (hours)/ duration of therapy (days)**
Mild Early stage haemarthrosis, mild muscle bleeding or mild oral bleeding	20 – 40	Repeat IV injection every 12 to 24 hours, for at least 1 day, until the bleeding episode, indicated by pain, has stopped or healing has been achieved.
Moderate More extensive haemarthrosis, muscle bleeding or haematoma	30 – 60	Repeat IV injection every 12 – 24 hours for 3 – 4 days or more, until pain and acute impairment have been eliminated.
Severe or life-threatening bleeding	60 – 100	Repeat IV injection every 8 – 24 hours until the risk has subsided.

[a] The required dose is calculated using the following formula:
Required units (IU) = body weight (in kg) × desired factor VIII rise (in %) (IU/dL) × 0.5 (IU/kg per IU/dL)
IV = intravenous

Perioperative care

The dosage and administration intervals during surgery depend on the procedure and local practice. The frequency of administration and duration of treatment should be adjusted based on the individual clinical response.

Table 2 contains general recommendations regarding ESPEROCT dosage for perioperative care. The aim should be to keep factor VIII activity at or above the target range.

Table 2 Dosing guide for ESPEROCT during perioperative care

Type of surgical procedure	Factor VIII level required (%) (IU/dL)[a]	Frequency of doses (hours)/ duration of treatment (days)
Minor procedures including tooth extraction	30 – 60	Every 24 hours for at least 1 day until healing is achieved.
Major procedures	80 – 100 (pre- and post-operative)	Repeat IV injections every 8 to 24 hours until adequate wound healing is achieved, then treat for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

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

Routine prophylaxis with ESPEROCT

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

Thereafter, the dosing schedule may be adjusted to 50 IU/kg every 3 – 4 days or 75 IU/kg every 7 days based on the patient's response (with a low bleeding rate of 0 – 2 bleeding episodes during the last 6 months prior to changing dose/dose frequency) and at the discretion of the treating physician. Following a change to dose regimen the treating physician should re-evaluate bleeding tendency and consider the need to re-measure factor VIII levels.

Children (below 12 years): One dose of 65 IU (50 – 75 IU) ESPEROCT per kg body weight administered twice a week.

Method of administration

ESPEROCT should be administered by intravenous injection (over about 2 minutes) after reconstitution of the lyophilised powder with 4 mL 0.9% sodium chloride solvent (provided).

ESPEROCT must not be mixed or reconstituted with solutions for injection other than the sodium chloride solvent provided.

After reconstitution, the solution appears as a clear and colourless liquid, free of visible particles. The reconstituted medicine 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 and administration, see package insert.

Always use an aseptic technique.

Do not administer reconstituted ESPEROCT in the same tubing or containers as other medicinal products.

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

An infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters will be also required for administration. These accessories are not included in the ESPEROCT pack.

If the medicinal product is to be administered by the patient or a carer, appropriate training must be given.

4.3 CONTRAINDICATIONS

Hypersensitivity to turoctocog alfa pegol or to any of the excipients. 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 discontinue use of ESPEROCT immediately 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 anaphylactic shock, standard medical treatment for shock should be implemented.

Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease and the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitors (low-titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days and a history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

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 a lower risk of insufficient clinical response than high-titre inhibitors.

All patients treated with coagulation factor VIII products must always be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma level is 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.

Cardiovascular events

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

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Excipient-related considerations

This medicine contains 30.5 mg sodium per reconstituted vial. This corresponds to 1.5 % of the WHO's recommended daily dose of sodium for adults of 2.0 g. Patients on a sodium-controlled diet should take this into consideration.

Use in the elderly

The safety of this product for use in the elderly population has not been established in clinical studies.

Paediatric use

The listed warnings and precautions apply both to adults and children. There is limited evidence of efficacy, long-term safety has yet to be established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Animal studies to determine the effects of turoctocog alfa pegol on fertility have not been performed. It is unknown whether ESPEROCT can affect human fertility.

Use in pregnancy – Pregnancy Category B2

Animal reproduction studies have not been conducted with turoctocog alfa pegol. Due to the rare occurrence of haemophilia A in women, clinical experience regarding the use of ESPEROCT during pregnancy is not available. It is not known whether ESPEROCT poses any risk to the fetus when administered to a pregnant woman. Therefore, ESPEROCT should be used during pregnancy only if clearly indicated.

Use in lactation

The safety of ESPEROCT for use in lactating women has not been established. It is not known if ESPEROCT or its metabolites (including the PEG component) are excreted in human milk. Therefore, ESPEROCT should be used during lactation only if clearly indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Hypersensitivity reactions and/or allergic reactions (such as hypersensitivity, skin rash, erythema and pruritus) have been observed and in some cases may develop into severe anaphylaxis (including anaphylactic shock).

Very rarely, development of antibodies to hamster proteins with related hypersensitivity reactions has been observed.

In patients with haemophilia A who are treated with factor VIII, including ESPEROCT, neutralising antibodies (inhibitors) may develop. If such inhibitors occur, this condition will manifest itself as an inadequate clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Table of adverse reactions

The frequencies of adverse reactions, which occurred in 270 individual previously treated patients (PTPs) with severe haemophilia A (< 1% endogenous factor VIII activity) and with no history of inhibitors in five prospective, multicentre clinical trials, are listed in Table 3. The information in the table is classified according to MedDRA (System Organ Class and Preferred Terms level).

Frequencies have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 3 Frequency of undesirable effects in PTPs*

MeDRA System Organ Class	Adverse reaction	Frequency* (%)
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon***
General disorders and administration site conditions	Injection site reactions**	Common
Immune system disorders	Hypersensitivity	Uncommon
Skin and subcutaneous tissue disorders	Rash	Common
	Erythema	Common
	Pruritus	Common
Investigations	Coagulation factor VIII level decreased	Unknown****

* PTPs: previously treated patients.
** Injection site reactions include: injection site reaction, vessel puncture site haematoma, infusion site reaction, injection site erythema, injection site rash, vessel puncture site pain and injection site swelling.
*** Frequency based on trials on all FVIII products, including in patients with severe haemophilia A.
**** Based on post marketing reports.

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.

Children and adolescents

Previously treated patients: In the safety profile of ESPEROCT, no difference was detected between previously treated children and adolescents and adults.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In clinical trials with ESPEROCT, overdose of ESPEROCT was reported at doses of up to 114 IU/kg. No clinical symptoms associated with overdoses of ESPEROCT have been reported.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII. ATC code: B02BD02

Mechanism of action

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a patient with haemophilia, factor VIII binds to the patient's von Willebrand factor. 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 X-chromosomal hereditary disorder of blood coagulation due to decreased levels or absence of factor VIII:C that results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma.

Turoctocog alfa pegol is a purified recombinant human factor VIII (rFVIII) product with 40 kDa polyethylene glycol (PEG), which is conjugated to 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 substitution of inadequate or absent factor VIII in patients with haemophilia A.

When turoctocog alfa pegol is activated by thrombin at the injury site, the a3 region and the B domains containing the PEG are cleaved off, producing active recombinant factor VIII (rFVIIIa), which is similar in structure to native factor VIIIa.

This replacement therapy raises factor VIII plasma levels, temporarily correcting the factor VIII deficiency and bleeding tendency.

Clinical trials

Clinical efficacy in the prophylaxis and treatment of bleeding episodes

The clinical efficacy of ESPEROCT in the prophylaxis and treatment of bleeding was investigated in five prospective, multicentre clinical trials in previously treated patients (PTPs) with severe haemophilia A. The haemostatic effect was confirmed in adults/adolescents and in children.

Routine prophylaxis in adults/adolescents

In adults/adolescents (12 years and above), the prophylactic effect of ESPEROCT was demonstrated with a dose of 50 IU per kg body weight every 3 to 4 days in 175 patients (see Table 4). The median annualised bleeding rate (ABR) in adults and adolescents who received ESPEROCT every 3 – 4 days was 1.18 (interquartile range [IQR]: 0.00; 4.25), while the annualised spontaneous bleeding was 0.00 (IQR: 0.00; 1.82), the annualised traumatic bleeding rate was 0.00 (IQR: 0.00; 1.74) and the annualised joint bleeding rate was 0.85 (IQR: 0.00; 2.84). Of the 175 adults/adolescents receiving prophylactic treatment, 70 (40%) had no bleeding at all.

Adults/adolescents with a low bleeding rate of 0 – 2 bleeding episodes over the last 6 months and who received at least 50 doses of ESPEROCT had the option of being randomised to receive prophylactic treatment with 75 IU/kg every 7 days or 50 IU/kg every 4 days. In total, 55 of the suitable patients decided in favour of this randomisation (17 for administration every 4 days, 38 for administration of 75 IU every 7 days). In part 2 of the extension phase, the prophylaxis treatment of patients could be changed to Q4D or Q7D, according to predefined rules and at the investigator's discretion. In total 61 patients received ESPEROCT 75 IU/kg every 7 days. The mean ABR was 2.88 (median 0.99) for patients receiving ESPEROCT 50 IU/kg every 4 days and 4.45 (median 1.94) for patients receiving ESPEROCT 75 mg/kg every 7 days.

Table 4 Efficacy of ESPEROCT in routine prophylaxis in adults/adolescents, median/estimated mean ABR by treatment regimen and bleed type

	Prophylaxis Regimen 50 IU/kg every 3–4 days		
	Prophylaxis 12 to 17 years N=25	**Prophylaxis 18 years and above N=150**	**Prophylaxis 12 years and above N=175**
Mean treatment duration (years)	0.85	0.81	0.82
No. of patients (%):			
Zero bleeds	6 (24%)	64 (43%)	70 (40%)
Zero spontaneous bleeds (%)	14 (56%)	85 (57%)	99 (57%)
Zero traumatic bleeds (%)	9 (36%)	93 (62%)	102 (58%)
Zero joint bleeds (%)	9 (36%)	76 (51%)	85 (49%)
All bleeds			
No. of bleeds	67	369	436
No. of pts with bleeds (%)	19 (76%)	86 (57%)	105 (60%)
Median ABR (IQR)	2.22 (0.87;4.73)	1.17 (0.00;3.71)	1.18 (0.00;4.25)
Estimated mean ABR (95% CI)	3.16 (2.06;4.83)	3.02 (2.37;3.85)	3.04 (2.45;3.77)
Spontaneous bleeds			
No. of bleeds	30	221	251
No. of pts with spontaneous bleeds (%)	11 (44%)	65 (43%)	76 (43%)
Median ABR (IQR)	0.00 (0.00;1.47)	0.00 (0.00;1.85)	0.00 (0.00;1.82)
Estimated mean ABR (95% CI)	1.41 (0.75;2.65)	1.81 (1.35;2.43)	1.75 (1.34;2.29)
Traumatic bleeds			
No. of bleeds	37	146	183
No. of pts with traumatic bleeds (%)	16 (64%)	57 (38%)	73 (42%)
Median ABR (IQR)	1.33 (0.00;2.58)	0.00 (0.00;1.42)	0.00 (0.00;1.74)
Estimated mean ABR (95% CI)	1.74 (1.13;2.69)	1.19 (0.89;1.60)	1.28 (0.99;1.64)
Joint bleeds			
No. of bleeds	37	288	325
No. of pts with joint bleeds	16 (64%)	74 (49%)	90 (51%)
Median ABR (IQR)	1.22 (0.00;2.84)	0.00(0.00;2.84)	0.85 (0.00;2.84)
Estimated mean ABR (95% CI)	1.74 (1.10;2.76)	2.36 (1.79;311)	2.27 (1.76;2.92)

ABR = annualised bleeding rate; CI = confidence interval; IQR = interquartile range; No = number; Pts = patients

No obvious differences in terms of ABR were found between different age groups.

Routine 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 (see Table 5). The median and estimated mean annualised bleeding rate in children below 12 years receiving ESPEROCT twice weekly was 1.95 and 2.13 (95% CI: 1.48;3.06), whereas the spontaneous ABR was 0.00 and 0.58 (95% CI: 0.24;1.40), traumatic ABR was 0.00 and 1.52 (95% CI:1.07;2.17) and joint ABR was 0.00 and 1.03 (95% CI: 0.59;1.81), respectively. Of the 68 children below 12 years on prophylaxis, 29 (42.6%) did not have any bleeds. The mean annual consumption for prophylaxis was 6475 IU/kg. 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).

Out of 13 patients with 17 target joints at baseline, 10 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).

Table 5 Efficacy of ESPEROCT in routine prophylaxis in children below 12 years, median/estimated mean ABR by bleed type

	Prophylaxis Regimen 65 IU/kg (50–75 IU/kg) twice weekly		
	0 to below 6 years N=34	**6 to below 12 years N=34**	**Below 12 years N=68**
Mean treatment duration (years)	0.46	0.51	0.48
No of patients (%):			
Zero bleeds	15 (44.1%)	14 (41.2%)	29 (42.6%)
Zero spontaneous bleeds (%)	28 (82%)	27 (79%)	55 (81%)
Zero traumatic bleeds (%)	19 (56%)	17 (50%)	36 (53%)
Zero Joint bleeds (%)	27 (79%)	22 (65%)	49 (72%)
All bleeds			
No. of bleeds	30	40	70
No. of pts with bleeds (%)	19 (56%)	20 (59%)	39 (57%)
Median (IQR)	1.94 (0.00;2.08)	1.97 (0.00;3.91)	1.95 (0.00;2.79)
Estimated mean ABR (95% CI)	1.94 (1.10;3.42)	2.30 (1.40;3.75)	2.13 (1.48;3.06)
Spontaneous bleeds			
No. of bleeds	9	10	19
No. of pts with spontaneous bleeds (%)	6 (18%)	7 (21%)	13 (19%)
Median (IQR)	0.00 (0.00;0.00)	0.00 (0.00;0.00)	0.00 (0.00;0.00)
Estimated mean ABR (95% CI)	0.58 (0.16;2.12)	0.57 (0.17;1.96)	0.58 (0.24;1.40)
Traumatic bleeds			
No. of bleeds	20	30	50
No. of pts with traumatic bleeds (%)	15 (44%)	17 (50%)	32 (47%)
Median (IQR)	0.00 (0.00;2.03)	0.88 (0.00;2.04)	0.00 (0.00;2.03)
Estimated mean ABR (95% CI)	1.29 (0.74;2.26)	1.72 (1.09;2.71)	1.52 (1.07;2.17)
Joint bleeds			
No. of bleeds	10	24	34
No. of pts with joint bleeds (%)	7 (21%)	12 (35%)	19 (28%)
Median (IQR)	0.00 (0.00;0.00)	0.00 (0.00;2.00)	0.00 (0.00;1.95)
Estimated mean ABR (95% CI)	0.65 (0.21;1.95)	1.38 (0.67;2.81)	1.03 (0.59;1.81)

ABR = annualised bleeding rate; CI = confidence interval; IQR = interquartile range; No = number; Pts = patients

Clinical efficacy of ESPEROCT in the 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 (see Table 6). The vast majority of bleeds that were treated with ESPEROCT were mild/moderate.

In the group of patients treated on demand, 1,126 bleeds were treated in 12 patients 18 years and above, with an average treatment dose of 38.1 IU/kg for mild/moderate bleeds. In total, 86.9% of the 1,126 bleeds were effectively treated after 1 injection of ESPEROCT. In total, 96.8% of the 1,126 bleeds were effectively treated after 1 – 2 injections of ESPEROCT.

Table 6 Efficacy of ESPEROCT in treatment of bleeding episodes by age group

	0 to below 6 years	6 to below 12 years	12 to below 18 years	18 years and above	Total
No. of patients	34	34	25	161	254
No. of bleeds	90	192	168	2316	2766
Haemostatic response* (excellent/good)	86.7%	76.6%	76.8%	89.5%	87.7%

* Including missing response as failure.

The overall success rate for the treatment of bleeds was 87.7%, with 94.4% of bleeds treated with one or two injections.

Clinical efficacy of ESPEROCT during major surgical procedures

A pre-surgery dose of ESPEROCT was administered to all patients at the day of surgery (mean dose 55.3 IU/kg; range: 27.2−86.2 IU/kg). A post-surgery dose was administered on the day of surgery in 29 cases (mean dose 31 IU/kg; range: 10.1−58.8 IU/kg). During post-operative Days 1−6, the mean ESPEROCT consumption was 33.5 IU/kg (range: 15.5−59.6 IU/kg). ESPEROCT was effective in maintaining haemostasis in major surgical procedures (in 43 out of 45, the effect was assessed as "excellent" or "good"), with a success rate of 95.6% in all major surgical procedures performed.

5.2 PHARMACOKINETIC PROPERTIES

In total, 129 single-dose pharmacokinetic (PK) profiles of ESPEROCT were evaluated in 86 patients (including 24 paediatric patients (0 – <12 years of age)).

All pharmacokinetic studies with ESPEROCT were conducted in previously treated patients with severe haemophilia A (factor VIII < 1%). The patients received a single dose of 50 IU/kg. Blood samples were taken before administration and at various times for up to 96 hours after administration. The pharmacokinetics of ESPEROCT were compared with unmodified factor VIII products, which consisted of both recombinant and plasma-derived products. The half-life of ESPEROCT was 1.6 times longer than that of unmodified factor VIII preparations.

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

In total, 108 single-dose pharmacokinetic profiles of 50 IU/kg ESPEROCT were evaluated in 69 patients. The single-dose pharmacokinetic parameters are similar in young children (0 to <6 years of age) and older children (6 to <12 years of age), and in adolescents (12 to 17 years of age) and adults (≥18 years of age).

As expected, incremental recovery was lower in children than in adolescents and adults, while body weight-adjusted clearance was higher. The general trend was that incremental recovery increased with age, while clearance (mL/h/kg) decreased. This effect has been described previously with other factor VIII products and reflects a higher volume of distribution per kg body weight in children than in adults (Table 7).

The single-dose pharmacokinetic parameters determined following 28 weeks of prophylactic treatment with ESPEROCT were consistent with the initial pharmacokinetic parameters.

Table 7 Single-dose pharmacokinetic parameters of ESPEROCT 50 IU/kg in children, adolescents and adults by age, determined using a chromogenic assay (geometric mean [CV%])

PK parameters n=number of patients	0 to below 6 years N=13	6 to below 12 years N=11	12 to below 18 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*h/dL)	2,147 (47)	2,503 (42)	3,100 (44)	3,686 (35)
CL (mL/h/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 (h)	17.0 (22)	17.3 (31)	21.7 (45)	25.2 (29)[b]

AUC = area under the factor VIII activity-time curve (profile); $t_{1/2}$ = terminal half-life; MRT = mean residence time; CL = clearance; Vss = volume of distribution; IR = incremental recovery.
[a] Incremental recovery and factor VIII were measured 30 minutes after administration in patients aged 12 years and above and 60 minutes after administration in children below 12 years (first sample).
[b] Calculated based on 67 profiles.

The mean steady-state factor VIII plasma activity level before administration during prophylactic treatment with ESPEROCT, administered at a dose of 50 IU/kg every 4 days, is 3.0 IU/dL (95% CI: 2.6; 3.4) in patients aged 12 years and above.

For patients below 12 years, who received 65 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

Genotoxicity

No genotoxicity studies have been performed with turoctocog alfa pegol.

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of turoctocog alfa pegol have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder: Sodium chloride, histidine, sucrose, polysorbate 80, methionine, calcium chloride dihydrate, sodium hydroxide (to adjust pH), hydrochloric acid (to adjust pH).

Solvent: Sodium chloride, water for injections.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Unopened vial (before reconstitution):

Store in a refrigerator at 2°C to 8°C. Do not freeze.

During its shelf life, the preparation can be stored:

- no longer than 12 months at temperatures ≤30 °C, or
- no longer than 3 months at temperatures >30 °C – 40 °C.

Once the product has been stored outside of the refrigerator, it must not be returned to the refrigerator.

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

After reconstitution

From a microbiological perspective, the medicine must be used immediately after reconstitution.

If storage is necessary, the solution should be kept in the vial and used within 24 hours when stored in the refrigerator (2 – 8 °C).

This product is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 2°C to 8°C. Do not freeze.

Store in original package to protect from light.

The reconstituted preparation must be stored in the vial.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack of ESPEROCT contains:

- 1 glass vial (type I) with powder and 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).

The rubber stopper, rubber tip cap and rubber plunger are not made of natural rubber latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Turoctocog alfa pegol is a recombinant human factor VIII product with a glycoPEGylation on the O-linked glycan (Ser750) of the 21 amino acid B-domain. The molecular mass of turoctocog alfa pegol protein part is 166 kDa. The size of the polyethylene glycol attached to the O-linked glycan is 40 kDa. The turoctocog alfa pegol molecule is a polypeptide containing a Heavy chain and a Light chain held together by non-covalent interactions. In native factor VIII these chains are connected by a native B-domain, while turoctocog alfa pegol has a truncated rFVIII containing 21 amino acids of the native B-domain.

CAS number

1309086-46-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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9 DATE OF FIRST APPROVAL

5 June 2023

10 DATE OF REVISION

Not applicable