Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Esperoct

Active ingredient/s: Turoctocog alfa pegol

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

October 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
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About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ABR	Annualised bleeding rate
ACM	Advisory Committee on Medicines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under concentration time curve
CFC	Clotting factor concentrate
CHO	Chinese hamster ovary
CMI	Consumer Medicines Information
COR-B	Comparable Overseas Regulator B
DCO	Data cutoff
DLP	Data lock point
ED	Exposure day
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
F8-KO	Factor VIII knockout mice
FDA	Food and Drug Administration (United States of America)
FVIII	Factor VIII
HCP	Host cell protein
Ig	Immunoglobin
N8-GP	Drug development code for Esperoct
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PI	Product Information
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
PSUR	Periodic safety update report
PTP	Previously treated patient
rFVIIIa	Active Factor VIII
RMP	Risk management plan

Abbreviation	Meaning
SAE	Serious adverse event
SmPC	Summary of product characteristic
t½	Half-life
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
WT	Wild type

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Esperoct
Active ingredient:	Turoctocog alfa pegol
Decision:	Approved
Date of decision:	31 May 2023
Date of entry onto ARTG:	5 June 2023
ARTG numbers:	389597,389598,389600,389599,389596
▼*Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Novo Nordisk Pharmaceuticals Pty Ltd Level 10 / 118 Mount Street, North Sydney, NSW 2060
Dose form:	Powder for injection
Strengths:	500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU
Containers:	Vial and pre-filled syringe
Pack size:	One vial, one prefilled syringe, one vial adaptor, and one plunger
Approved therapeutic use for the current submission:	*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.*
Route of administration:	Intravenous
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.

	For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B2
	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
	Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Novo Nordisk Pharmaceuticals Pty Ltd (the sponsor) to register Esperoct (turoctocog alfa pegol) 500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU, powder for injection, vial with solvent for the following proposed indication:[1]

> *For the treatment and prophylaxis of bleeding in previously treated patients with haemophilia A (congenital factor VIII deficiency).*

Turoctocog alfa pegol;[2] (N8-GP) is a human Factor VIII (FVIII) produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells, covalently conjugated to a 40 kDa polyethylene glycol (PEG). It was developed based on the Novoeight (turoctocog alfa, N8) product, which was previously registered in Australia from 8 January 2014 to 22 December 2020.

The mechanism of action for N8-GP is based on the replacement of deficient or absent Factor VIII in patients with haemophilia A. By adding recombinant FVIII, the coagulation cascade can run uninterruptedly ensuring that the end-product, fibrin, is generated and a haemostatic plug is formed. GlycoPEGylation of FVIII does not influence functionality of N8-GP. As PEG is attached to the B-domain, both are released when N8-GP is converted to active FVIII (rFVIIIa) upon thrombin activation. Animal models and in vitro tests confirmed cofactor activity and specific activity of N8-GP are similar to that of Novoeight and Advate (octocog alfa).

PEGylation increases the half-life of the protein, and the prolonged circulation time is believed to arise from a reduction in the efficiency of various elimination processes such as renal excretion, receptor mediated uptake, and proteolytic degradation.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.
[2] N8-GP is the drug development code for Esperoct.

Condition

Haemophilia A is a bleeding disorder characterised by congenital underproduction of or dysfunction of FVIII, an essential protein in promoting clot formation. The severity of (and bleeding risk associated with) haemophilia A is classified according to patient's endogenous FVIII activity in their plasma. Those with FVIII activity levels less than 1% have severe disease; between 1% and 5%, moderate disease; and between 5% and 40%, mild disease. Globally, patients with severe disease account for approximately 40%, moderate disease 25%, and mild disease 35% of all patients with haemophilia A.

Severe haemophilia is characterised by spontaneous, recurrent bleeds into joints and muscles which can lead to chronic arthropathy, muscular atrophy, and deformities. Converting the clinical phenotype of haemophilia from severe to moderate has been the rationale for prophylaxis.

As X-chromosome-linked recessive disorders, haemophilia A and B affect hemizygous males while heterozygous females (carriers) do not typically express haemophilia symptoms.

Current treatment options

Clotting factor concentrates (CFCs) are the treatment of choice for people with haemophilia as they are very safe and effective for treating and preventing bleeds. There are two main types of CFCs: virally inactivated plasma derived product made from plasma donated by human blood donors; and recombinant products manufactured using genetically engineered cells and recombinant technology.

Replacement therapy may be 'on-demand' where treatment is given when a haemorrhage occurs, or prophylactic where FVIII is administered at regular intervals in an attempt to prevent the onset of haemorrhage. According to current Australian guidelines, regular continuous prophylactic therapy prior to the onset of joint disease is the standard of care in patients with severe haemophilia in Australia. These products are given intravenously.

There are currently multiple standard half-life recombinant FVIIIs marketed for the treatment of Haemophilia A. These include Xyntha (moroctocog alfa)and Advate (octocog alfa). Extended half-life recombinant FVIII products include Eloctate (efmoroctocog alfa) and Adynovate (rurioctocog alfa pegol).

Other coagulation therapies include:

- Novoseven RT (eptacog alfa), a recombinant FVIIa bypassing agent with indications that include the control of bleeding and surgical prophylaxis in patients with inhibitors to coagulation Factors VIII or IX.
- Hemlibra (emicizumab), a humanised monoclonal modified immunoglobin (Ig) G4 antibody with a bispecific antibody structure bridging Factor IXa and Factor X. It is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. It is given via subcutaneous injection with weekly through to monthly dose regimens.
- Desmopressin injection (subcutaneous or intravenous) is an alternative treatment option for patients with mild haemophilia A. The anti-fibrinolytic agent tranexamic acid is also used as adjunctive therapy in the treatment of skin and mucosal haemorrhages.

The World Federation of Hemophilia updated its treatment guideline in 2020.[3] The Australian guidelines for management of haemophilia were published in 2016;[4] and were based on an earlier World Federation of Hemophilia guideline. Longer acting recombinant CFCs were largely approved subsequent to publications of the Australian guideline.

This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process, using evaluation reports from Swissmedic. The full dossier was submitted to the TGA.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

In addition to Swissmedic approval, Esperoct was approved by: the European Medicines Agency (EMA) in June 2019; United States of America (USA) Food and Drug Administration (FDA) in February 2019; Health Canada in July 2019; and Japanese Pharmaceuticals and Medical Devices Agency in September 2019.

The indications and populations for the product are the same in each jurisdiction with the exception of the European Union (EU) where Esperoct is not indicated for use in children under 12-years.

The European public assessment report (EPAR) for Esperoct;[5] states the following regarding use in children: '*The observed adverse event profile is in general considered comparable to that of other licensed FVIII products and did not give rise to concern. The safety database available generally complies with guideline requirements. However, due to major uncertainties regarding a potential tissue accumulation of PEG, the risk profile of Esperoct treatment is currently not outweighed by its benefit for all age groups. Due to potential risks to brain development, Esperoct should not be used in children*.'

There are differences in the dosing for routine prophylaxis across regulatory jurisdictions.

- Switzerland:

Adults and adolescents (age 12 and over): initial dose 50 IU /kg every 4 days. After this, the dosage schedule can be adjusted to 50 IU/kg every 3 to 4 days or 75 IU/kg every 7 days based on the patient's response (low bleeding rate of 0 – 2 bleeding episodes over the last 6 months) and at the treating physician's discretion.

Children (under 12): One dose of 65 IU (50 to 75 IU)/kg once every two weeks.

- European Union:

Adults: 50 IU/kg every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency.

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

- Canada:

Adults and adolescents (12 years and above): starting dose 50 IU/kg every 4 days.

Children (below 12 years): 60 IU/kg (50 to 75 IU)/kg once every two weeks.

[3] World Federation of Hemophilia treatment guideline available at https://www1.wfh.org/publications/files/pdf-1863.pdf

[4] Guidelines for the management of haemophilia in Australia available at https://www.blood.gov.au/system/files/HaemophiliaGuidelines-interactive-updated-260317v2.pdf

[5] https://www.ema.europa.eu/en/documents/overview/esperoct-epar-medicine-overview_en.pdf

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

- Japan:

Patients aged at least 12 years 50 IU/kg every 4 days, adjust to 50 IU per kg body weight twice weekly or 75 IU per kg body weight once weekly based on patient response. For patients aged younger than 12 years of age 60 IU/kg once every two weeks, adjust to 50 to 75 IU/kg once every two weeks or every 3 days based on the patient response.

- United States of America:

Adults and adolescents (at least 12 years): starting dose is 50 IU /kg every 4 days. Adjust to less or more frequent dosing based on bleeding episodes.

Children (younger than 12 years): 65 IU/kg once every two weeks. This regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.

The prophylaxis dose regimen proposed for Australia is the same as has been approved in Switzerland and is similar to that of the USA except for the adjustment recommendations for children aged < 12 years.

Additionally, the EMA's EPAR for Esperoct includes the following: '*During the course of the site inspections and the sponsor inspection, significant deficiencies in relation to data quality and integrity as well as rights and safety of patients were observed. Considering the observed deficiencies, a triggered inspection at additional two investigator sites has been requested, to complete the verification of the data integrity and the impact of these findings on the study. According to the final integrated inspection report and despite of the ICH GCP breaches reported, the data is considered reliable enough to support the application submitted for Esperoct.*'[5]

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Submission PM-2022-01578-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	3 June 2022
First round evaluation completed	30 August 2022
Sponsor provides responses on questions raised in first round evaluation	21 October 2022
Second round evaluation completed	6 March 2023
Delegate's Overall benefit-risk assessment	29 March 2023

Description	Date
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	31 May 2023
Administrative activities and registration on the ARTG completed	5 June 2023
Number of working days from submission dossier acceptance to registration decision*	144

* The COR-B process has a 175 working day evaluation and decision timeframe.

Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Esperoct turoctocog alfa pegol is provided as a white to off-white powder for injection containing the active ingredient turoctocog alfa pegol with a prefilled syringe of 0.9% sodium chloride, a solvent for reconstitution. Five strengths are proposed for registration: 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU. After reconstitution, the solution appears as a clear and colourless liquid, free from visible particles, and each 1 mL Esperoct contains approximately 125 IU, 250 IU, 375 IU, 500 IU or 750 IU turoctocog alfa pegol for intravenous injection, respectively.

The container for Esperoct consists of a 5 mL Type I glass vial, a rubber stopper, and an aluminium seal with a plastic snap-off cap, packaged together with one sterile vial adapter for reconstitution, one prefilled syringe of 4 mL solvent (0.9% sodium chloride solution) with backstop (polypropylene), a rubber plunger (bromobutyl) and a rubber tip cap (bromobutyl), and one plunger rod (polypropylene), packaged in a carton box.

The manufacturing and quality control assessment is based largely on a COR-B report from oversea regulator evaluation reports.

The following additional assessments were carried out which were deemed necessary to meet Australian Requirements.

- The Good Manufacturing Practice for the drug substance and drug products
- Shelf life and containers for drug substance and drug products
- Product Information, CMI and labels.

There are no objections on quality grounds to the approval of Esperoct (turoctocog alfa pegol).

Quality related proposed conditions of registration

- Laboratory testing & compliance with Certified Product Details (CPD)

i. All batches of Esperoct supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

ii. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://cwww.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website [for the form] https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines [for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-product-details

Nonclinical

There were no nonclinical objections to the registration of Esperoct (turoctocog alfa pegol) for the proposed indication.

The evaluator noted the following:

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biotechnology derived pharmaceutical medicines (ICH S6 [R1]). All pivotal safety-related studies were Good Laboratory Practice compliant.
- *In vitro*, turoctocog alfa pegol bound to rat, pig, dog, cynomolgus monkey and human von Willebrand factor with approximately similar picomolar affinity to that of unPEGylated rFVIII (turoctocog alfa and Advate [octocog alfa]). Turoctocog alfa pegol rates of activation and inactivation, and plasma stability were overall comparable to those of turoctocog alfa and/or Advate. Turoctocog alfa pegol binding to receptors implicated in the clearance of FVIII was reduced compared with turoctocog alfa. In vivo, turoctocog alfa pegol displayed longer lasting prophylactic efficacy in FVIII knockout mice (F8-KO) and haemophilia A dogs compared to turoctocog alfa or Advate. These studies offer support for efficacy for the proposed indication.
- Safety pharmacology endpoints were examined in the repeat-dose toxicity study in cynomolgus monkeys. No adverse effects on CNS, cardiovascular or respiratory function are predicted in patients.
- Overall, the pharmacokinetic profile of turoctocog alfa pegol in mouse (wild-type [WT] and F8-KO), rats (WT and Rowett nude), rabbits, dogs (haemophilia A model) and cynomolgus monkeys was qualitatively similar to that of humans with retention in the plasma compartment and long plasma half-lives. Tissue distribution of drug-related material was wide. Some distribution was noted in choroid plexus, and reproductive organs but only

limited penetration into brain was seen. Excretion of drug-related material was via urine and faeces.

- Turoctocog alfa pegol had a low order of acute oral toxicity in rats.
- Repeat-dose toxicity studies by the clinical route (intravenous) were conducted with turoctocog alfa pegol in WT rats and cynomolgus monkeys (two weeks) and immune-deficient Rowett nude rats (up to 12 months). Maximum exposure to turoctocog alfa pegol were subclinical to low in WT rats, moderate in Rowett nude rats and subclinical cynomolgus monkeys. Turoctocog alfa pegol was well tolerated in both species, with no target organs for toxicity identified.
- Standard genotoxicity and carcinogenic studies were not conducted with turoctocog alfa pegol, in line with ICH guidelines.
- No reproductive or developmental studies were conducted with turoctocog alfa pegol. This is considered acceptable given the nature of the product. Placement in pregnancy category B2,[6] as the sponsor proposed, is supported.
- There were no turoctocog alfa pegol-related local reactions at injection sites.
- Immunogenicity of turoctocog alfa pegol was demonstrated by generation of anti-drug antibodies and neutralising antibodies within two weeks of dosing in WT rats and cynomolgus monkeys, with a consequential reduction in turoctocog alfa pegol exposures. Therefore, anti-drug antibodies in patients may result in reduced turoctocog alfa pegol exposures and possibly reduced efficacy.

Clinical

Summary of clinical studies

The clinical development programme consisted of five completed studies in previously treated patients (PTPs) with haemophilia A.

- One first human dose trial, Study NN7088-3776;
- One Phase I trial, Study NN7088 4033, and
- Three Phase III studies, Studies NN7088-3859, NN7088-3860 and NN7088-3885.

Pharmacology

Pharmacokinetics

Pharmacokinetic (PK) studies with Esperoct (N8-GP) were conducted in previously treated patients with severe Haemophilia A (FVlll <1 %) and who had no history of FVIII inhibitors. In total, 129 single dose PK profiles of Esperoct were evaluated in 86 patients (including 24 paediatric patients, aged 0 to 11 years). No patients with renal or hepatic impairment were

[6] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

included in the development programme. All patients were male reflecting the genetics of the underlying condition.

Pharmacokinetic data was collected in four studies, (Studies NN7088-3776, -3859, -4033 and -3885). The volume of distribution at steady state Vd_{ss} (mL/kg (geometric mean (CV)) was 39.09 (25.66) at initial PK evaluation in Study 3859 and 34.51 (21.45) at 28-weeks (approximately).

The mean terminal half-life across studies was 13.6 hours for patients aged 0 to 5 years, 14.2 hours for patients aged 6 to 11 years, 15.8 hours for patients aged 12 to 17 years and 19.9 hours for patients aged 18 years and older.

Clearance is higher and area under concentration time curve (AUC) as well as half-life is lower in the younger patients as is seen with other FVIII products.

Results from a single 50 IU dose by age group are shown in Table 2 below.

Table 2: Studies- 3776, 3859, 4033 and 3885 Single dose pharmacokinetic parameters by age (chromogenic assay using PSS as calibrator) - 50 IU/kg N8-GP

Parameter	0–5 years	6–11 years	12–17 years	≥18 years
Incremental recovery 30 min post-dosing ([IU/dL]/[IU/kg])[a)]				
N	-	-	5	79
Geometric Mean (CV%)	-	-	2.79 (12.19)	2.63 (22.09)
Median	-	-	2.93	2.68
Min ; Max	-	-	2.38 ; 3.22	1.50 ; 4.16
Incremental recovery 60 min post-dosing ([IU/dL]/[IU/kg])				
N	13	11	5	79
Geometric Mean (CV%)	1.80 (29.14)	1.99 (24.91)	2.59 (8.58)	2.43 (23.43)
Median	1.83	2.22	2.70	2.52
Min ; Max	1.01 ; 3.20	1.29 ; 2.64	2.34 ; 2.85	1.20 ; 3.71
$AUC_{(0\text{-inf})}$ (IU×h/dL)				
N	13	11	5	79
Geometric Mean (CV%)	2147 (47)	2503 (42)	3100 (44)	3686 (35)
Median	2246	2261	2358	3574
Min ; Max	988 ; 4932	1645 ; 6065	2232 ; 5243	1652 ; 7122
Terminal half-life, $t_{½}$ (h)				
N	13	11	5	79
Geometric Mean (CV%)	13.6 (20.4)	14.2 (26.1)	15.8 (43.2)	19.9 (34.2)
Median	13.0	13.5	12.4	19.8
Min ; Max	10.6 ; 18.3	10.9 ; 24.0	11.2 ; 25.6	9.8 ; 52.3
Clearance (mL/h/kg)				
N	13	11	5	79
Geometric Mean (CV%)	2.6 (44.7)	2.4 (39.6)	1.5 (42.8)	1.4 (32.1)
Median	2.7	2.7	1.9	1.4
Min ; Max	1.2 ; 5.4	1.2 ; 3.8	0.9 ; 2.2	0.8 ; 3.2

N: Number of patients, CV: Coefficient of variation, PSS: product specific standard, $AUC_{(0\text{-inf})}$: Area under the curve extrapolated to infinity.

[a)] The first sampling in children < 12 years of age was after 1 hour in accordance with the EMA guideline for FVIII products[14]

Pharmacodynamics

Esperoct is a recombinant FVIII product intended for intravenous administration as a replacement for missing native FVIII in patients with haemophilia A. No specific pharmacodynamic (PD) studies have been conducted. Given that the pharmacokinetic parameters of Esperoct were based on FVIII activity and this is known to correlate with clinical efficacy of FVIII products this is acceptable.

Efficacy

The efficacy of Esperoct in previously treated patients with severe haemophilia A was evaluated in three Phase IIIa studies: 3859 (prophylaxis and treatment in adolescents and adults), 3885 (prophylaxis and treatment in children) and 3860 (perioperative management). These were multinational, multi-centre, non-controlled, and open-labelled studies to investigate the safety and efficacy of Esperoct.

Additional data on haemostatic efficacy were captured in Study 4033, a Phase I trial in adults and adolescents evaluating and comparing the pharmacokinetics and safety of the formulation from the pivotal process vs. the commercial process. Summary information from these studies is shown in Table 3 below.

Table 3: Overview of clinical trials evaluating the efficacy of Esperoct

Trial ID/Status	Trial design	N8-GP dose and treatment regimen[a]	Number of patients (age range)[b]	Primary endpoint
Trials in previously treated patients				
Trial 3859 Pivotal part of the trial (Interim report): Completed	*Pivotal trial* Open-label, non-controlled Treatment groups: on-demand and prophylaxis (non-randomised)	Main phase: *Prophylaxis*: 50 IU/kg Q3−4D. *Treatment of bleeds*: 20–75 IU/kg	186 patients (12−66 years)	Co-primary endpoints: incidence of inhibitory antibodies against FVIII defined as titre ≥0.6 BU and ABR for patients on prophylaxis
Extension phase part 1 (Interim report): Completed	Treatment groups: on-demand and 50 IU/kg Q3−4D prophylaxis (non-randomised); 75 IU/kg Q7D and 50 IU/kg Q4D prophylaxis (randomised 2:1)	Extension phase part 1: *Prophylaxis*: 50 IU/kg Q3−4D or 75 IU/kg Q7D. *Treatment of bleeds*: 20–75 IU/kg	150 patients	
Extension phase part 2 (Interim report): Ongoing	Treatment groups: on-demand and prophylaxis (non-randomised)	Extension phase part 2: *Prophylaxis*: 50 IU/kg Q3−4D or 75 IU/kg Q7D. *Treatment of bleeds*: 20–75 IU/kg	139 patients	
Trial 3885 Main phase (Interim report): Completed Extension phase (Interim report): Ongoing	*Paediatric trial* Open-label, non-controlled, single-arm	*Prophylaxis*: ~60 IU/kg (50−75) twice-weekly* *Treatment of bleeds*: 20–75 IU/kg	68 patients (1−11 years)	Incidence of inhibitory antibodies against FVIII defined as titre ≥0.6 BU.
Trial 3860 (Interim report): Ongoing	*Surgery trial - Major surgeries* Open-label, non-controlled, single-arm	*Pre-surgery period*: Pre-operative dose aiming for a FVIII activity level of 80−100%. *Post-operative period* *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 patients; 45 surgeries (15−69 years)	Haemostatic effect during surgery evaluated on a four-point scale.
Trial 4033: Completed	*Pharmacokinetics & safety of N8-GP from the pivotal and commercial processes* Randomised, double-blind, cross-over Treatment groups: N8-GP pivotal process and N8-GP commercial process (randomised 1:1)	*Single−dose PK*: 50 IU/kg *Treatment of bleeds*: 20–75 IU/kg N8-GP from the pivotal process[a].	21 patients 25−71 years	Area under the FVIII activity-time curve from 0 to 96 hours post injection.

PK: pharmacokinetics; WFH: World Federation of Hemophilia

[a] Bleeds were treated according to the severity and location of the bleed. Additional doses for treatment of a bleed could be given at the investigator's discretion.

[b] Number of exposed patients shown; all patients had severe haemophilia A with FVIII activity <1%.

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; ABR: annualised bleeding rate; BU: Bethesda unit. *Dosing frequency could be adjusted at the discretion of the investigator based on patient response. a Bleeds were treated according to the severity and location of the bleed. Additional doses for treatment of a bleed could be given at the investigator's discretion. b Number of exposed patients shown; all patients had severe haemophilia A with FVIII activity <1%.

Study 3859

Study 3859 was a multi-centre, multi-national, open label, non-randomised study conducted in 77 sites in 22 countries including three sites in Australia. It commenced in January 2012 with the main phase finalised in January 2014. The extension phase was ongoing with the most recent data cutoff (DCO) of October 2017.

Co-primary objective were:

- To evaluate the immunogenicity of N8-GP in previously treated patients with Haemophilia A.

- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeds during prophylaxis).

Secondary objectives were:

- To evaluate the clinical efficacy of N8-GP when treating bleeds in patients with haemophilia A.

The study was conducted in previously treated male patients (aged 12 to 66 years) with severe haemophilia A and at least 150 exposure days (EDs) to FVIII. It consisted of a main (pivotal) phase followed by an extension phase. The main phase included an on-demand arm (20 to 75 IU/kg) and a prophylaxis arm (50 IU/kg of N8-GP every 4 day). The treatment (on demand or prophylaxis) was non-randomised and based on the choice of the patient and investigator. All patients were to continue in the main phase until the last patient initiated in the prophylaxis arm had received at least 50 EDs of N8-GP (except for patients having had surgery as part of Study 3860) and the average exposure to N8-GP would therefore be more than 1 year. An ED was defined as each date on which N8-GP was administered; hence, if N8-GP was administered more than once during the same day, this would still count as one ED.

The extension phase of the study had two parts. In Part 1, patients were offered the option of being randomised to treatment every 7 days or every 4 days (2:1 randomisation) if they were on every 4 days prophylaxis with N8-GP in the main phase of the trial and had 0 to 2 bleeds during the last 6 months before entering the extension phase. Patients with 3 or more bleeds within the last 6 months of the main phase and patients with low bleeding rates who were unwilling to be randomised continued on every 4 days N8-GP. When patients had completed Part 1 (6 months of treatment), extension phase Part 2 was opened. In Part 2, patients could continue on prophylaxis but could change between every 4 days and every 7 days dosing. The doses for the extension phase Parts 1 and 2 were 50 IU/kg of N8-GP for every 4 days prophylaxis and 75 IU/kg of N8-GP for every 7 days prophylaxis. Patients treated on demand throughout the main phase were to continue with the on-demand regimen in the extension phase.

In the main phase of this study data was to be collected until the last patient on N8-GP prophylaxis was expected to reach 50 EDs. The sample size was increased from 120 to 160 patients after an interim analysis was performed. After sample size adjustment, approximately 172 patients were planned to be enrolled in the main phase of the trial including at least 12 patients receiving on-demand treatment and 160 patients receiving prophylaxis treatment. In total 186 patients received study treatment, of these 25 were adolescents (12 to 17 years). Patients had severe congenital haemophilia A (FVIII activity below 1%, according to medical records), a documented history of at least 150 EDs to other FVIII products and were at least 12 years of age with and body weight at least 35 kg (except for Croatia, France, Russia, Israel and the Netherlands where the lower age limit was 18 years). Major exclusion criteria were: HIV, history of FVIII inhibitors, and FVIII inhibitors above or equal to 0.6 Bethesda units at screening.

As of October 2017, the mean time in the trial was 1265 days (range: 5 to 1975 days) and mean number of EDs was 294 days (range: 1 to 556 days).

Efficacy criteria were:

- Annualised bleeding rate for patients receiving prophylaxis treatment;
- The haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure;

- Terminal half-life (t½), (h), based on the subgroup of patients with full PK sessions at Visits 2 and 7 (separated by 28 weeks).

A prophylactic effect of N8-GP would be concluded, if the annualised bleeding rate was significantly below 8.5. The null hypothesis was tested against the alternative hypothesis as given by: H_0: annualised bleeding rate (ABR) ≥ 8.5 against haemophilia A:ABR < 8.5. The endpoint was analysed by a Poisson regression model on number of bleeding episodes per patient allowing for overdispersion (using Pearson's chi-square divided by the degrees of freedom) and using log planned observation duration as an offset.

Estimates of the ABRs were provided with 95% confidence intervals. Efficacy based on haemostatic response would be concluded if the one sided lower 97.5% confidence limit for the success rate was above 65%.

A total of 165 patients completed the main phase of the study and 150 continued into the extension phase; 139 completed six months of treatment in Part 1 and all 139 patients continued into Part 2. In total, 120 patients were still in the extension phase as of October 2017.

Eighty-eight patients continued on prophylaxis every 3 or 4 days in the non-randomised arm and 7 patients continued on-demand treatment in extension phase Part 1. A total of 55 patients continuing in the extension phase were randomised to prophylaxis groups, 38 patients were randomised in the every 7 days arm and 17 in the every 4 days arm. In Part 2 of the extension phase, the prophylaxis treatment of patients could be changed to every 4 days or every 7 days, according to predefined rules and at the investigator's discretion. During extension phase Part 1, 9 patients were switched from every 7 days to every 3 or 4 days. At entry to extension phase Part 2, 12 patients transferred from every 3 or 4 days to every 7 days prophylaxis and 2 patients transferred from on-demand treatment to every 3 or 4 days prophylaxis. Thus, at the start of the extension phase 94 patients were receiving every 3 or 4 days prophylaxis treatment, 40 were receiving every 7 days prophylaxis and 5 were receiving on-demand treatment. During the extension phase Part 2, 13 patients transferred from every 3 or 4 days to every 7 days prophylaxis and 23 patients transferred from every 7 days to every 3 or 4 days prophylaxis.

At Baseline mean age was 31.1 years (range 12 to 66 years old) and mean body weight of 75.5 kg (range from 39 to 122 kg), 74.2% were White and 18.8% were Asian. Fifty-five (34.4%) patients had clinically significant abnormal findings in the musculoskeletal system at Baseline, three patients had pre-existing anti-N8-GP antibodies and 13 patients had pre-existing anti-PEG antibodies measured before dosing with N8-GP. At Baseline, 10 patients were positive for HIV antibodies, 109 patients were positive for hepatitis C antibodies and 6 patients were positive for hepatitis B antibodies.

Results

Table 4: Study 3859 Annualised bleeding rates full analysis set

	Prophylaxis	On-demand	Total
Number of patients*	175	12	186
Number of patients with bleeds, N (%)	105 (60.0)	12 (100.0)	117 (62.9)
Number of patients with LOCF	12	1	13
Number of observed bleeds	436	532	968
Number of bleeds using imputation**	576	539	1115
Number of patients with less than 1 month exposure	7	0	7
Bleeds per patient (min ; max)	0.0 ; 45.0	7.0 ; 131.0	0.0 ; 131.0
Mean treatment period (years)***	0.89	1.35	0.92
Individual ABRs			
N	175	12	186
Mean (SD)	3.73 (5.90)	31.95 (19.09)	5.48 (9.99)
Median	1.33	30.87	1.60
Interquartile range	0.00 ; 4.61	18.64 ; 38.51	0.00 ; 5.88
Min ; Max	0.00 ; 28.42	4.75 ; 74.18	0.00 ; 74.18
Poisson estimate of ABR+	3.70	-	-
95% CI	2.94 ; 4.66	-	-
P-value++	<0.001	-	-
Negative binomial estimate of ABR+++	3.70	-	-
95% CI	2.93 ; 4.66	-	-
P-value++	<0.001	-	-

The analysis is based on a Poisson regression model allowing for over-dispersion. For patients withdrawing prematurely, the log planned observation duration is used as offset; for completers, the log actual observation duration is used.
* 1 patient who switched from on-demand to prophylaxis during the trial is counted in both columns.
** Imputation: For patients withdrawing prematurely, the number of bleeding episodes is imputed up to what would be expected if they had completed the trial, as described in the protocol. For patients withdrawing within one month, the annual bleeding rate is imputed as 24 episodes per year for the missing period.
*** For patients withdrawing prematurely, the planned observation duration is used; for completers, the actual treatment period is used.
+ Primary results based on a Poisson model, as specified in the protocol.
++ P-values are from the 1-sided test of the null hypothesis that the ABR is at least 8.5 evaluated at the 2.5% level.
+++ Additional sensitivity analysis based on a negative binomial model.

A total of 186 patients were assessed with 117 patients (63%), including prophylaxis and on-demand patients, treated for 968 bleeds during pivotal part of the trial (Table 4). The majority of bleeds (99%) were classified as mild/moderate, eight bleeds (1%) were classified as severe. Sixty-nine percent (69%) of the bleeds were spontaneous, 30% were traumatic, and 1% were after minor surgery. In the pivotal part, 96% (924 bleeds) of all bleeds were treated with 1 to 2 injections of N8-GP and 4% (44 bleeds) were resolved with at least 3 injections.

Table 5: Study 3895 Haemostatic response

Phase	Dose	Number of bleeds	Success rate*
Pivotal part	20–75 IU/kg	968 (includes 4 missing responses)	84.2% (95% CI: 80.0; 87.7)
Main + Extension phase part 1	20–75 IU/kg	1436 (includes 16 missing responses)	83.3% (95% CI: 79.4; 86.6)
Main, Extension phase part 1 and 2	20–75 IU/kg	2479 (includes 41 missing responses)	84.0% (95% CI: 80.6; 86.9)

*Includes all bleeds treated with N8-GP that occurred in on-demand and prophylaxis patients; bleeding episodes without haemostatic responses were counted as failures

For the 12 patients who received on-demand treatment, 1126 bleedings were treated with a mean treatment dose of 38.1 IU/kg and mean annual consumption of 1457 IU/kg (Table 4). Of the total 1126 bleeds, 86.9% were effectively treated with one injection and 96.8% were effectively treated with 1 to 2 injections of N8-GP.

Patients who had a bleeding rate of 0 to 2 bleeding episodes during the last 6 months of the main phase of the study and had obtained at least 50 doses of N8-GP had the option of being randomised to prophylaxis treatment every 7 days (75 IU/kg every 7 days) or every 4 days (50 IU/kg every 4 days). A total of 55 of the 120 eligible patients chose to be randomised (17 to the every 4 days dosing and 38 to the 75 IU every 7 days). Of the 38 patients randomised to every 7 days dosing prophylaxis, 22 patients (58%) did not have any bleeds during extension phase Part 1 and the remaining 16 patients had a total of 25 bleeds. The ABR for randomised patients was 1.77 (0.59; 5.32) for treatment every 4 days and 3.57 (2.13; 6.00) for once weekly prophylaxis. Nine of these patients reverted back to prophylaxis every 4 days during the randomised study phase. Overall, including all extensions parts, 31 of 61 patients on every 7 days prophylaxis switched back to every 4 days treatment.

Study 3860

Study 3860 was multi-centre, multi-national, open-label, non-randomised, and single-arm study to assess the efficacy and safety of N8-GP during surgical procedures in patients with severe haemophilia A. It was conducted at 25 sites, in 13 countries including 1 site in Australia. It commenced in August 2012 and was ongoing in 2017 when the study report was finalised.

Patients were recruited from Study 3859 and must have received at least 5 doses of N8-GP. Patients were offered trial entry if they needed major surgery. The trial period was estimated to have a total duration of 2 to 5 weeks for each patient. All patients attended a screening Visit 0 to 3 weeks prior to surgery. Surgery was performed at Day 0. During Days 1 to 6 in the post-operative period, assessments were done daily. During Days 7 to 14 in the post-operative period, assessments were done once. If the late post-operative period was extended beyond Day 14, the investigator/medically qualified person performed a visit schedule with the patient once every week until the postoperative control was finalised. Upon completion of this trial, patients returned to Study 3859.

Efficacy of N8-GP during surgical procedures was assessed using a 4-point scale of: excellent, good, moderate, or none. In addition, transfusion requirements, consumption and estimated blood loss were recorded as part of the efficacy assessment. Blood sampling for FVIII activity and laboratory safety parameters was done at all trial visits.

Thirty-four patients were screened and all 34 patients were exposed to trial product with 33 patients completing the study. Forty-five surgeries were completed; 10 of the 33 patients re-entered the trial: four patients had two surgeries, three patients had three surgeries, one patient had four surgeries and two patients who initially withdrew re-entered the trial to have a surgery at a later time point.

N8-GP was administered as a slow bolus intravenous injection. The administrations were performed both at home and in hospital. Dosing was done at the investigators' discretion (except a fixed dose of 50 IU/kg at Visit 1). The dose level of N8-GP during this trial was chosen following the FVIII activity levels recommended by World Federation of Hemophilia guidelines.[3] Higher levels could be necessary depending on type of surgery and standard practice at site. The World Federation of Hemophilia guidelines for desired FVIII levels in major surgery are as follows: pre-surgery (Day 0): 80 to 100%; post-surgery Days 1 to 3: 60 to 80%; Days 4 to 6: 40 to 60%; Days 7 to 14: 30 to 50%. For treatment of a bleeding episode, all patients were treated with doses between 20 to 75 IU/kg. The maximum dose to be administered to a patient within 24 hours was 200 IU/kg.

The following efficacy criteria were assessed:

- Haemostatic effect of N8-GP during surgery (4-point scale of excellent to none) assessed by the investigator/surgeon at the day of surgery;
- Estimated blood loss during surgery
- Average consumption of N8-GP during surgery
- Haemostatic effect of N8-GP during the post-operative period Days 1 to 6
- Average consumption of N8-GP during the post-operative period Days 1 to 6
- Number of transfusions during the post-operative period Days 1 to 6
- Haemostatic effect of N8-GP during the post-operative period Days 7 to 14
- Health economics: length of stay in the hospital and days in intensive care assessed at the end of the trial

No formal sample size calculations were performed. This was a descriptive study.

Results

Mean age was 40.8 years (range: 15 to 69 years), mean body mass index was 25.4 kg/m^2 (range: 18.4 to 36.7 kg/m^2), 28 (82.4%) patients were White, five (14.7) were Asian and 1 (2.9%) was Black or African American. Forty-two of the surgeries were elective, three were emergency and 41 were for orthopaedic surgery.

- The success rate for the haemostatic effect of N8-GP during surgery was 95.6%, 43 out of 45 surgeries had the effect rated as excellent or good.
- Two surgeries (4.4%) had the effect rated as moderate.
- Most of the surgeries (41) were orthopaedic surgeries, including arthroscopic interventions (N = 9, 20%), joint replacements (N = 15, 33%), and other orthopaedic interventions (N = 17, 38%).
- The mean and median estimated blood loss during surgery was 339 mL and 50 mL, respectively, and the range was 0 to 4520 mL.
- A pre-surgery dose of N8-GP was administered to all patients on the day of surgery; the mean dose was 55.3 IU/kg (range: 27.2 to 86.2 IU/kg). In one surgery, a dose of N8-GP was administered during surgery (20.7 IU/kg). In 29 surgeries, a post-surgery dose was administered on the day of surgery; the mean dose was 31 IU/kg (range: 10.1 to 58.8 IU/kg).
- The post-surgery success rate was rated as excellent or good in 3 of the 4 bleeding episodes: two bleeds during Days 1 to 6 post-surgery (one assessed as good, assessment was missing for the other) and two bleeds during Days 7 to 14 post-surgery (one assessed as excellent, the other as good).
- The mean N8-GP consumption per day during Days 1 to 6 post-surgery was 33.5 IU/kg (range: 15.5 to 59.6 IU/kg).
- During Days 1 to 6 post-surgery, a total of nine blood product transfusions were administered in five surgeries.
- The mean number of days at the hospital during the trial was 10.11 days (range: 0 to 39 days). One patient was admitted to an intensive care unit during this trial; that patient was admitted for one day.

Study 3885

A multinational, open-label, non-controlled study on safety, efficacy and pharmacokinetics of N8-GP in previously treated paediatric patients with severe haemophilia A. The study was conducted at 36 sites in 15 countries, including Canada, UE countries and the UK, commencing in February 2013. At the DOC for the study report of 1 September 2017, this study was ongoing. It was primarily a safety study.

The primary objective was to evaluate immunogenicity of N8-GP. Secondary objectives were:

- To evaluate safety other than immunogenicity of N8-GP
- To evaluate efficacy of N8-GP in prophylaxis and treatment of bleeding episodes
- To evaluate pharmacokinetic properties of N8-GP and compare to previous FVIII product (only pharmacokinetic assessments)
- To support a population-based PK model for N8-GP (only PK assessments)

- To evaluate patient reported outcomes (PRO)

N8-GP was given for prophylaxis and treatment of bleeding episodes to patients below 12 years of age with severe haemophilia A who had greater than 50 (0 to 5 year age group) or greater than 150 (6 to 11 year age group) exposure days (EDs) with previous FVIII product. One ED was defined as any day during which the patient had been exposed to N8-GP, regardless of dose frequency within 24 hours. The study consisted of a main phase and an extension phase. The duration of the main phase for each patient was approximately 26 weeks (corresponding to 50 EDs). Dose-regimen in the prophylaxis arm was 60 IU/kg twice weekly with a dose range of 50-75 IU/kg.

Inclusion/exclusion criteria: Male patients with severe congenital haemophilia A (FVIII activity level below 1%); body weight at least 10 kg; documented history of greaterthan 50 ED to FVIII products for patients aged 0 to 5 years and greater than 150 EDs to FVIII products for patients aged 6 to 11 years. Patients were excluded if there was any history of FVIII inhibitors.

The duration of the trial main phase for each patient was approximately 26 weeks (corresponding to 50 EDs). After completion of the main phase, patients could continue in an extension phase lasting until N8-GP became commercially available.

Twelve patients within each age group were planned to complete PK assessment with both their previous FVIII product and with N8-GP.

In the main phase all patients were treated prophylactically with a fixed dose of N8-GP via intravenous injection twice weekly. The recommended dose level and range was chosen based on data from the Phase 1 PK trial (Study NN7088-3776). The regimen was expected to give measurable FVIII trough activity greater than 1% in the majority of patients. The dose was approximately 60 IU/kg with a dose range of 50 to 75 IU/kg enabling whole mL dosing. Minor surgeries, dental extractions and placement of central venous access ports could be performed while participating in this trial by administering an extra dose of N8-GP equivalent to dose administered for a severe bleeding episode, or aligned to local practice. Patients in need of major surgery were to be withdrawn from the study. The dose ranges for prophylaxis treatment and for bleeding episodes are shown in Table 6 below.

Table 6: Study 3885 Overview of treatments

Phase	Treatment	Dose	Frequency
PK sessions (12 patients from each age-group only)	Previous FVIII and N8-GP	50 U/kg BW	Visit 1 and 2
Main	Prophylaxis	Approximately 60 U/kg BW	Twice weekly[a]
	Treatment of bleeding episodes	20-75 U/kg BW	Investigator's discretion
Extension	Prophylaxis	Approximately 60 U/kg BW	As in main phase[b]
	Treatment of bleeding episodes	20-75 U/kg BW	Investigator's discretion

PK= pharmacokinetics, BW=body weight.
[a] An increase in dose frequency from twice weekly to every third day was permitted at the investigators discretion (based on bleeding pattern).
[b] After 12 months treatment with N8-GP (main phase and extension phase combined) the investigator was permitted to prescribe extra coverage before physical activities.

Efficacy was assessed by: ABR during prophylactic treatment; consumption of N8-GP per bleeding episode (number of injections and IU/kg); consumption of N8-GP during prophylaxis (number of injections and IU/kg per month and year).

Haemostatic effect was rated on a 4 point scale from excellent to none with responses of excellent or good considered a success.

- 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
- None: No improvement, or worsening of symptoms

No formal sample size calculations were performed. The sample size was based the EMA guideline: Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products.[7] The haemostatic response was analysed using logistic regression accounting for repeated measures within patient assuming compound symmetry working correlation. The estimated ABRs were calculated based on a Poisson regression model with age group as a factor allowing overdispersion and using treatment duration as an offset.

Results

A total of 68 patients received treatment with 34 patients aged 0 to 5 years and 34 aged 6 to 12 years. 80.9% of patients were White, 7.4% were Asian. At Baseline, for patients in the 0 to 5 years age group, the mean (range) age was 3 (1 to 5) years, height: 99.3 (80 to 120) cm, and body weight: 16.1 (10.9 to 23) kg. For patients in the 6 to 11 year age group mean (range) age was : 8.9 (6 to 11) years, height: 136.0 (111.1 to 160.5) cm, and body weight: 34.1 (17 to 60.4) kg.

Prior to enrolment in the trial, 65 patients (96% of full analysis set) were on prophylactic treatment (61 patients on recombinant FVIII products and four patients on plasma-derived FVIII products). The remaining three patients (4%; all in the 0 to 5 year age group) were on on-demand treatment. At Baseline, six (8.8%) patients (three in each age group) had clinically significant abnormal findings in the musculoskeletal system, possibly associated with their haemophilia A condition. All patients were negative for HIV and hepatitis C at baseline.

For all patients (N = 68), the median ABR was 1.95 bleeds/patient/year in the main phase and 0.98 bleeds/patient/year including data from the main and extension phases (Table 7).

[7] EMA guideline on clinical investigation of recombinant and human plasma-derived factor VIII products available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf

Table 7: Study 3885Annualised bleeding rate – full analysis set

	Younger children (0-5 years)	Older children (6-11 years)	Total
Number of patients	34	34	68
Number of patients with bleeds, N(%)	25 (73.5)	29 (85.3)	54 (79.4)
Number of bleeds	90	192	282
Bleeds per patient (min ; max)	0; 11	0; 29	0; 29
Mean treatment period (years)	3.118	3.766	3.442
Individual ABRs			
N	34	34	68
Mean (SD)	3.10 (9.73)	1.51 (1.67)	2.30 (6.97)
Median	0.60	1.06	0.98
Interquartile range	0.00; 1.28	0.27; 1.91	0.27; 1.44
Min ; max	0.00;45.66	0.00; 7.89	0.00;45.66
Poisson estimate of ABR	0.85	1.50	1.20
95% CI	0.49; 1.47	1.03; 2.18	0.88; 1.64
Negative binomial estimate of ABR	0.93	1.50	1.26
95% CI	0.62; 1.38	1.08; 2.10	0.96; 1.64
LOCF sensitivity analysis			
Number of patients with less than 30 days of exposure	4	0	4
Number of patients with LOCF	5	0	5
Bleeds per patient (min ; max)	0; 13	0; 29	0; 29
Mean treatment period (years)	3.178	3.766	3.472
Poisson estimate of ABR	1.25	1.50	1.39
95% CI	0.62; 2.53	0.83; 2.71	0.90; 2.14
Negative binomial estimate of ABR	2.99	1.50	2.16
95% CI	1.80; 4.98	0.94; 2.41	1.51; 3.10

ABR: Annualised bleeding rate.
LOCF: Last observation carried forward.
Based on a Poisson regression model with age group as a factor allowing over-dispersion and using treatment duration as an offset.
A sensitivity analysis was carried out using the negative binomial model with treatment duration as an offset.

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Seventy treatment-requiring bleeding episodes were reported in 57.4% (39 out of 68 patients) with a success rate of 78.6%. The success rate was similar in the two age-groups, and the remaining 29 patients (42.6%) reported no bleeding episodes throughout the study.

The majority of the bleeds (71.4%) were traumatic, 27.1% were spontaneous bleeds, and a single bleed (1.4%) was due to minor surgery. The most frequent location of bleeds was in a joint, which accounted for 34 (that is 48.6%), divided in 10 joint bleeds in the 0 to 5 years age group and 24 joint bleeds in the 6 to 11 year age group. All bleeds were classified as mild or moderate, and no re-bleeds during the study were reported. The mean (range) duration of bleeds among the 0 to 5 years age group was 53 (0.4 to 209.6) hours compared to 35.2 (1 to 136.2) hours in the 6 to 11 year age group. Of the 15 patients who reported target joint at Baseline, 11 patients did not report any target joint bleeding episodes during the trial. The remaining four patients reported six bleeding episodes involved a target joint, that is two bleeding episodes in the 0t o 5 year age group (both spontaneous) and four bleeding episodes in the 6 to 11 year age group (two spontaneous and two traumatic).

For spontaneous bleeds, the success rate was 72.6%, which was lower than the success rate obtained for traumatic bleeds (82.8%). Comparable success rates were observed between age-groups for both the spontaneous bleeds and the traumatic bleeds.

Overall, 56 out of 70 (80.0%) bleeding episodes were treated with less than or equal to 2 injections of N8-GP. The mean (range) dose used from start to stop of a bleed was 123 (44.9 to 436) U/kg in the 0 to 5 year age group and 99 (49.9 to 296.4) U/kg in the 6 to 11 year age-group. After six injections with N8-GP, two bleeding episodes still remained to be successfully treated:

- a spontaneous bleed to right elbow in a two year old treated immediately after bleeding onset with a total N8-GP consumption of 435.5 U/kg during nine days. The investigator classified the bleeding episode as mild/moderate with a good treatment outcome

- a traumatic bleed to left knee in a five year old treatment started approximately 18 hours after bleeding onset with a total N8-GP consumption of 422.5 U/kg during eight days. The investigator classified the bleeding episode as mild/moderate with a moderate treatment outcome.

The mean consumption per patient, including prophylaxis, treatment of bleeds, minor surgeries, and PK doses was 6870 U/kg/year in the 0 to 5 year age group with mean dose of 63.7 U/kg (median 67.1 U/kg). In the 6 to 12 year age-group mean consumption was 6670 U/kg/year with mean dose 62.3 U/kg (median 62.3 U/kg).

Haemostatic effect in bleeding episodes

Overall, 203 of the 254 patients reported bleeds during the N8-GP clinical development programme (pooled across Studies 3859, 4033 or 3885). A total of 2766 bleeds; 1126 occurred in 12 patients who received on-demand treatment and 1640 occurred in 193 patients who received prophylaxis. Patients who received on-demand treatment had more spontaneous than traumatic bleeds (76% and 23%, respectively), whereas patients who received prophylaxis treatment had similar proportions of spontaneous and traumatic bleeds (53% and 47%, respectively) (Table 8). A combined analysis using data from the three studies assessed the haemostatic response to bleeding episodes and the dose of Esperoct required to manage the episodes.

Table 8: Studies 3859, 4033 and 3885 Haemostatic response by age - full analysis set

	0-5 years	6-11 years	12-17 years	>=18 years	Total
Number of patients	34	34	25	161	254
Number of patients with bleed N(%)	25 (73.5)	29 (85.3)	22 (88.0)	127 (78.9)	203 (79.9)
Number of bleeds	90	192	168	2316	2766
Haemostatic response, N(%)					
N	90 (100.0)	192 (100.0)	168 (100.0)	2316 (100.0)	2766 (100.0)
Excellent	37 (41.1)	85 (44.3)	68 (40.5)	1281 (55.3)	1471 (53.2)
Good	41 (45.6)	62 (32.3)	61 (36.3)	792 (34.2)	956 (34.6)
Moderate	8 (8.9)	37 (19.3)	30 (17.9)	203 (8.8)	278 (10.1)
None	2 (2.2)	2 (1.0)	-	8 (0.3)	12 (0.4)
Missing	2 (2.2)	6 (3.1)	9 (5.4)	32 (1.4)	49 (1.8)
Success/Failure					
N	88 (100.0)	186 (100.0)	159 (100.0)	2284 (100.0)	2717 (100.0)
Success	78 (88.6)	147 (79.0)	129 (81.1)	2073 (90.8)	2427 (89.3)
Failure	10 (11.4)	39 (21.0)	30 (18.9)	211 (9.2)	290 (10.7)
Success/Failure (incl. missing as failure)					
N	90 (100.0)	192 (100.0)	168 (100.0)	2316 (100.0)	2766 (100.0)
Success	78 (86.7)	147 (76.6)	129 (76.8)	2073 (89.5)	2427 (87.7)
Failure	12 (13.3)	45 (23.4)	39 (23.2)	243 (10.5)	339 (12.3)
Success rate					
Rate	87.5	80.8	82.6	85.9	85.0
95% CI	74.8 ; 94.3	72.7 ; 86.9	72.1 ; 89.7	82.6 ; 88.7	82.2 ; 87.5
Success rate (incl. missing as failure)					
Rate	86.0	77.8	78.0	85.1	83.4
95% CI	74.6 ; 92.8	70.0 ; 84.0	64.8 ; 87.3	81.8 ; 87.9	80.5 ; 86.0

Success rate analysed using logistic regression accounting for repeated measures within subject assuming compound symmetry working correlation.
For all trials data are included from main and extension phases.

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

Safety

The clinical development program of Esperoct is in accordance with the current guidelines on the clinical investigation of recombinant and human plasma-derived FVIII products.

Previously treated patients:

- Trial 3776 – Phase I first human dose trial in adult patients (at least 18 years)

- Trial 3859 – Phase III trial in adult and adolescent patients (at least 12 years);
- Trial 3860 – Phase III surgery trial (at least 12 years)
- Trial 3885 – Phase III trial in paediatric patients (younger than 12 years);
- Trial 4033 – Phase I trial (at least 12 years)

Previously untreated patients:

- Trial 3908 – Phase III trial in previously untreated patients (younger than 6 years) (no study report but included in the immunogenicity report only)

In clinical development quite long exposure times to Esperoct were reached. Out of a total of 270 patients treated in PTPs, 192 patients (including 63 children) were treated for more than three years, 139 patients (including 15 children) were treated for more than four years and 18 patients (no children) were treated for more than five years. Only three patients were at least 65 years of age and 6 were younger than 2 years of age at the time of inclusion in trial.

In the surgery Study 3860, a total of 34 patients (all of whom were already participating in trial 3859) were exposed for 979 exposure days corresponding to a total of 6.4 patient-years exposure. There was a change in the manufacturing process during the clinical trial period. N8-GP from the commercial process was introduced in the extension phase of Studies 3859 and 3885. As of the data cutoff date, 92 out of 254 patients had been switched from N8-GP from the pivotal process to N8-GP from the commercial process.

Safety data from all completed and ongoing trials in previously treated patients were pooled (Studies 3776, 3859, 4033 and 3885), except safety during surgery (trial 3860). All patients were diagnosed with severe haemophilia A and had a FVIII activity level less than 1%. The mean age was 25 years, ranging from 1 to 66 years, 75% were White (75%), 16% were 16% Asian and 6% were Black or African American. At Baseline, none of the patients aged younger than 18 years were positive for hepatitis C, hepatitis B or HIV. 120 of 177 (68%) of the adult patients were hepatitis C positive, 6 patients were hepatitis B positive (three of these patients were also hepatitis C positive), and 13 of the patients with available data on HIV status were HIV positive.

A total of 2307 adverse events were reported in 239 (89%) patients. The overall rate was 2.6 adverse events per patient-years exposure. The most commonly reported adverse events were viral upper respiratory tract infection (130 events in 78 [29%] patients), upper respiratory tract infection (105 events in 57 [21%] patients), headache (118 events in 56 [21%] patients), arthralgia (66 events in 43 [16%] patients), cough (53 events in 37 [14%] patients), diarrhoea (39 events in 31 [12%] patients) and influenza (42 events in 29 [11%] patients). Adverse events reported for more than 5% of the patients are summarised in Table 9 below.

Table 9: Studies 3776, 3859, 4033 and 3885Summary of most frequent adverse events (preferred term > 5%)

	Total N(%) E[R]
Number of patients	270
Patient years of exposure	882.13
Exposure days	79446
All adverse events	239(88.5) 2307[2.62]
Infections and infestations	
Viral upper respiratory tract infection	78(28.9) 130[0.15]
Upper respiratory tract infection	57(21.1) 105[0.12]
Influenza	29(10.7) 42[0.05]
Gastroenteritis	20(7.4) 28[0.03]
Tonsillitis	18(6.7) 24[0.03]
Rhinitis	15(5.6) 19[0.02]
Bronchitis	15(5.6) 17[0.02]
Musculoskeletal and connective tissue disorders	
Arthralgia	43(15.9) 66[0.07]
Pain in extremity	22(8.1) 30[0.03]
Musculoskeletal pain	17(6.3) 18[0.02]
Back pain	15(5.6) 18[0.02]
Injury, poisoning and procedural complications	
Contusion	20(7.4) 32[0.04]
Laceration	19(7.0) 21[0.02]
Fall	17(6.3) 19[0.02]
Limb injury	16(5.9) 26[0.03]
Gastrointestinal disorders	
Diarrhoea	31(11.5) 39[0.04]
Vomiting	20(7.4) 24[0.03]
Nausea	17(6.3) 22[0.02]
Toothache	15(5.6) 16[0.02]
Respiratory, thoracic and mediastinal disorders	
Cough	37(13.7) 53[0.06]
Oropharyngeal pain	29(10.7) 35[0.04]
Rhinorrhoea	15(5.6) 20[0.02]
Nervous system disorders	
Headache	56(20.7) 118[0.13]
Skin and subcutaneous tissue disorders	
Eczema	15(5.6) 19[0.02]
Rash	14(5.2) 18[0.02]
General disorders and administration site conditions	
Pyrexia	25(9.3) 41[0.05]
Investigations	
Alanine aminotransferase increased	14(5.2) 21[0.02]
Vascular disorders	
Hypertension	19(7.0) 20[0.02]
Immune system disorders	
Seasonal allergy	14(5.2) 19[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event.
E: Number of adverse events.
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0.

One death was reported, a 67 years old patient died of '*pancreatic carcinoma metastatic*' reported after 88 days of exposure. That death was not considered related to N8-GP. Sixty-seven serious adverse events (SAE) were reported in 47 (17%) patients. Sixty-seven adverse events (AE) were considered to be serious with four of these judged as possibly or probably related to N8-GP by the investigator (intervertebral discitis, FVIII inhibition, hypersensitivity and haemorrhage).

Withdrawals due to AEs and their relationship to N8-GP are shown in Table 10.

Table 10: Studies 3776, 3859, 4033 and 3885 Adverse events leading to withdrawal

Patient ID/ Trial	Age	Preferred term	ED	Relationship[a]	Severity	Serious	Outcome
255001/ 3859	66	Pancreatic carcinoma metastatic	88	Unlikely	Moderate	Yes	Fatal
408001/ 3859	49	Hepatocellular carcinoma	135	Unlikely	Moderate	Yes	Not recovered
501005/ 3859	27	Duodenal ulcer	94	Unlikely	Severe	Yes	Recovered
541002/ 3859	23	Road traffic accident	150	Unlikely	Moderate	Yes	Recovered
904001/ 3859	14	Ankle fracture	156	Unlikely	Severe	Yes	Recovered
924001/ 3859[b]	17	Factor VIII inhibition	97	Probable	Moderate	Yes	Not recovered
172001/ 3885	3	Haemorrhage	4	Probable	Moderate	Yes	Recovered
607002/ 3885	4	Joint swelling	8	Unlikely	Mild	No	Recovered
604001/ 3885[b]	3	Hypersensitivity	4	Probable	Severe	Yes	Recovered

ED: Exposure day

a: The relationship to N8-GP as judged by the investigator.

b: Both patients were withdrawn as they met a withdrawal criterion related to safety; thus, both patients are included in the table even though the reason for withdrawal was not stated as due to an adverse event. Patient ID 604001 also had other adverse events (non-serious) related to allergic reactions; see Appendix 7.1, Listing 65.

Study 3860: 118 AEs were reported in 37 (77%) surgeries and five of the events were serious. The most commonly reported adverse events were constipation (11 events in 11 [23%] surgeries) and nausea (six events in six [13%] surgeries); none of these events were judged to be related to N8-GP by the investigator.

A total of 19 adverse events in five (10%) surgeries were judged to be possibly or probably related to N8-GP by the investigator. The majority of these events (17 out of 19 events) were non-serious adverse events, and the outcome of the events was stated as recovered or recovering (18 events) or recovered with sequelae (one event). The majority of the adverse events were evaluated of mild or moderate severity.

No deaths were reported during surgery. Of the five serious adverse events, two (in one surgery) were evaluated as possibly related to N8-GP by the investigator (haemorrhage and ischemia). No patients were withdrawn from the trial due to adverse events. Two adverse events were reported as medical events of special interests (allergic dermatitis and blister); the events were judged as unlikely related to trial product. No FVIII inhibitors and no thromboembolic events were reported.

Safety assessments of special interest included: immunogenicity, allergic reactions, thromboembolic events, medical errors, injection site reactions, and safety assessment related to PEG.

The following was noted in the oversea evalutor safety assessment: Anti-N8-GP antibodies were identified in six patients, two of whom had already been positive prior to N8-GP exposure. Three patients developed transient anti-N8-GP antibodies, while one patient developed persistent anti-N8-GP antibodies (this patient was the one with FVIII inhibitor antibodies). Anti-PEG antibodies were identified in 43 patients, 32 of whom had been positive prior to N8-GP exposure.

Eleven patients developed anti-PEG antibodies after dosing with N8-GP, all were only temporarily positive. Of the 32 patients with pre-existing anti-PEG antibodies, 20 had no measurable anti-PEG antibodies after N8-GP administration.

Anti-CHO-host cell proteins (HCP) antibodies were identified in 11 patients, two of whom had been positive prior to N8-GP exposure. Nine patients developed anti-CHO HCP antibodies with low titres. Of the 9 patients, 3 had persistent anti-CHO HCP antibodies. Overall, there was no correlation between the detection of anti-N8-GP antibodies, anti-PEG antibodies and anti-CHO HCP antibodies, and any relevant adverse events or reduced incremental FVIII activity, except in

a patient who had transient anti-N8-GP antibodies and transiently reduced incremental FVIII activity. That patient responded well to the study medication throughout the study.

There was no evidence of an increased risk of FVIII inhibitor development or allergic reactions with N8-GP compared to other FVIII products. Some injection site reactions of mild or moderate severity have been reported; such reactions are known and occurred with injections of other FVIII products.

The potential clinical impact of PEG following treatment with N8-GP was assessed, including assessment of renal and hepatic function, as well as neurological and psychiatric findings. No safety concerns were identified.

Other (post-marketing reports)

There were observations of decreased FVIII activity in some PTPs. An addendum to the clinical overview considered data from post-marketing, clinical experience and relevant literature to support a proposed labelling changes (both for professionals and patients) to be submitted globally via national procedures. Data presented is based on analysis with cut-off of date 13 October 2021.

As of 13 October 2021, more than 800 patients had been exposed to N8-GP during the post-marketing period, out of which 15 cases have been reported which could be possibly associated with decreased factor VIII activity. In the target population, decreased FVIII activity in PTPs after switching to N8-GP was of heterogenous nature.

The overall conclusion in the addendum was that the occurrence of decreased FVIII activity levels in PTPs requires monitoring of FVIII activity in combination with the patient's clinical treatment response in relation to switching to N8-GP treatment. It was stated that this is also considered a routine clinical practice while treating haemophilia patients.

The cases are summarised below:

- In 14 cases, patients were negative for inhibitors and in one case the information about inhibitor development was not reported.
- FVIII activity levels were measured in nine patients within first few hours of N8-GP administration, and they were lower than expected.
- In four cases patients had prior PEGylated drug exposure.
- In six cases the samples were centrally analysed for anti-PEG antibodies, and four patients showed an anti-PEG antibody titre of clinical relevance.
- In the majority of cases, patients (9 patients) were switched to another FVIII products and in 2 cases patients continued the treatment with N8-GP.
- In 1 case, the patient experienced possible mild hypersensitivity to N8-GP.

The vast majority of use of Esperoct at the time of submission has been in the EU where it is not indicated in children, therefore it is not possible from the available exposure information to examine whether anti-PEG antibodies would be a more frequent cause of loss of efficacy in children under 12 years of age than in the population as a whole. This was not apparent in the clinical trial in paediatric patients aged younger than 12 years however only 68 patients were included in that study.

The sponsor has now proposed to include in the Warnings and Precautions section of PI the same statement as was negotiated for the SmPC and as recommended by the TGA's RMP evaluator:

> '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.'

The additional entry in the ADR table in the PI is the same as has been agreed with the EMA (Table 11).

Table 11: Frequency of adverse drug reaction in clinical trials for previously treated patients

System organ class	Preferred term	Frequency (%)	Frequency
Investigations	Coagulation factor VIII level decreased	N/A	Unknown *****

***** Based on post-marketing reports

The available Swiss PI (last updated February 2020), US PI (dated 2019) and Canadian (updated April 2020) and Japanese PIs have no statement regarding the possible effect of anti-PEG antibodies observed in the post-market period.

The Canadian PI does include the following paragraph in the Paediatrics subsection:

> 'In some previously untreated patients, a decreased FVIII recovery has been observed in the absence of detectable Factor VIII inhibitors [see Clinical Trial Adverse Reactions/ Previously untreated patients (8.2)]. Close monitoring of previously untreated patients including monitoring of the patient's clinical status and post dose FVIII activity is recommended until the incremental recovery is normalized.'

Additionally both the US and Canadian PIs have a subheading for immunogenicity whereas the SmPC, Swiss or Japanese PIs do not. The EMA summary of product characteristics (SmPC) contains similar information to that below, which was extracted from the US PI.

> '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 in assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.'

The SmPC also included the following statement: '*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.'* That statement, as it appears in the SmPC, was added to the draft Australian PI during the evaluation period.

Risk management plan

Esperoct is proposed to be used for the treatment and prophylaxis of bleeding in previously treated patients with haemophilia A (congenital factor VIII deficiency). Esperoct is not indicated for the treatment of von Willebrand's disease.

The proposed 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 sponsor has submitted EU/Global risk management plan (RMP) version 1.0 (date of sign-off 7 June 2019; data lock point (DLP) 15 August 2017) and Australia specific annex (ASA) version 0.1 (dated 26 April 2022) in support of this application. At second round of evaluation, the sponsor provided updated EU/Global RMP version 2.1 (dated 14 August 2022; DLP 13 October 2021) and ASA version 0.2 (dated 12 October 2022).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 12. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 12: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Inhibitor development	✓*	✓†‡	✓	–
	Allergic/hypersensitivity reactions	✓*	✓†‡	✓	–
Important potential risks	Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs	✓*	✓†‡	✓	–
	Anti-PEG antibodies	✓	–	✓	–
	Thromboembolic events	✓	–	✓	–
Missing information	Use in pregnant and lactating women	✓	–	✓	–

*Follow-up questionnaires/questions

† Multinational non-interventional PASS

‡ EUHASS registry study

The summary of safety concerns in the ASA aligns with the EU/Global RMP. There are no Australia-specific safety concerns identified. The safety concerns are similar to those of similar products. The summary of safety concerns is acceptable from an RMP perspective.

Routine and additional pharmacovigilance activities have been proposed. Routine pharmacovigilance includes specific adverse reaction follow-up forms for the important identified risks: an Immunogenicity questionnaire for adverse events potentially related to inhibitor development and a Hypersensitivity questionnaire for allergic/hypersensitivity reactions. Furthermore, there will be follow-up questions to assess and characterise the occurrence of long-lasting headache potentially due to PEG accumulation after long-term treatment, an important potential risk. Additional pharmacovigilance activities include a multinational non-interventional post-authorisation safety study (PASS) and a European Haemophilia Safety Surveillance (EUHASS) registry study. The pharmacovigilance plan is acceptable.

Routine risk minimisation activities only have been proposed. This includes the PI and CMI as a package insert. The sponsor has addressed the recommendations regarding the PI and CMI in the response to TGA's questions. The risk minimisation plan is acceptable.

Proposed wording for conditions of registration

> 'The Esperoct EU-Risk Management Plan (RMP) (version 2.1, dated 14 August 2022, data lock point 13 October 2021), with Australian Specific Annex (version 0.2, dated 12 October 2022), included with submission PM-2022-01578-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.'

As Esperoct is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Esperoct (turoctocog alfa pegol) is to be included in the Black Triangle Scheme. The PI and CMI for Esperoct must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

Risk-benefit analysis

Delegate's considerations

Overall turoctocog alfa pegol achieves bleeding control rates consistent with that of other FVIII products with a reduced dosing frequency compared with many of these products. Use on demand and prior and during surgery are also satisfactory. The major issues of concern are the possibility of PEG accumulation and the dosing recommendations.

The EMA has not approved use in patients aged younger than 12 years due to major uncertainties regarding a potential tissue accumulation of PEG and an associated potential risk to brain development in that age group. That approach has not been taken by SwissMedic.

The FDA has granted marketing authority for both turoctocog alfa pegol and rurioctocog alfa pegol for previously treated patients without regard to age. Damoctocog alfa pegol is not indicated in patients aged younger than 12 years due to immune reactions to PEG and increased hypersensitivity reactions compared with adults and adolescents. Rurioctocog alfa pegol is approved for use in paediatric patients in Australia.

The SmPC for rurioctocog alfa pegol contains nonclinical safety statement regarding safety of that product in juvenile animals:

Rurioctocog alfa pegol: '*In the repeat dose toxicity study in Cynomologous monkey, two animals showed vacuolation in the kidney in the mid dose group (350 IU/kg). The vacuolations did not recover after 2 weeks. The human relevance of kidney vacuolation observed in the preclinical study is unknown. Nonclinical data are limited to 1 month exposure and no studies in juvenile animals were conducted with Adynovi. Thus it was not possible to conclude on the potential risks of PEG accumulation in various tissues/organs relevant for chronic use of Adynovi in the paediatric population. No studies on genotoxicity, carcinogenicity or reproductive toxicity have been performed with Adynovi.*'

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

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

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

In the clinical trial in PTP children (Study 3885) the starting dose was 60 IU/kg twice weekly with a dose range of 50 to 75 IU/kg. I note that in the draft PI the starting dose is 65 IU/kg twice a week.

A general rule regarding Factor VIII dosage is that one unit of Factor VIII per kg body weight increases the Factor VIII plasma level by 2% (as IU/dL). Generally accepted dose recommendations for Factor VIII substitution are based on an empirical level of substitution achieved by one or more infusions when there is a specific clinical condition (that is minor or major bleeding episodes, surgery). The prophylactic dosing schedules for adults and children were based on the potency of turoctocog alfa pegol against an established Factor VIII activity standard and the pharmacokinetic equivalence of turoctocog alfa pegol with an established recombinant Factor VIII product. The sponsor has stated that adjustment to compensate for higher Factor VIII clearance in children was evaluated in clinical Study 3885 and performed for paediatric prophylactic dosing.

Swissmedic evaluators noted that there are significant substance-dependent differences in N8-GP FVIII activity. The applicant was requested to provide specific instructions, as with Adynovi, for example, as to which validated tests for therapeutic monitoring should be used. The agreed statements have been included in the PI proposed to the TGA.

It is not clear why some regulators opted for a starting dose of 60 IU/kg once every two weeks for routine prophylaxis in children aged younger than 12 years and others for 65 IU/kg once every two weeks as the starting dose however given the median doses for that population were greater than 60 IU/kg/ dose it is reasonable to start with the 65 mg/kg once every two weeks. The Delegate considered that given this is somewhat arbitrary and would be adjusted according to response in any case, that the starting IU/kg dose should be the same for adults and patients aged younger than 12 years. This is also consistent with the expert advice received.

Given the comments regarding the listing of uses of Esperoct in patients with haemophilia A in the indication, the Delegate requested that the indication be amended to separately refer to routine prophylaxis, on-demand use and peri-operative use. The patient age group need not be included in the indication however the *Paediatric use* subsection in section 4.4 *Special Warnings and Precautions* should be amended to include the statement recommended by the expert advisor.

Proposed action

Pending finalisation of the Product Information, the Delegate proposed to approve Esperoct for the following indication:

> *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.*

Independent expert advice

1. ***The sponsor has not proposed separating the various uses of Esperoct within the indication. Does the expert advisor consider these uses should be specified in the indication?***

It is likely that the primary therapeutic role of Esperoct and similar long-acting rFVIII products will be for control and prevention of acute bleeding episodes, for perioperative management and for intermittent prophylaxis in patients with mild (FVIII > 5%) or moderate haemophilia A and no prior bleeding for specific circumstances such as high-impact physical activities, joint bleeding, or surgical procedures. Emicizumab is not effective for acute bleeding, and Esperoct is likely to be a valuable addition to the therapeutic armamentarium for these indications.

The expert advisor was of the opinion that it would materially improve the usefulness and readability of the PI to separate the indications for Esperoct into the suggested subheadings of on demand treatment and prevention of bleeding episodes, routine prophylaxis and peri-operative management, maintaining the same divisions for dosing recommendations.

2. ***The assessment of safety and efficacy in children aged < 12 years is quite limited. I note that the EU has not approved use in that age group due to a lack of long term safety data. Use in that age group has been approved in other jurisdictions. What is the expert advisor's opinion on whether the submission as a whole contains sufficient evidence of the safety and efficacy of Esperoct in children younger than 12 years of age.***

Study 3885 examined prophylactic treatment in patients aged younger than 12 years with severe haemophilia A with significant previous exposure to another FVIII product, and who did not have FVIII inhibitors. Exposure in the main trial phase was 26 weeks, with extension allowed for responding patients until commercial availability of Esperoct. Sixty-eight patients were enrolled, of whom 65 were already on prophylactic treatment, the vast majority with a rFVIII product. Despite this, there was a clinically significant reduction in median ABR from 1.95

bleeds/patient/year to 0.98 bleeds/patient /year, with nearly 20% of patients having no bleeding during the entire trial.

Median follow-up was 4.9 years at the time of publication in July 2020. The proportion of patients with no annual bleeds increased with time, with 56% experiencing no bleeds during the fourth year of exposure. No FVIII inhibitor development or other new safety concerns were detected. The expert advisor regarded these data as persuasive in concluding that clinical efficacy of Esperoct for prophylactic use in patients younger than 12 years of age has been established, although the study experience is relatively small and time limited. However, given the rarity of the indication and the difficulty in recruiting paediatric patients to trials such as these, it is fairly typical of publications in the field.

The expert advisor noted that the EMA has expressed concern regarding the long-term effects of the PEG component of Esperoct in paediatric populations, given the observation of vacuolation of phagocytic cells like macrophages, and some non-phagocytic cells such as kidney and choroid plexus in animal toxicological studies, raising the as yet unconfirmed possibility of risks to brain development which are likely to be particularly pertinent to paediatric populations.

The pathological findings did not appear to be associated with adversity or in vivo functional changes in the animals. As far as I am aware, there have been no reports of unexpected toxicity in patients receiving prophylactic therapy with Esperoct, although experience is, of course, quite limited.

Overall, the data from the Study 3885 does appear to give reasonable evidence of the efficacy of Esperoct in paediatric patients, albeit with fairly small patient numbers, with no emergence of novel or unexpected safety concerns. Follow-up is relatively short, and the expert advisor agreed with the EMA statement in the summary of product characteristics that '*In children below 12 years long-term safety has not been established*'.

Given the many now-established and emerging new therapies for haemophilia which have been approved, are under review or in clinical trials, there would appear to be a very limited potential role for Espercot in prophylactic therapy, particularly in children younger than 12 years of age. There are now many possible approaches including FVIII mimetics (particularly emicizumab), small interfering RNAs which block endogenous production of antithrombin (fitusiran), a monoclonal antibody anti-tissue factor pathway inhibitor (concizumab) that promotes thrombin generation through the extrinsic coagulation pathway, and the prospect of FVIII gene therapy which is in late-stage clinical trials. In addition, a recently published Phase III trial of efanesoctocog alfa has demonstrated a mean FVIII trough level of 15% and ABR of 0 among patients receiving once weekly treatment with this new extended half-life rFVIII.

Efanesoctocog alfa avoids the half-life ceiling effect of von Willebrand Factor stabilisation of FVIII by incorporating a portion of the vWF molecule which decouples the natural binding of FVIII to vWF. In addition, it is fused to a dimeric Fc domain as well as two hydrophilic polypeptides that extend its half-life to about 47 hours by steric shielding. The molecule does not contain PEG, and further studies are ongoing in paediatric populations to establish efficacy and longer term safety. It is likely that this will become a product of choice for treatment of severe haemophilia B with rFVIII when regulatory approval has been achieved, especially as it has the added advantage of being able to be measured by standard laboratory assays to allow for monitoring and dose adjustments when necessary.

On balance, the expert advisor considered that there is evidence of efficacy for prophylactic treatment of children younger than 12 years of age with Esperoct, but for the reasons outlined above, it would not be a treatment of choice, given the relatively limited patient exposures reported and some lingering concerns regarding long-term effects of exposure to PEG moieties,

as well as the increasing availability of better choices for prophylactic and other forms of therapy for haemophilia B.

For these reasons, it was the expert advisor's view that the possible use of Esperoct in children younger than 12 years should be allowed, but there should be a statement which cautions against use unless no other suitable options exist (see also comments under question 4 below). The expert suggested the following, which is in part modified from the EMA summary of product characteristics:

> *Paediatric Populations*
>
> *The dose in adolescents (12 years of age and above) is the same as for adults.*
>
> *In children below 12 years of age, although there is limited evidence of efficacy, long-term safety has yet to be established, and uncertainties remain regarding potential tissue accumulation of PEG and possible risks to brain development. Treatment with Esperoct should therefore be avoided in this age group unless it is considered by the treating clinician that no other suitable options are available, and informed consent to receive treatment has been obtained from the patient or their guardian.*

3. ***The proposed initial dose regimen for prophylaxis in children aged younger than 12 years is 65 IU/kg Q2W. In the clinical trial conducted with children (Study 3885), the starting dose was 60 IU/kg once every two weeks which was then adjusted according to response within a recommended range of 50 to 75 IU/kg. In that study the mean consumption per patient, including prophylaxis, treatment of bleeds, minor surgeries, and PK doses was 6870 IU/kg/year in the 0-5 year age-group with mean dose of 63.7 IU/kg (median 67.1 IU/kg). In the 6 to 12 year age-group mean consumption was 6670 IU/kg/year with mean dose 62.3 IU/kg (median 62.3 IU/kg).***

   Please provide an opinion on which starting dose for prophylactic treatment of children aged younger than 12 years is adequately supported by the data.

The expert advisor noted the variability of starting doses for children younger than 12 years of age that have been approved by a variety of international regulators, the reasons for which are not immediately clear. Considering the data from the pivotal Study 3885, the mean and median doses were midway between 60 and 65 IU/kg, which would support rounding either up or down, provided that the regimen is individually adjusted to less or more frequent dosing based on bleeding episodes. In view of the reported use of a starting dose of 60 IU/kg in Study 3885, it would seem logical to opt for this as the approved starting dose, which also has the virtue of being the slightly more conservative option. However, the expert advisor noted that any use of Esperoct in children younger than 12 years of age should be firmly discouraged, as discussed above in Question (2) and (4).

4. ***The EMA has not approved use in children aged younger than 12 years due to major uncertainties regarding a potential tissue accumulation of PEG associated with potential risks to brain development. A risk of PEG accumulation associated with a pegylated rFVIII product has been accepted for Esperoct in other regulatory jurisdictions. Additionally the TGA has approved another pegylated rFVIII product, Adynovate (rurioctocog alfa pegol), which is indicated for use in haemophilia A regardless of patient age.***

   The evidence of potential harm associated with the PEG component of Esperoct is unclear and the sponsor has been requested to provide further information on the CHMP's consideration of that issue. Does the expert advisor consider this is sufficient to preclude use of Esperoct in children aged younger than 12 years?

As previously noted, given the many now-established and emerging new therapies for haemophilia which are available for treatment of paediatric patients with severe haemophilia A, avoidance of PEGylated products is both possible and prudent. Nonetheless, no new safety concerns have emerged during the approximately 5-year follow up period for Study 3885, or for other PEGylated products, despite some 25 years having now elapsed since reports of cellular vacuolation containing PEG occurring in ependymal cells as a result of animal toxicological studies were published. As the Delegate noted, there is also some apparent inconsistency in regulatory approval or prohibition of use for other similar PEGylated rFVIII products in paediatric populations. On balance, the expert advisor considered that the risk profile does not absolutely exclude the use of Esperoct in paediatric patients, and there is some limited evidence of efficacy, but the perception is that there is no benefit in the use of this product over alternative agents which avoid the possibility of PEG accumulation.

For these reasons, the expert advisor considered it was reasonable to allow the possibility of use of Esperoct in paediatric populations, while warning strongly against this unless no other suitable alternative is available to the treating clinician, and only then with informed patient or guardian consent. This seems to the expert to reflect the clinical trial data submitted in the application, while allowing for individual clinical judgement on the part of the treating clinician. The expert have reflected this in the suggested wording for the PI outlined above.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Esperoct (turoctocog alfa pegol) 500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU, powder for injection, vial, indicated for:

> *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.*

Specific conditions of registration applying to these goods

- Esperoct (turoctocog alfa pegol) is to be included in the Black Triangle Scheme. The PI and CMI for Esperoct must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The Esperoct EU-RMP (version 2.1, dated 14 August 2022, DLP 13 October 2021), with ASA (version 0.2, dated 12 October 2022), included with Submission PM-2022-01578-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (revision 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Laboratory testing & compliance with Certified Product Details (CPD):

  - i All batches of Esperoct supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  - ii When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://cwww.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website [for the form] https://www.tga.gov.au/form/certified-product-details-cpd-biologicalprescription- medicines

  [for the CPD guidance] https://www.tga.gov.au/resources/resource/guidance/guidance-7-certified-product-details

- The final report for clinical trial NN7088-3908 in previously untreated patients should be submitted to the TGA within 6 months of completion.

Attachment 1. Product Information

The PI for Esperoct approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #