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

AUSTRALIAN PRODUCT INFORMATION – ALTUVIIIO® (EFANESOCTOCOG ALFA)

1 NAME OF THE MEDICINE

Efanesoctocog alfa

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains nominally 250, 500, 1000, 2000, 3000, or 4000 International Units (IU) of efanesoctocog alfa.

Each pre-filled syringe contains 3mL of solvent.

Efanesoctocog alfa is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterised. Efanesoctocog alfa is manufactured without addition of human- or animal-derived components and purified by a combination of multiple chromatography steps, a detergent viral inactivation step, a nano filtration step for viral clearance, and ultrafiltration steps.

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

3 PHARMACEUTICAL FORM

Powder for injection.

ALTUVIIIO is formulated as a sterile, non-pyrogenic, lyophilised, white to off-white cake to powder for intravenous (IV) administration in a single-use vial.

Solvent for injection is sterilised water for injections (sWFI) in a pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ALTUVIIIO is a long-acting recombinant anti-haemophilic factor (coagulation FVIII) indicated in adults, adolescents and children with haemophilia A (congenital FVIII deficiency) for:

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Treatment and control of bleeding episodes

- Perioperative management of bleeding (surgical prophylaxis)

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

4.2 DOSE AND METHOD OF ADMINISTRATION

For Intravenous Use Only After Reconstitution.

ALTUVIIIO is administered by intravenous infusion after reconstitution of the drug powder with the solvent.

The entire dose of ALTUVIIIO should be injected intravenously slowly over 1 to 10 minutes, based on the patient's comfort level.

Treatment with ALTUVIIIO should be initiated under the supervision of a qualified healthcare professional experienced in the treatment of haemophilia A. Healthcare professionals should monitor the patient for hypersensitivity reactions during the infusion and to establish the rate of infusion most appropriate for the patient. Doses may be given by the patient or the patient's caregiver only when they are properly trained in monitoring hypersensitivity reactions and the patient or caregiver are comfortable administering ALTUVIIIO outside of a healthcare setting.

- Each vial label of ALTUVIIIO states the FVIII potency in international units (IU). One IU corresponds to the activity of FVIII contained in one millilitre of normal human plasma.
- Potency assignment is determined using an activated partial thromboplastin time (aPTT)-based one-stage clotting assay with the Actin®-FSL reagent (see Section 5.2 Pharmacokinetic properties). It is recommended to use a validated one-stage clotting assay to determine plasma factor VIII activity of ALTUVIIIO. Throughout the clinical development an Actin-FSL-based one-stage clotting assay was used.
- According to the findings of a comparative analysis of clinical study samples, results obtained using a chromogenic assay should be divided by 2.5 to approximate the patient's factor VIII activity (see Section 4.4 Special Warnings and Precautions). In addition, a field study comparing different aPTT reagents indicated approximately 2.5-fold higher factor VIII activity levels when using Actin-FS instead of Actin-FSL in the one-stage clotting assay and approximately 30% lower results when using SynthASil.

For the dose of 50 IU/kg, the expected in vivo peak increase in FVIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

Estimated Increment of FVIII (IU/dL or % of normal) = 50 IU/kg x 2 (IU/dL per IU/kg)

Routine Prophylaxis

The recommended dosing for routine prophylaxis for adults, adolescents and children is 50 IU/kg of ALTUVIIIO administered once weekly.

Treatment and Control of Bleeding Episodes

ALTUVIIIO dosing for the treatment and control of bleeding episodes is provided in Table 1.

Table 1 - Dosing for Treatment and Control of Bleeding Episodes

Type of Bleeding	Recommended dose	Additional information
Minor and Moderate For example: Uncomplicated joint bleeds, minor muscular bleeds, mucosal or subcutaneous bleeds	Single dose of 50 IU/kg	For minor and moderate bleeding episodes occurring within 2 to 3 days after a prophylactic dose, a lower dose of 30 IU/kg dose may be used. Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered.
Major For example: Intracranial, retroperitoneal, iliopsoas and neck bleeds, muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the hemoglobin level	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered

When resuming prophylaxis after treatment of a bleed, it is recommended to allow an interval of at least 72 hours between the last 50 IU/kg dose for treatment of a bleed. Thereafter, prophylaxis can be continued as usual on the patient's regular dosing schedule.

Perioperative Management

ALTUVIIIO dosing for perioperative management is provided in Table 2.

Table 2 - Dosing for Perioperative Management

Type of Surgery	Pre-operative dose	Post-operative dose
Minor surgery	Single dose of 50 IU/kg	An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.
Major surgery For example: Intracranial, intra-abdominal, joint replacement surgery, or complicated dental procedures	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered as clinically needed for postoperative management.

4.3 CONTRAINDICATIONS

ALTUVIIIO is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to the product or its components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity Reactions

Allergic type hypersensitivity reactions, including anaphylaxis, have occurred with ALTUVIIIO. Advise patients to discontinue use of ALTUVIIIO if hypersensitivity symptoms occur and to contact a physician and/or seek immediate emergency care.

Neutralising Antibodies (Inhibitors)

Formation of neutralising antibodies (inhibitors) to Factor VIII has been reported following administration of ALTUVIIIO. Monitor all patients for the development of FVIII inhibitors, by appropriate clinical observations and laboratory tests. If the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after ALTUVIIIO administration, the presence of an inhibitor (neutralising antibodies) should be suspected and appropriate testing performed (see Monitoring Laboratory Tests).

Monitoring Laboratory Tests

Routine monitoring of FVIII activity levels for prophylactic dose adjustment is not necessary based on experience from clinical studies. If assessment of plasma FVIII activity is needed, it is recommended to use a validated aPTT-based one-stage clotting assay (see Section 4.2 Dose and Method of Administration). The same assay, reagent, qualified laboratory, and equipment are recommended when it is considered necessary to monitor a patient's FVIII activity over time.

Monitor for the development of FVIII inhibitors. If bleeding is not controlled with ALTUVIIIO and the expected FVIII activity plasma levels are not attained, perform an assay to determine if FVIII inhibitors are present (use Bethesda Units to titre inhibitors).

Use in hepatic impairment

Specific studies of ALTUVIIIO in patients with hepatic impairment have not been performed (see Section 5.2 Pharmacokinetic properties).

Use in renal impairment

Specific studies of ALTUVIIIO in patients with renal impairment have not been performed (see Section 5.2 Pharmacokinetic properties).

Use in the elderly

Clinical studies of ALTUVIIIO did not include a sufficient number of subjects 65 years of age and older to determine whether or not such subjects respond differently from younger subjects.

Paediatric use

Safety, efficacy, and pharmacokinetics of ALTUVIIIO have been evaluated in 99 previously treated patients (PTPs) < 18 years of age, who received at least one dose of ALTUVIIIO as

part of routine prophylaxis, treatment of bleeding episodes, or perioperative management. Adolescents (12 to < 18 years of age) were enrolled in the Phase 3 study (XTEND-1), and children < 12 years of age were enrolled in the Phase 3 paediatric study (XTEND-Kids). Thirty-eight subjects (38.4%) were <6 years of age, 36 (36.4%) subjects were 6 to <12 years of age, and 25 subjects (25.2%) were adolescents. Data from the paediatric study (74 subjects) showed no dosing adjustment was required for children < 12 years of age compared to adolescents and adults (see Section 5.2 Pharmacokinetic Properties).

Effects on laboratory tests

No clinically meaningful changes were observed in any of the haematology or chemistry parameters.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no known drug interactions reported with ALTUVIIIO. No drug interactions studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Efanesoctocog alfa has not been evaluated in animal fertility studies. It is not known whether ALTUVIIIO can affect fertility or sperm development in haemophilia A patients.

Use in pregnancy (Category B2)

Animal embryofetal development studies have not been conducted with efanesoctocog alfa. It is not known whether ALTUVIIIO can cause fetal harm when given to a pregnant woman. Based on the rare occurrence of haemophilia A in women, experience regarding the use of ALTUVIIIO treatment during pregnancy is not available. Healthcare professionals should balance the potential risks and only prescribe ALTUVIIIO to a pregnant woman if clearly needed.

Use in lactation

The safety of ALTUVIIIO for use in lactating women has not been established. It is not known whether efanesoctocog alfa or its metabolites are excreted into human milk. Healthcare professionals should balance the potential risks and only prescribe ALTUVIIIO to a breastfeeding woman if clearly needed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

The safety of ALTUVIIIO has been evaluated in 159 subjects from a completed Phase 3 study (XTEND-1) in previously treated patients (PTPs) with severe haemophilia A (< 1% endogenous FVIII activity or a genetic mutation consistent with severe haemophilia A) who received at least one dose of ALTUVIIIO for either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management. Of the 159 evaluated subjects, 134 (84.3%) were adults (18 years of age and older) and 25 (15.7%) were adolescents (12 to < 18 years of age). There were 154 (96.9%) subjects treated for at least 26 weeks and 98 (61.6%) subjects treated for at least 52 weeks. A total of 152 (95.6%) subjects achieved at least 25 exposure days and 115 (72.3%) subjects achieved at least 50 exposure days with a median of 53.0 (range 2-63) for both exposure days and injections per subject. Adverse events (AEs) were monitored for a total of 151.5 subject-years.

In the pediatric study (XTEND-Kids), the safety of ALTUVIIIO was evaluated in 74 male PTPs <12 years of age with severe haemophilia A who received at least one dose of ALTUVIIIO. Sixty-six (89.2%) subjects achieved at least 50 exposure days with a median of 53.0 (range 3-72).

Adverse events were monitored for a total of 479.4 subject-years in one on-going Phase 3 long-term safety extension study (XTEND-ed [LTS16294]; subjects rolled over from the 2 completed pivotal studies and continued treatment with ALTUVIIIO 50 IU/kg once weekly) and 2 completed clinical studies in PTPs. Adverse drug reactions (ADRs) (summarised in Table 3) were reported in 105 (37.9%) of the 277 subjects treated with routine prophylaxis or on-demand therapy. The most common ADRs (>10%) in adults and adolescents were arthralgia and headache (23.9% each) and in children below 12 years pyrexia (13.5%) and vomiting (10.8%).

Table 3 - Adverse Drug Reactions reported for ALTUVIIIO

System Organ Class	Preferred Term	N=277*	
		Number of Subjects (%)	Frequency Category**
Nervous system disorders	Headache	45 (16.2)	Very common
Musculoskeletal and connective tissue disorders	Arthralgia	46 (16.6)	Very common
	Pain in extremity	16 (5.8)	Common
	Back pain	12 (4.3)	Common
Gastrointestinal disorders	Vomiting	10 (3.6)	Common
Skin and subcutaneous tissue disorders	Eczema	6 (2.2)	Common
	Rash[2]	5 (1.8)	Common
	Urticaria[3]	3 (1.1)	Common
General disorders and administration site conditions	Pyrexia	17 (6.1)	Common
	Injection site reaction[4]	2 (0.7)	Uncommon

System Organ Class	Preferred Term	N=277*	
		Number of Subjects (%)	Frequency Category**

* 277 subjects across the Phase 3 clinical studies

** The following CIOMS frequency rating is used, when applicable: Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%; Rare ≥ 0.01 and < 0.1%; Very rare ≥ 0.01%; Not known (cannot be estimated from available data).

1 Headache, including migraine

2 Rash, including rash maculo papular.

3 Urticaria, including urticaria papular.

4 Injection site reaction, including injection site haematoma and injection site dermatitis.

Thromboembolic events occurred in 1% (3/261) of patients in the long-term safety extension study; these three subjects had pre-existing risk factors for thromboembolic events.

Immunogenicity

All subjects were monitored for neutralising antibodies (inhibitors) to FVIII during the ALTUVIIIO Phase 3 clinical studies. No subjects developed neutralising antibodies to FVIII, consistent with results expected for PTPs switching to a new treatment.

The detection of antibodies that are reactive to FVIII is highly dependent on many factors, including the patient population studied (PTPs vs previously untreated patients [PUPs]), sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, it may be misleading to compare the incidence of antibodies to ALTUVIIIO with the incidence of antibodies to other FVIII products. Since PUPs have not been enrolled in clinical studies, it is not yet possible to estimate inhibitor development to ALTUVIIIO.

During the ALTUVIIIO phase 3 studies (median treatment duration 96.3 weeks), 4/276 (1.4%) of evaluable patients developed transient treatment-emergent anti-drug antibodies (ADAs).

Post Marketing Experience

In post-marketing experience, the following adverse reactions have been reported:

Factor VIII inhibitor development

Allergic type hypersensitivity reactions, including anaphylaxis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia).

4.9 OVERDOSE

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII

Mechanism of action

Efanesoctocog alfa is a recombinant fusion protein incorporating FVIII that temporarily replaces the missing coagulation FVIII in haemophilia A patients that is needed for effective haemostasis. The drug molecule contains additional components that act to extend its plasma half-life and has demonstrated a 3- to 4-fold prolonged half-life relative to other standard and extended half-life FVIII molecules.

Efanesoctocog alfa has been designed to be independent of endogenous von Willebrand factor (VWF) and overcomes the FVIII half-life limit imposed by VWF clearance. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a rFVIII-Fc fusion protein provides protection and stability to FVIII and prevents FVIII interaction with endogenous VWF.

Efanesoctocog alfa incorporates the Fc region of human immunoglobulin G1 (IgG1), which binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation and thus prolonging the plasma half-life of the fusion protein.

Efanesoctocog alfa contains 2 XTEN polypeptides, which further increases its half-life. In efanesoctocog alfa, the natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN polypeptide, inserted in between FVIII N745 and E1649 amino acid residues; and the second XTEN polypeptide is inserted in between the D'D3 domain and Fc.

Clinical Trials

The safety, efficacy, and pharmacokinetics of ALTUVIIIO were evaluated in two multicenter, prospective, open-label clinical studies (one study in adults and adolescents (XTEND-1) and one paediatric study in children < 12 years of age (XTEND-Kids)) in PTPs with severe haemophilia A (< 1% endogenous FVIII activity or a documented genetic mutation consistent with severe haemophilia A). The safety and efficacy of ALTUVIIIO have not been evaluated in previously untreated patients.

All studies evaluated the efficacy of routine prophylaxis with a weekly dose of 50 IU/kg and determined hemostatic efficacy in the treatment of bleeding episodes and during perioperative management in subjects undergoing major or minor surgical procedures. Furthermore, the efficacy of ALTUVIIIO prophylaxis compared with previous prophylactic FVIII was also evaluated in subjects who had participated in a prospective observational study (OBS16221) prior to enrolment in XTEND-1 study.

The adult and adolescent study enrolled a total of 159 PTPs (158 male and 1 female subjects) with severe haemophilia A. Subjects were aged 12 to 72 years and included 25 adolescent subjects aged 12 to 17 years. All 159 enrolled subjects received at least one dose of

ALTUVIIIO and were evaluable for efficacy. A total of 149 subjects (93.7%) completed the study.

The paediatric study enrolled 74 male PTPs < 12 years of age with severe haemophilia A (38 subjects were 1 to 5 years of age and 36 were 6 to 11 years of age). Of the 74 enrolled subjects, all received at least 1 dose of ALTUVIIIO.

Routine prophylaxis to prevent and reduce bleeding episodes

Adult and adolescent study (XTEND-1)

The efficacy of weekly 50 IU/kg ALTUVIIIO as routine prophylaxis was evaluated as estimated by the mean annualised bleeding rate (ABR) and by comparing the ABR during on-study prophylaxis vs. the ABR during pre-study factor VIII replacement. A total of 133 adults and adolescents, who were on pre-study FVIII prophylaxis, were assigned to receive ALTUVIIIO for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks (Arm A). Of the 133 subjects, 128 subjects had at least 26 weeks of exposure to ALTUVIIIO and are included in the efficacy evaluation set. An additional 26 subjects, who were on pre-study episodic (on-demand) treatment with FVIII, received episodic (on-demand) treatment with ALTUVIIIO at doses of 50 IU/kg IV for 26 weeks, followed by routine prophylaxis at a dose of 50 IU/kg IV once weekly for 26 weeks (Arm B). Overall, 115 subjects received at least a total number of 50 exposure days (EDs) in Arm A and 17 subjects completed at least 25 EDs of routine prophylaxis in Arm B. A total of 149 subjects (93.7%) completed the study.

The ABR in subjects evaluable for efficacy are summarised in Table 4. Routine prophylaxis resulted in a mean ABR (95% CI) of 0.71 (0.52, 0.97), a median (IQR) ABR of 0.00 (0.00, 1.04), and a median (IQR) annualised joint bleeding rate of 0.00 (0.00, 1.02). Eighty-six of 133 (64.7%) subjects experienced no bleeding episodes, and 96 of 133 (72.2%) subjects experienced no joint bleeding episodes while on routine prophylaxis for a median of 52 weeks in Arm A.

Table 4 - Summary of Annualised Bleeding Rate (ABR) with ALTUVIIIO prophylaxis, ALTUVIIIO on-demand treatment, and after switch to ALTUVIIIO prophylaxis in subjects ≥ 12 Years of Age

Endpoint[1]	Arm A Prophylaxis[2]	Arm B On demand[3]	Arm B Prophylaxis[3]
	N=128	N=26	N=26
Bleeds			
Mean ABR (95% CI)[4]	0.71 (0.51, 0.97)	21.41 (18.81, 24.36)	0.70 (0.33, 1.48)
Median ABR (IQR)	0.00 (0.00, 1.04)	21.13 (15.12, 27.13)	0.00 (0.00, 0.00)
subjects with zero bleeds, n (%)	82 (64.1)	0	20 (76.9)
Spontaneous bleeds			
Mean ABR (95% CI)[4]	0.27 (0.18, 0.40)	15.83 (12.27, 20.43)	0.44 (0.16, 1.20)
Median ABR (IQR)	0 (0, 0)	16.69 (8.64, 23.76)	0.00 (0.00, 0.00)
subjects with zero bleeds, n (%)	103 (80.5)	1 (3.8)	22 (84.6)
Joint bleeds			

Endpoint[1]	Arm A Prophylaxis[2]	Arm B On demand[3]	Arm B Prophylaxis[3]
	N=128	N=26	N=26
Mean ABR (95% CI)[4]	0.50 (0.35, 0.71)	17.48 (14.88, 20.54)	0.62 (0.25, 1.52)
Median ABR (IQR)	0 (0, 1.02)	18.42 (10.80, 23.90)	0.00 (0.00, 0.00)
subjects with zero bleeds, n (%)	92 (71.9)	0	21 (80.8)

ABR = annualised bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile.
[1] All analyses of bleeding endpoints are based on treated bleeds
[2] Subjects assigned to receive ALTUVIIIO prophylaxis for 52 weeks
[3] Subjects assigned to receive ALTUVIIIO for 26 weeks
[4] Based on negative binomial model

An intra-subject comparison of ABRs during on-study and pre-study prophylaxis demonstrated a statistically significant reduction of 77% in ABR based on treated bleeds (95% CI: 58%, 87%) during routine prophylaxis with ALTUVIIIO compared to pre-study FVIII prophylaxis (see Table 5).

Table 5 - Intra-Subject Comparison of Annualised Bleeding Rate (ABR) with ALTUVIIIO Prophylaxis versus Pre-study FVIII Prophylaxis in Subjects ≥ 12 Years of Age

Endpoint	On-study prophylaxis with ALTUVIIIO 50 IU/kg QW (N = 78)		Pre-study standard of care FVIII Prophylaxis[2] (N = 78)
Median Observation Period (weeks)(IQR)	50.09 (49.07, 51.18)		50.15 (43.86, 52.10)
Bleeds			
Mean ABR (95% CI)[1]	0.69 (0.43,1.11)		2.96 (2.00, 4.37)
% reduction (95% CI)		77 (58, 87)	
p-value		<0.0001	
% subjects with zero bleeds	64.1		42.3
Median ABR (IQR)	0.00 (0.00, 1.04)		1.06 (0.00, 3.74)

ABR = annualised bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile.
[1] Based on negative binomial model
[2] Prospective observational study (OBS16221)

An intra-subject comparison (N = 26) of ABR during the first 26 weeks of on-demand ALTUVIIIO treatment versus ABR in the following 26 weeks on weekly ALTUVIIIO prophylaxis (Arm B) showed a clinically important bleeding reduction of 97% for the weekly prophylactic regimen and an increase of subjects with zero bleeds from 0 to 76.9%.

Paediatric Study (XTEND-Kids)

The efficacy of weekly 50 IU/kg ALTUVIIIO as routine prophylaxis in children <12 years was evaluated as estimated by the mean ABR. A total of 74 children (38 children <6 years of age and 36 children 6 to <12 years of age) were enrolled to receive ALTUVIIIO for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks. Routine prophylaxis resulted in a mean ABR (95% CI) of 0.6 (0.4, 0.9) and a median (Q1, Q3) ABR of 0 (0, 1.0) for treated bleeds. For all bleeds (treated and non-treated), the mean ABR (95% CI) was 2.6 (1.6,

4.0) and the median (Q1, Q3) ABR was 0 (0, 2.0) in patients treated according to the protocol (N=73).

Table 6 - Summary of Annualised Bleeding Rate (ABR) with ALTUVIIIO Prophylaxis in Patients <12 Years of Age

Endpoint*	<6 years	6 to < 12 years	Overall
	N = 38	N = 35†	N = 73†
Treated bleeds			
Mean ABR (95% CI)‡	0.5 (0.3, 0.8)	0.8 (0.4, 1.4)	0.6 (0.4, 0.9)
Median ABR (Q1, Q3)	0 (0, 1.0)	0 (0, 1.1)	0 (0, 1.0)
% subjects with zero bleeds, n (%)	24 (63.2)	23 (65.7)	47 (64.4)
Treated spontaneous bleeds			
Mean ABR (95% CI) ‡	0.2 (0.1, 0.4)	0.2 (0, 0.6)	0.2 (0, 0.3)
Median ABR (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
% subjects with zero bleeds, n (%)	32 (84.2)	32 (91.4)	64 (87.7)
Treated joint bleeds			
Mean ABR (95% CI) ‡	0.2 (0.1, 0.6)	0.4 (0.2, 0.9)	0.3 (0.2, 0.6)
Median ABR (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
% subjects with zero bleeds, n (%)	34 (89.5)	27 (77.1)	61 (83.6)
All bleeds (treated and untreated)*			
Mean ABR (95% CI) ‡	2.8 (1.4, 5.6)	2.3 (1.3, 4.1)	2.6 (1.6, 4.0)
Median ABR (Q1, Q3)	0 (0, 2.0)	1.0 (0, 2.9)	0 (0, 2.0)
% subjects with zero bleeds, n (%)	21 (55.3)	16 (45.7)	37 (50.7)

ABR = annualised bleed rate; CI = confidence interval; Q1= 25th percentile, Q3=75th percentile.

* Reflects all bleeds reported by patients including those where no ALTUVIIIO was administered.
† A subject in the 6 to <12 years old age group who received an intense consolidation treatment (2 to 3 injections per week for 15 weeks) after treatment of 2 traumatic hip joint bleeds was excluded from the efficacy analysis as the subject did not receive the weekly prophylaxis treatment as specified in the protocol for an extended period.
‡ Based on negative binomial model.

Routine prophylaxis: physical functioning and pain

The adult and adolescent study (XTEND-1) evaluated the effect of routine prophylaxis in subjects who were on stable pre-study FVIII prophylaxis (Arm A) on physical functioning, pain and joint health as protocol defined endpoints of interest. Patient-reported haemophilia-related quality of life outcomes were assessed with the Haemophilia-Specific Quality of Life (Haem-A-QoL) questionnaire for adults (≥ 17 years of age). The Physical Health Score of Haem-A-QoL (i.e., painful swellings, presence of joint pain, pain with movement, difficulty walking far and needing more time to get ready) was used to evaluate physical functioning. For the evaluation of pain the PROMIS Pain Intensity 3a instrument was used, specifically

the first question that rates the worst pain experienced during the last 7 days, on a 5-point Likert scale.

Weekly routine prophylaxis resulted in a statistically significant and clinically meaningful improvement in the pre-specified endpoints of Haem-A-QoL Physical Health Score and PROMIS Pain Intensity 3a first question at the Week 52 assessment. Lower scores represent better quality of life and pain intensity; therefore, a negative change from baseline represents improvement during the course of the study. The overall change from baseline suggests that subjects on pre-study FVIII prophylaxis reported an improvement in their physical functioning and pain after being treated with weekly prophylaxis with ALTUVIIIO.

Table 7 provides a summary of the changes from baseline to week 52 in Haem-A-QoL Physical Health Scale score and PROMIS Pain Intensity 3a.

Table 7 - Mean Change in Haem-A-QoL Physical Health Score (≥ 17 Years of Age) and PROMIS Pain Intensity 3a T-score from Baseline to Week 52.

Change from baseline at Week 52	ALTUVIIIO Prophylaxis 50 IU/kg QW	Baseline with pre-study standard of care FVIII Prophylaxis
Haem-A-QoL Physical Health Scores (range 0-100)[1]		
Number of subjects[2]	104	104
Mean (SD)	29.66 (23.40)	37.02 (23.83)
Mean change (95% CI)[3]	-6.74 (-10.13, -3.36)	
p-value	0.0001	
PROMIS Pain Intensity 3a (range 1-5)[4]		
Number of subjects[2]	127	125
Mean (SD)	2.21 (1.21)	2.47 (1.15)
Mean change (95% CI) [3]	-0.21 (-0.41, -0.02)	
p-value	0.0276	

1 Lower scores are reflective of better functioning.
2 Number of subjects ≥ 17 years of age who completed the Haem-A-QoL questionnaire.
3 LS mean based on mixed-effect model with repeated measures (MMRM) with visit as fixed effect, and baseline score as a covariate.
4 worst pain experienced during the last 7 days (1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = severe pain, 5 = very severe pain)

Routine prophylaxis: joint health

In the adult and adolescent study the mean estimated Annualised joint bleeding rate (AJBR) was 0.51 (95% CI: 0.36 to 0.72) during weekly prophylaxis with ALTUVIIIO (Arm A). During on-demand treatment in Arm B the mean estimated AJBR was 17.48 (95% CI: 14.88 to 20.54), decreasing to 0.62 (95% CI: 0.25 to 1.52) after switching to prophylaxis with ALTUVIIIO.

The adult and adolescent study also evaluated the effect of weekly prophylaxis on joint health using the Haemophilia Joint Health Score (HJHS). The HJHS is a functional measure of joint health evaluating ankle, knee and elbow (to access flexion, extension, range of movement, muscle strength, swelling, duration of swelling, crepitus, gait, pain, and muscle atrophy). The

assessment is performed by a healthcare professional trained in the use of anthropometric measures. The total score is the sum of scores from all six joints plus the gait score (range from 0 to 124, with 0 being normal and 124 being the most severe disease). A statistically significant mean change of -1.54 (-2.70, -0.37) from baseline was observed in HJHS total score in subjects on prophylaxis with ALTUVIIIO (Arm A).

Efficacy in control of bleeding

In the adult and adolescent study (XTEND-1), a total of 362 bleeding episodes were treated with ALTUVIIIO, most occurring during on-demand treatment in Arm B. Majority of bleeding episodes were localised in joints. Response to the first injection was assessed by subjects at least 8 hours after treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Efficacy in control of bleeding episodes in subjects ≥ 12 years of age is summarised in Table 8. Control of bleeding episodes was similar across the treatment arms.

Table 8 - Summary of Efficacy in Control of Bleeding in Subjects ≥ 12 Years of Age

Number of bleeding episodes		**(n=362)**
Number of injections to treat bleeding episode (%)	1 Injection	350 (96.7)
	2 Injections	11 (3.0)
	> 2 Injections	1 (0.3)
Median total dose to treat a bleeding episode (IU/kg) (IQR)		50.93 (50.00; 51.85)
Number of evaluable injections		**(n=332)**
Response to treatment of a bleeding episode (%)	Excellent or good	315 (94.9)
	Moderate	14 (4.2)
	No response	3 (0.9)

The efficacy of ALTUVIIIO in control of bleeding in children < 12 years of age was assessed in the paediatric study, excluding one subject who did not receive the weekly prophylaxis treatment as specified in the protocol for an extended period. A total of 43 bleeding episodes were treated with ALTUVIIIO. Bleeding was resolved with a single 50 IU/kg injection of ALTUVIIIO in 95.3% of bleeding episodes. The median (Q1; Q3) total dose to treat a bleeding episode was 52.6 IU/kg (50.0; 55.8).

Perioperative management of bleeding

Major surgeries

Perioperative haemostasis was assessed in 14 major surgeries in 13 subjects (11 adults and 2 paediatrics) across the two Phase 3 studies. Of the 14 major surgeries, 13 surgeries required a single pre-operative dose to maintain haemostasis during surgery; for 1 major surgery occurring during routine prophylaxis, no pre-operative loading dose was administered on the day of/or on the day before surgery. The clinical evaluation of haemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or poor/none. The haemostatic effect of ALTUVIIIO was rated as “excellent” in 14 of 14 surgeries (100%).

Minor surgeries

Perioperative haemostasis was assessed in 32 minor surgeries in 28 subjects (15 adults and 13 adolescents and children) across the Phase 3 studies. The haemostatic response was evaluated by the investigator/surgeon in 25 of these minor surgeries; an excellent response was reported in all (100%).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of ALTUVIIIO were evaluated in 159 adults and adolescents and 74 children <12 years old, respectively, receiving weekly IV injections of 50 IU/kg. Among children <12 years old, 36 subjects had ALTUVIIIO single-dose PK profiles available.

PK parameters following a single dose of ALTUVIIIO are presented in Table 9. The PK parameters were based on plasma FVIII activity measured by the aPTT-based one-stage clotting assay using the Actin® FSL reagent. After a single dose of 50 IU/kg, ALTUVIIIO exhibited high sustained FVIII activity with prolonged half-life across age cohorts. There was a trend of increasing AUC, and decreasing clearance, with increasing age in the paediatric cohorts. The PK profile at steady state (Week 26) was comparable with the PK profile obtained after the first dose.

Table 9 - Pharmacokinetic parameters following a single dose of ALTUVIIIO by age (one-stage clotting assay with the Actin® FSL reagent)

PK parameters (mean SD)	Pediatric Study		Adult and Adolescent Study	
	1 to < 6 Years N=18	6 to < 12 Years N=18	12 to < 18 years N=25	Adults N=134
AUC (IU*h/dL)	6800 (1120)[b]	7190 (1450)	8350 (1550)	9850 (2010)[a]
$t_{1/2}$ (h)	38.0 (3.72)	42.4 (3.70)	44.6 (4.99)	48.2 (9.31)
CL (mL/h/kg)	0.742 (0.121)	0.681 (0.139)	0.582 (0.115)	0.493 (0.121)[a]
V_{ss} (mL/kg)	36.6 (5.59)	38.1 (6.80)	34.9 (7.38)	31.0 (7.32)[a]
MRT (hr)	49.6 (5.45)	56.3 (5.10)	60.0 (5.54)	63.9 (10.2)[a]

$AUC_{0\text{-}tau}$ = area under the activity-time curve over the dosing interval, CL = clearance, MRT = mean residence time, SD = standard deviation, $t_{1/2z}$ = terminal half-life, V_{ss} = volume of distribution at steady state
a Calculation based on 128 profiles.
b N=17

In XTEND-1, ALTUVIIIO at steady state maintained normal to near normal (>40 IU/dL) FVIII activity for a mean (SD) of 4.1 (0.7) days with once-weekly prophylaxis in adults. The FVIII activity over 10 IU/dL was maintained in 83.5% of adults and adolescent subjects throughout the study. In children <12 years ALTUVIIIO maintained normal to near normal (>40 IU/dL) FVIII activity for 2 to 3 days and >10IU/dL FVIII activity for approximately 7 days (see Table 10).

Table 10 - Pharmacokinetic parameters at steady state of ALTUVIIIO by age (one-stage clotting assay with the Actin® FSL reagent)

PK parameters Mean (SD)	Pediatric study[a]		Adult and Adolescent study[a]	
	1 to <6 years	6 to <12 years	12 to <18 years	Adults
	N=37	N=36	N=24	N=125
Peak (IU/dL)	136 (48.9) (N=35)	131 (36.1) (N=35)	124 (31.2)	150 (35.0) (N=124)
IR (kg*IU/dL/IU)	2.22 (0.83) (N=35)	2.10 (0.73) (N=35)	2.25 (0.61) (N=22)	2.64 (0.61) (N=120)
Time to 40 IU/dL (h)	68.0 (10.5)[b]	80.6 (12.3)[b]	81.5 (12.1)[c]	98.1 (20.1)[c]
Time to 20 IU/dL (h)	109 (14.0) [b]	109 (14.0) [b]	109 (14.0) [b]	109 (14.0) [b]
Time to 10 IU/dL (h)	150 (18.2) [b]	173 (17.1) [b]	179 (20.2) [c]	201 (35.7) [c]
Trough (IU/dL)	10.9 (19.7) (N=36)	16.5 (23.7)	9.23 (4.77) (N=22)	18.0 (16.6) (N=123)

Peak = 15 min post dose at steady state, IR = incremental recovery, Trough = predose FVIII activity value at steady state, SD = standard deviation
a Steady state peak, trough and IR were computed using available measurements at week 52/End of study PK sampling visit
b Time to FVIII activity was predicted using population PK model for paediatric study
c Time to FVIII activity was predicted using population PK model for adult study

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with efanesoctocog alfa. As a large protein molecule, efanesoctocog alfa is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies have been conducted with efanesoctocog alfa.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder

Sucrose

Calcium chloride dihydrate

Histidine

Arginine hydrochloride

Polysorbate 80

Solvent

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage conditions

Unopened vials should be stored under controlled refrigeration (2°C - 8°C). The product may be stored at room temperature (up to 30°C) for a single 6-month period. The date that the product is removed from refrigeration should be noted on the carton.

Do not use beyond the expiration date printed on the carton and the vial or six months after removing the carton from refrigeration, whichever is earlier.

Do not freeze. Protect from light.

In use shelf-life

The reconstituted product can be stored at room temperature (up to 30°C) for 3 hours. Protect product from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded.

ALTUVIIIO is for use in one patient on one occasion only.

The appearance of the reconstituted product should be clear and colourless to slightly opalescent.

Do not administer reconstituted ALTUVIIIO if it contains particles, is discoloured or is cloudy.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack contains a powder vial (type 1 glass) with a chlorobutyl rubber stopper and an aluminum seal with a coloured polypropylene flip-off cap, 3 mL solvent in a pre-filled syringe (type 1 glass) with a bromobutyl rubber plunger stopper and tamper proof tip cap, and a sterile vial adapter reconstitution device.

Pack size

- 1 vial with powder
- 1 pre-filled syringe with solvent
- 1 vial adapter

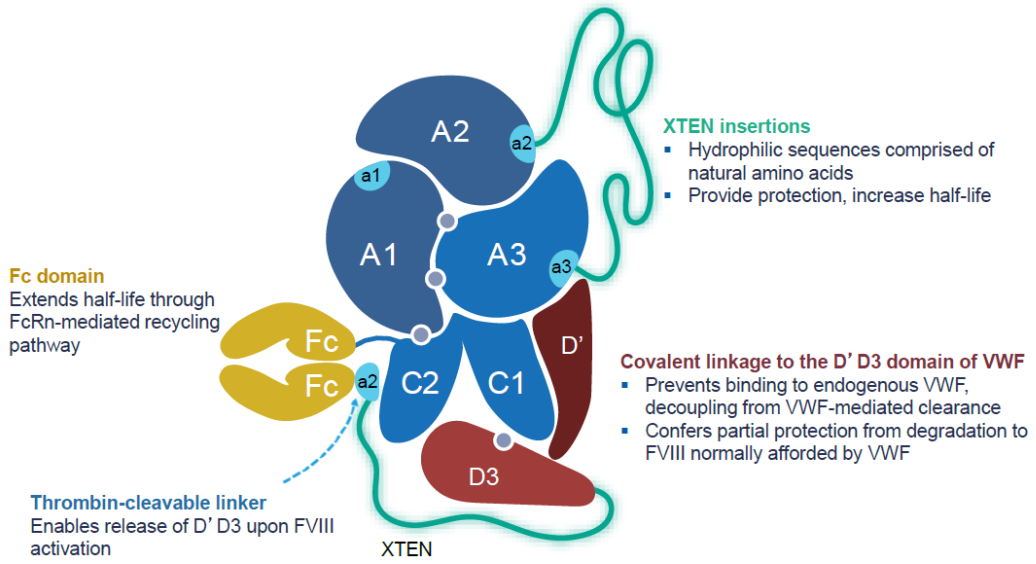
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

ALTUVIIIO (efanesoctocog alfa) is a fully recombinant fusion protein comprising a single chain B-domain deleted (BDD) analogue of human Factor VIII (FVIII) covalently fused to the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D'D3 domain of human von Willebrand factor (VWF), and 2 XTEN polypeptides. Efanesoctocog alfa contains 2829 amino acids with an apparent molecular weight of 312 kDa. Efanesoctocog alfa is synthesised as 2 polypeptide chains which are covalently linked by 2 Fc hinge disulfide bonds. The first FVIII-XTEN-Fc polypeptide chain comprises the A1A2 domain of FVIII along with 5 amino acids from B-domain (1-745 amino acids) fused to the 288-XTEN polypeptide in place of natural FVIII B-domain, the A3C1C2 domain of FVIII (1649-2332) and the Fc domain of human IgG1. The second VWF-XTEN-a2-Fc polypeptide chain comprises the D'D3 domain of VWF (1-477 amino acids) fused to the 144-XTEN polypeptide, a thrombin cleavable acidic region 2 sequence from FVIII and the Fc domain of human IgG1. The Fc domain includes the hinge, CH2, and CH3 domains of IgG1. The Fc, VWF, and XTEN polypeptide portions of the molecule extend the half-life of efanesoctocog alfa in plasma.



Abbreviations: Fc: fragment crystallizable region of IgG1; FcRn: neonatal Fc receptor; FVIII: factor VIII; VWF: von Willebrand factor; a1, a2 and a3: FVIII acidic region1, 2 and 3; XTEN polypeptide: unstructured polypeptides, composed of repeating motifs of 6 natural amino acids (G, A, P, E, S, T)
Note: Green lines: XTEN polypeptides

CAS number

2252477-42-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
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Sydney NSW 2000
Toll Free Number (medical information): 1800 818 806
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9 DATE OF FIRST APPROVAL

24 June 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New document