AUSTRALIAN PRODUCT INFORMATION – ELOCTATE (EFMOROCTOCOG ALFA) (RHU) POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Efmoroctocog alfa

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each pre-filled syringe contains 3 mL of solvent.

Efmoroctocog alfa is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterised. The HEK cell line expresses efmoroctocog alfa into a defined cell culture medium that does not contain any proteins derived from animal or human sources. The purification process utilises a series of chromatography and multiple viral clearance steps. The viral clearance steps include affinity chromatography, 15nm virus-retaining nano-filtration step, and detergent viral inactivation. No human or animal derived additives are used in the purification and formulation processes.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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

The liquid diluent (sterile water for injections) is in a pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ELOCTATE is a long-acting antihaemophilic factor (recombinant) indicated in adults and children with haemophilia A (congenital factor VIII deficiency) for:

- Control and prevention of bleeding episodes.

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
- Perioperative management (surgical prophylaxis).

ELOCTATE 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.

Treatment should be initiated and supervised by qualified healthcare professionals experienced in the diagnosis and treatment of haemophilia A. The ability of a patient to self-inject intravenously should be assessed.

Consult Directions for Use provided at the end of this document for detailed reconstitution instructions.

Each vial of ELOCTATE has the recombinant FVIII potency in International Units stated on the label. It is recommended that prescribed doses of ELOCTATE are expressed as "International Units", written in full.

Careful control of replacement therapy is especially important in cases of life-threatening bleeding episodes or major surgery (see Table 1 and Table 2).

Although dosing can be estimated by the guidelines below, it is recommended that standard routine laboratory tests such as factor VIII activity assays be performed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Method of Calculating Initial Estimated Dose

1 IU of ELOCTATE per kg body weight is expected to increase the circulating level of factor VIII by 2% [IU/dL].

ELOCTATE has been shown to have a prolonged circulating half-life. Although patients may vary in their pharmacokinetic (e.g. half-life, *in vivo* recovery) and clinical responses to ELOCTATE, the expected *in vivo* peak increase in factor VIII level expressed as IU/dL (or % of normal) or the required dose can be estimated using the following formulas:

IU/dL (or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

OR

Dose (IU) = body weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Dose adjustment may be necessary in paediatric patients under 12 years of age (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric Use). For patients 12 years of age or older, dose adjustment is not usually required.

Control and Prevention of Bleeding Episodes

The following table can be used to guide dosing in bleeding episodes:

Table 1 - Guide to ELOCTATE Dosing for Treatment of Bleeding

Severity of Bleed	Desired Peak Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)/ Frequency of Doses (hrs)
Minor and Moderate For example: joint, superficial muscle/no neurovascular compromise (except iliopsoas), deep laceration and renal, superficial soft tissue, mucous membranes.	40-60	20-30 IU/kg Repeat every 24-48 hours (12-24 hours for patients less than 12 years of age) until bleeding is resolved.
Major For example: iliopsoas and deep muscle with neurovascular injury, or substantial blood loss, retroperitoneum, CNS, throat and neck, gastrointestinal.	80-100	40-50 IU/kg Repeat every 12-24 hours (8-24 hours for patients less than 12 years of age) until bleeding is resolved.

Adapted from WFH 2012

Subsequent dosage and duration of treatment depends on the individual clinical response, the severity of the factor VIII deficiency, and the location and extent of bleeding (Section 5.2 PHARMACOKINETIC PROPERTIES).

Perioperative Management

Careful control and monitoring of dose and duration of treatment is especially important in cases of major surgery. Verify target activity has been achieved prior to surgery. The following table can be used to guide dosing for perioperative management (surgical prophylaxis):

Table 2 - Guide to ELOCTATE Dosing for Perioperative Management (Surgical Prophylaxis)

Type of Surgery	Target Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)/ Frequency of Doses (hrs)
Minor Minor operations including uncomplicated dental extraction	50-80	25-40 IU/kg A single infusion may be sufficient. Repeat every 24 hours (12-24 hours for patients less than 12 years of age) as needed to control bleeding.
Major Major operations including intra-abdominal, joint replacement surgery.	80-120	An initial preoperative dose of 40-60 IU/kg followed by a repeat dose of 40-50 IU/kg after 8-24 hours (6-24 hours for patients less than 12 years of age) and then every 24 hours to maintain FVIII activity within the target range. ELOCTATE (rFVIIIFc) has a longer half-life than plasma and recombinant FVIII products [See Section 5.2 PHARMACOKINETIC PROPERTIES].

Routine Prophylaxis

For individualised prophylaxis, the recommended regimen is 50 IU/kg every 3-5 days. The dose may be adjusted based on patient response in the range of 25-65 IU/kg (See Section 5.2 PHARMACOKINETIC PROPERTIES). More frequent or higher doses up to 80 IU/kg may be required in children less than 12 years of age.

For weekly prophylaxis, the recommended dose is 65 IU/kg.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The clinical response to ELOCTATE may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined, and a sufficient dose of ELOCTATE should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after ELOCTATE administration, the presence of an inhibitor (neutralising antibodies) should be suspected, and appropriate testing performed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Monitoring Laboratory Tests).

Anaphylaxis and Severe Hypersensitivity Reactions

Allergic type hypersensitivity reactions, including anaphylaxis, are possible with factor replacement therapies. Hypersensitivity reactions have been reported with ELOCTATE. Advise patients to discontinue use of ELOCTATE if hypersensitivity symptoms occur and contact a physician and/or seek immediate emergency care.

Neutralising Antibodies (Inhibitors)

Inhibitors have been reported with factor replacement therapy in the treatment of haemophilia A. Patients using ELOCTATE should be monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported with ELOCTATE in the treatment of haemophilia A, including in previously untreated patients (PUPs). If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after ELOCTATE administration, the presence of an inhibitor (neutralising antibodies) should be suspected, and appropriate testing performed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Monitoring Laboratory Tests).

Cardiovascular events

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

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Monitoring Laboratory Tests

Monitor plasma factor VIII activity levels by performing the one-stage clotting assay to confirm adequate factor VIII levels have been achieved and maintained, when clinically indicated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

Use in renal impairment

ELOCTATE has not been studied in patients with renal impairment.

Use in hepatic impairment

Specific studies of ELOCTATE in patients with hepatic impairment have not been performed.

Use in the elderly

Clinical studies of ELOCTATE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for patients aged 65 and older should be individualised (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use

Safety, efficacy, and pharmacokinetics of ELOCTATE have been evaluated in previously treated paediatric and adolescent patients (PTPs). Safety and efficacy of ELOCTATE have been evaluated in PUPs <6 years of age (median 0.58 year; range: 0.02-4.00 years) in Study 4 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). In adolescent patients 12 years of age and older, no dose adjustment is required. In comparison with adolescents and adults, children less than 12 years of age may have a higher clearance and a shorter half-life. These differences should be taken into account when dosing. More frequent or higher dosing may be needed in patients less than 12 years of age (see Section 5.2 PHARMACOKINETIC PROPERTIES, Paediatric Pharmacokinetics).

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 ELOCTATE. No drug interactions studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been conducted in animals with efmoroctocog alfa. It is not known whether ELOCTATE can affect fertility or sperm development in haemophilia A patients. Animal studies have not identified adverse effects in male or female reproductive organs following treatment with efmoroctocog alfa.

Use in pregnancy

Pregnancy Category C

Animal reproductive studies have not been conducted with efmoroctocog alfa, however efmoroctocog alfa has been shown to cross the placenta in small amounts in a placental transfer study in mice.

Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. It is not known whether ELOCTATE can affect reproductive capacity. Fc fusion products, including efmoroctocog alfa, may pass through the placenta. The effects on the developing foetus are unknown.

ELOCTATE should be used during pregnancy only if the potential benefit justifies the potential risk.

Use in lactation

Lactation studies have not been conducted with ELOCTATE. It is not known whether efmoroctocog alfa is excreted into human milk. Caution should be exercised if ELOCTATE is administered to nursing mothers. ELOCTATE should be used only if clinically indicated.

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

Previously treated patients (PTPs)

ELOCTATE has been evaluated in five completed studies (Study 1, 2, 3 and two pharmacokinetic studies) in PTPs with severe haemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe haemophilia A). A total of 276 subjects have been treated with ELOCTATE. Sixty-nine (25.06%) were paediatric subjects <12 years of age, 25 (9.1%) were adolescents (12 to <18 years of age), and 182 (65.9%) were adults (18 years of age and older). There were 200 subjects treated for at least 104 weeks (2 years), 151 subjects treated for at least 156 weeks (3 years) and 107 subjects treated for at least 208 weeks (4 years). The total number of exposure days (EDs) was 80,848 with a median of 294 (range 1-735) EDs per subject. The subjects received a total of 80,024 injections with a median of 303.5 injections of ELOCTATE (range 1-755) per subject.

Adverse drug reactions (ADRs) are considered adverse events assessed as related to treatment with ELOCTATE.

ADRs were reported in 11 of 276 (4.0%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. The ADRs with an incidence ≥0.5% for ELOCTATE were arthralgia, malaise, myalgia, headache and rash. No serious ADRs were reported in subjects who received

ELOCTATE. No age-specific differences in ADRs were observed between paediatric and adult subjects. ADRs in PTPs are summarised in Table 3.

One (1) subject was withdrawn from a study due to an adverse drug reaction of rash. In the studies, no inhibitors were detected and no events of anaphylaxis were reported.

Table 3 - Adverse Drug Reactions reported for ELOCTATE in PTPs

MedDRA[2] System Organ Class	MedDRA Preferred Term	N=276*	
		Number of Subjects n (%)	Frequency Category[3]
			Uncommon (≥1/1,000 to <1/100)
Nervous system disorders	Headache	2 (0.7)	Uncommon
	Dizziness	1 (0.4)	Uncommon
	Dysgeusia	1 (0.4)	Uncommon
Cardiac disorders	Bradycardia	1 (0.4)	Uncommon
Vascular disorders	Hypertension	1 (0.4)	Uncommon
	Hot Flush	1 (0.4)	Uncommon
	Angiopathy[1]	1 (0.4)	Uncommon
Respiratory, thoracic, and mediastinal disorders	Cough	1 (0.4)	Uncommon
Gastrointestinal disorders	Abdominal pain, lower	1 (0.4)	Uncommon
Skin and subcutaneous tissue disorders	Rash	2 (0.7)	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	2 (0.7)	Uncommon
	Myalgia	2 (0.7)	Uncommon
	Back pain	1 (0.4)	Uncommon
	Joint swelling	1 (0.4)	Uncommon
General disorders and administration site conditions	Malaise	2 (0.7)	Uncommon
	Chest pain	1 (0.4)	Uncommon
	Feeling cold	1 (0.4)	Uncommon
	Feeling hot	1 (0.4)	Uncommon
Injury, poisoning, and procedural complications	Procedural hypotension	1 (0.4)	Uncommon

*The ELOCTATE clinical program included 276 previously treated patients (PTPs) on routine prophylaxis or episodic (on-demand) therapy from 5 completed studies.

[1] Investigator term: vascular pain after injection of study drug

[2] MedDRA version 15.0

[3]ADR frequency is based upon the following scale: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000)

Previously untreated patients (PUPs)

ELOCTATE safety was also evaluated in 1 completed study (Study 4) in 103 subjects with severe haemophilia A (<1% endogenous FVIII activity). At enrolment, the median age was 0.58 year (range: 0.02-4 years). Overall, the median number of weeks on treatment was 64.24 weeks (range: 0.0-206.8 weeks). The number of subjects with at least 10 exposure days (EDs) was 87 (84.5%), at least 20 EDs was 85 (82.5%), and at least 50 EDs was 81 (78.6%).

Adverse events were monitored for a total of 140.44 subject-years. ADRs were reported in 29 of 103 (28.2%) subjects treated with ELOCTATE. ADRs in PUPs are summarised in Table 4.

Table 4: Adverse Drug Reactions Reported for ELOCTATE in PUPs

MedDRA[1] System Organ Class	MedDRA Preferred Term	N=103[2]	
		Number of Subjects n (%)	Frequency Category[3] Common (≥1/100 to <1/10) Very Common (>1/10)
Blood and lymphatic system disorders	Factor VIII inhibition	28 (27.2)	Very Common
General disorders and administration site conditions	Device related thrombosis[4]	2 (1.9)	Common
Skin and subcutaneous tissues disorders	Rash papular	1 (1.0)	Common

[1]MedDRA version 22.0

[2]The ELOCTATE clinical program included 103 previously untreated patients (PUPs) on routine prophylaxis or episodic (on-demand) therapy from 1 study

[3]ADR frequency is based upon the following scale: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000)

[4]Includes 1 subject with device related thrombosis and 1 subject with deep vein thrombosis, each event occurred in association with an indwelling central venous catheter

Immunogenicity

No PTPs developed neutralising antibodies (inhibitors) to Factor VIII in clinical studies (Study 1, 2, 3 and two pharmacokinetic studies).

In Study 4 in PUPs, development of neutralising antibodies (inhibitors) was observed in 28 subjects, 14 of them had a high-titre inhibitor. Based on subjects with an inhibitor test following an exposure day (ED) milestone or who developed an inhibitor at any time during the study, the incidence of Factor VIII inhibitor development was:

- 28/90 subjects (31.11%) with at least 10 EDs
- 28/86 subjects (32.56%) with at least 50 EDs

The median time to inhibitor development for the 28 subjects was 9 EDs (interquartile range: 6.5-12).

Post Marketing Experience

In post-marketing experience, the following adverse reactions have been reported:
Factor VIII inhibitors development
Hypersensitivity

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No symptoms of overdose have been reported. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The factor VIII/Von Willebrand Factor (FVIII/VWF) complex consists of 2 molecules (FVIII and Von Willebrand Factor) with different physiological functions. Upon activation of the clotting cascade, FVIII is converted to activated FVIII (FVIIIa) and released from VWF. Activated factor VIII acts as a co-factor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X on phospholipid surfaces, and which ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.

Haemophilia A is an X-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII activity and results in profuse bleeding into joints, muscles, or internal organs, either spontaneously or as a result of accidental or surgical trauma. The FVIII portion of efmoroctocog alfa is a glycoprotein comparable to the 90+80 kDa form of endogenous FVIII that is found in human plasma. When injected, efmoroctocog alfa binds to von Willebrand factor in an individual's circulation, and replaces all functions of the missing FVIII.

ELOCTATE (efmoroctocog alfa) is a long-acting, fully recombinant fusion protein comprised of recombinant B domain-deleted human factor VIII (BDD FVIII) covalently linked to the Fc domain of human IgG1, and is produced by recombinant DNA technology.

The other portion of efmoroctocog alfa is the Fc region of human IgG1 that binds to the neonatal Fc receptor (FcRn). This receptor is expressed throughout life and is part of a naturally occurring pathway that protects immunoglobulins from lysosomal degradation by cycling these proteins back into circulation, resulting in their long plasma half-life. Binding to FcRn delays lysosomal degradation and allow for longer plasma half-life of efmoroctocog alfa than endogenous FVIII.

Haemophilia A is a bleeding disorder characterised by a deficiency of functional clotting factor VIII (FVIII), which leads to a prolonged clotting time in the activated partial thromboplastin time (aPTT) assay, a conventional in vitro test for the biological activity of FVIII. Treatment with ELOCTATE normalises the clotting time over the effective dosing period.

ELOCTATE is used as a replacement therapy to increase plasma levels of factor VIII, thereby enabling a temporary correction of the factor deficiency and the bleeding tendency.

Clinical trials

The safety, efficacy, and pharmacokinetics of ELOCTATE was evaluated in two multinational, open-label, pivotal studies in PTPs; a Phase 3 study in adults and adolescents (Study 1) and a Phase 3 paediatric study (Study 2). Patients from these studies could subsequently enrol in the long-term extension study (Study 3). The safety and efficacy of ELOCTATE was also evaluated in PUPs with severe haemophilia A (Study 4).

Previously Treated Patients (PTPs)

Study 1

Study 1 compared the efficacy of each of 2 prophylactic treatment regimens to episodic (on-demand) treatment; determined haemostatic efficacy in the treatment of bleeding episodes; and determined haemostatic efficacy during perioperative management in subjects undergoing major surgical procedures.

The study enrolled a total of 165 previously treated male patients with severe haemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe haemophilia A). PTPs were defined as those patients having at least 150 documented prior exposure days to any recombinant and/or plasma-derived FVIII, and/or cryoprecipitate products, excluding fresh frozen plasma. Subjects were aged 12-65, including 13 adolescent subjects aged 12 to 17 years. Hepatitis C Virus (HCV) status was positive in 82 of 165 (49.7%) subjects on study. Of the 165 enrolled subjects, 164 received at least 1 dose of ELOCTATE, and 163 were evaluable for efficacy. A total of 153 subjects (92.7%) completed the study.

Subjects on prophylaxis regimens prior to entering the study were assigned to the individualised prophylaxis arm. Those subjects on episodic (on-demand) therapy prior to entry either entered the individualised prophylaxis arm or were randomised to the weekly prophylaxis or episodic (on-demand) arms. Subjects requiring surgery could receive perioperative management (surgical prophylaxis) with ELOCTATE during the study. Subjects were followed for up to 54 weeks.

Of the 118 subjects enrolled in the individualised prophylaxis arm, 117 received ELOCTATE starting with a twice weekly regimen consisting of 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. The dose and interval were adjusted within the range of 25-65IU/kg every 3-5 days to maintain trough between 1 and 3% above baseline or higher as clinically indicated to prevent bleeding. The median dosing interval was 3.51 days (interquartile range, 3.17, 4.43) and the median total weekly dose was 77.90 IU/kg (interquartile range 72.35, 91.20). For 112 subjects with ≥ 6 months on study, approximately 30% achieved a mean dosing interval of ≥ 5 days during the last three months on study. Subjects were on study for a median period of 32.1 weeks (range, 9, 54).

Twenty-four (24) subjects in the weekly prophylaxis arm were to receive 65 IU/kg of ELOCTATE once weekly. Twenty-three (23) subjects were evaluable for efficacy due to the withdrawal of one subject prior to entering the efficacy period. Subjects were on study for a median period of 28 weeks (range, <1, 38).

Twenty-three (23) subjects in the episodic (on-demand) arm received ELOCTATE as needed, for the treatment of bleeding episodes. Subjects were on study for a median period of 28.9 weeks (range, 15, 32).

Study 2

Study 2 enrolled a total of 71 previously treated male paediatric patients with severe haemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe haemophilia A). Of the 71 enrolled subjects, 69 received at least 1 dose of ELOCTATE and were evaluable for efficacy. Subjects were less than 12 years of age (35 were < 6 years of age and 34 were 6 to < 12 years of age).

Sixty-nine (69) subjects received ELOCTATE on an individualised prophylactic dose regimen starting with a twice weekly regimen consisting of 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. The dose could be adjusted within the range of 25-80 IU/kg with a minimum allowable interval of every 2 days to maintain trough between 1 and 3% above baseline or as clinically indicated to prevent bleeding. The median dosing interval was 3.49 days (interquartile range, 3.46 to 3.51 days) with no difference in the median dosing interval between age cohorts. 89.9 % of subjects remained on a twice weekly interval. The median weekly dose of ELOCTATE for subjects <6 years of age was 91.63 IU/kg (interquartile range, 84.72 to 104.56 IU/kg). For subjects in the 6 to <12 years of age cohort, the median weekly dose was 86.88 IU/kg (interquartile range, 79.12 to 103.08 IU/kg).

Study 3

Study 3 was an open-label, multicentre, long-term study in PTPs with haemophilia A who had completed Study 1, Study 2, or any other study. The study evaluated the long-term safety and efficacy of routine prophylaxis, on-demand treatment, and perioperative management with ELOCTATE. During the study, subjects could change treatment groups. Subjects <12 years of age entering from another study were not offered weekly or on-demand treatment options until they reached 12 years of age.

The majority of subjects stayed on their treatment regimen throughout the extension study, with 21 subjects (22.6%) switching treatment regimens once or twice during the study. Fifteen subjects were part of the surgery subgroup.

Of the 240 subjects in Study 3 (aged 2 - 66), 190 subjects participated in the individualised prophylaxis arm. Subjects enrolled in individualised prophylaxis had dosing that was 25- 65 IU/kg every 3 to 5 days, or dosing 2 times per week at 20 IU/kg to 65 IU/kg on Day 1 and 40 - 65 IU/kg on Day 4. In paediatric subjects, doses could be adjusted up to a maximum prophylactic dose of 80 IU/kg and the interval decreased to every 2 days, as clinically indicated to prevent bleeding.

Thirty-four (34) subjects received weekly prophylaxis during Study 3. Subjects on the weekly prophylaxis regimen received 65 IU/kg of ELOCTATE once weekly.

Twenty-Six (26) subjects received the personalized prophylaxis regimen. Subjects were enrolled in the personalized prophylaxis regimen if optimal prophylaxis could not be achieved using either of the above options. Dosing of ELOCTATE was adjusted to meet the needs of individual subjects.

Thirteen (13) subjects received episodic (on-demand) treatment as needed, for the treatment of bleeding episodes.

Table 5 - Treatment groups, dose and dosage intervals for subjects from Study 1 who participated in Study 3

	Individualised prophylaxis	Weekly prophylaxis	Personalised prophylaxis	Episodic treatment
Number of subjects in Study 3	190	34	26	13
Average1 Weekly Dose	79.54 IU/kg (73.67 – 100.91)	65.66 IU/kg (61.88 – 67.19	70.61 IU/kg (62.25 – 90.40	N/A
Average1 dosing interval	3.52 days (3.46 – 4.98)	7.00 days (6.98 – 7.06)	5.00 days (3.97- 6.92)	
Average weekly duration in study	176.66 weeks (3.9 – 274.6)	226.68 weeks (69.9 – 270.4)	150.00 weeks (51.0 – 254.0)	27.62 weeks (0.1 – 248.4)

[1]Median (interquartile range)

Table 6 - Treatment groups, dose and dosage intervals for subjects from Study 2 who participated in Study 3

	Individualised prophylaxis	Personalised prophylaxis
Number of subjects from Study 2	59	3
	Subjects <6 years	
Number of subjects	29	2

	Individualised prophylaxis	Personalised prophylaxis
Average[1] dosing interval	3.50 days (3.49 - 3.52)	3.91 days (2 5 - 0.51)
Median average weekly dose	101.90 IU/kg (88.72 - 118.68 IU/kg)	100.12 IU/kg (81.51 - 118.73 IU/kg)
	Subjects 6 - <12 years	
Number of subjects	30	1
Average[1] dosing interval	3.50 days (3.49 - 3.52	3.48 days
Median average weekly dose	94.90 IU/kg (81.71 - 109.07 IU/kg)	84.52 IU/kg (84.52 - 84.52 IU/kg)

[1]Median (interquartile range)

Previously Untreated Patients (PUPs)

Study 4

Study 4 evaluated the safety and efficacy of ELOCTATE in prevention and treatment of bleeding episodes in PUPs. The study enrolled 108 PUPs <6 years old with severe haemophilia A (<1% endogenous FVIII (activity), of whom 103 received at least one dose of ELOCTATE. At enrolment, the median age was 0.58 year (range: 0.02-4 years), 77.7% of subjects were <1 year old, and median weight was 8.65 kg (range: 3.5-16.1 kg). Overall, the median number of weeks on ELOCTATE was 64.24 weeks (range: 0.0-206.8 weeks), including immune tolerance induction (ITI). The median number of weeks for the episodic treatment regimen was 23.57 weeks (range: 0.4-107.8 weeks) and for the prophylactic treatment regimen, the median number of weeks was 43.97 weeks (range: 0.0-96.6 weeks). Overall, the median number of EDs was 100 days (range: 0-649 days), including ITI.

Subjects could be treated episodically (optional), until a prophylactic regimen was initiated. Subjects who developed a high-titre inhibitor or select subjects with a low-titre inhibitor with poorly controlled bleeding were eligible to undergo the ITI regimen.

Eighty-nine PUPs received prophylaxis with ELOCTATE. The recommended initial dose on the prophylactic regimen was 25–80 IU/kg at 3–5-day intervals, with adjustments to dosing and dosing intervals based on pharmacokinetic data, levels of physical activity, and bleed patterns. For subjects on prophylaxis, the median average weekly dose was 101.4 IU/kg (range: 28.5-776.3 IU/kg) and the median dosing interval was 3.87 days (range: 1.1-7 days).

Efficacy in Routine Prophylaxis

Study 1 (≥ 12 Years)

Using a negative binomial model to calculate the annualized bleeding rate (ABR), there was a statistically significant reduction in annualised bleed rate (ABR) of 92% (p<0.001, 95% CI: 87%, 95%) for subjects in the individualised prophylaxis arm and a statistically significant reduction of 76% (p<0.001, 95% CI: 54%, 88%) for subjects in the weekly prophylaxis arm compared to the episodic (on demand) arm.

Fifty-three (53) of 117 (45.3%) subjects experienced no bleeding episodes while on individualised prophylaxis and 4 of 23 (17.4%) subjects experienced no bleeding episodes while on weekly prophylaxis.

A comparison of the median ABRs in subjects evaluable for efficacy is summarised in Table 7

Table 7 - Summary of Median (IQR) [1] Annualised Bleeding Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age

Bleeding Episode Aetiology	Individualised Prophylaxis (N=117)	Weekly Prophylaxis (N=23)	Episodic (On-Demand) (N=23)
Overall ABR	1.60 (0.0, 4.69)	3.59 (1.86, 8.36)	33.57 (21.14, 48.69)
Spontaneous ABR	0.00 (0.0, 2.03)	1.93 (0.0, 4.78)	20.24 (12.21, 36.81)
Traumatic ABR	0.00 (0.0, 1.83)	1.69 (0.00, 3.27)	9.25 (1.74, 11.92)
Joint ABR	0.00 (0.00, 3.11)	1.93 (0.00, 7.62)	22.76 (15.07, 39.02)

[1] Median (interquartile range, 25th and 75th percentiles)

Study 2 (< 12 Years)

For paediatric subjects, 32 (46.4%) experienced no bleeding episodes (18 subjects (51.4%) <6 years of age and 14 subjects (41.2%) 6 to <12 years of age). A comparison of the median ABRs in paediatric subjects evaluable for efficacy is summarized in Table 8.

Table 8 - Summary of Median (IQR)[1] Annualized Bleeding Rate (ABR) in Paediatric Subjects < 12 Years of Age

Bleeding Episode Aetiology	<6 Years (n=35)	6 to <12 Years (n=34)	Total (< 12 Years) (n=69)
Overall ABR	0.00 (0.00, 3.96)	2.01 (0.00, 4.04)	1.96 (0.00, 3.96)
Spontaneous ABR	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Traumatic ABR	0.00 (0.00, 2.01)	0.00 (0.00, 2.12)	0.00 (0.00, 2.04)
Joint ABR	0.00 (0.0, 1.93)	0.00 (0.0, 2.04)	0.00 (0.00, 2.02)

[1] Median (interquartile range, 25th and 75th percentiles)

Study 3 (Extension Study)

(≥ 12 Years)

For adult and adolescent subjects enrolled from Study 1, forty (40) subjects on prophylaxis had 0 bleeding episodes. Thirty-five of 110 subjects (31.8%) on individualised prophylaxis, 2 of 27 subjects (7.4%) on weekly prophylaxis, 3 of 21 subjects (14.3%) on personalised prophylaxis , and 3 of 13 subjects (23.1%) on episodic treatment had no bleeding episodes. A summary of the median ABRs in subjects evaluable for efficacy is summarised in Table 9.

Table 9 - Summary of Median (IQR)[1] Annualised Bleeding Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age[2]

Bleeding Episode Aetiology	Individualised Prophylaxis (N=110)	Personalised Prophylaxis (N=21)	Weekly Prophylaxis (N=27)	On-Demand (N=13)
Overall ABR	0.74 (0.00, 2.68)	4.11 (1.19, 8.78)	2.24 (0.43, 5.09)	19.10 (15.12, 30.46)
Spontaneous ABR	0.10 (0.00, 1.06)	1.37 (0.43, 3.90)	1.50 (0.00, 2.74)	14.61 (10.88, 16.37)
Traumatic ABR	0.23 (0.00, 1.10)	0.91 (0.21, 2.96)	0.45 (0.21, 0.97)	1.39 (0.00, 5.02)
Spontaneous Joint ABR	0.00 (0.00, 0.71)	1.00 (0.00, 2.84)	1.04 (0.00, 2.51)	9.22 (4.35, 15.70)

[1] Median (interquartile range, 25th and 75th percentiles)
[2] Study subjects could change treatment groups during the study

(< 12 Years)

For paediatric subjects enrolled from Study 2, three (3) of 29 subjects (10.3%) on individualised prophylaxis had no bleeding episodes. A summary of the median ABRs in paediatric subjects evaluable for efficacy is summarised in Table 10.

Table 10 - Summary of Median (IQR)[1] Annualised Bleeding Rate (ABR) by Treatment Arm in Subjects < 12 Years of Age[2]

Bleeding Episode Aetiology	Individualised Prophylaxis	Personalised Prophylaxis
< 6 Years	**(N=29)**	**(N=2)**
Overall ABR	1.18 (0.60, 2.37)	3.72 (3.35,4.09)
Spontaneous ABR	0.56 (0.00, 0.85)	2.54 (2.01, 3.07)
Traumatic ABR	0.41 (0.00, 0.87)	1.18 (1.02, 1.34)
Spontaneous Joint ABR	0.00 (0.00, 0.55)	2.20 (1.34, 3.07)
6-12 Years	**(N=30)**	**(N=1)**
Overall ABR	1.59 (0.55, 3.55)	1.01
Spontaneous ABR	0.30 (0.00, 0.89)	0.00
Traumatic ABR	1.00 (0.00, 2.06)	1.01
Spontaneous Joint ABR	0.00 (0.00, 0.55)	0.00

[1] Median (interquartile range, 25th and 75th percentiles)
[2] Study subjects could change treatment groups during the study

Study 4

A summary of the median (IQR) ABRs in PUPs evaluable for efficacy is presented in **Table 11**.

Table 11 Summary of Median (IQR)[1] Annualised Bleeding Rate (ABR) in PUPs <6 Years of Age

Bleeding Episode	Prophylaxis N=89
Overall ABR	1.49 (0.00, 4.40)
Spontaneous ABR	0.00 (0.00, 0.00)
Traumatic ABR	0.83 (0.00, 3.43)
Spontaneous Joint ABR	0.00 (0.00, 0.00)

IQR=interquartile range, 25th and 75th percentiles

Immune Tolerance Induction (ITI)

The use of ELOCTATE for ITI has been investigated in 15 PUPs who had developed inhibitors (12 with high-titre inhibitors and 3 with low-titre inhibitors). Among these 15 subjects, 5 subjects met the criteria for complete success (3 with low-titre and 2 with high-titre) and came off study. No subjects relapsed during ITI tapering or relapse monitoring. Two subjects had partial success, and 3 subjects (all with high-titre inhibitors) terminated ITI early due to lack of efficacy. Five subjects had ITI ongoing at the end of the study, including 1 subject who developed a recurrent positive inhibitor titre during ITI. There is experience from real world use of ELOCTATE for ITI.

Efficacy in Control of Bleeding

Study 1 (≥ 12 Years)

A total of 757 new bleeding events were observed during the study. Assessment of response to each injection was recorded by subjects at 8 to 12 hours post-treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Bleeding episodes are summarised in Table 12.

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

New bleeding episodes		(n= 757)
# of Injections to treat bleeding episodes	1 injection	661 (87.3%)
	2 injections	79 (10.4%)
	3 injections	13 (1.7%)
	≥4 injections	4 (0.5%)
		(n=755)

New bleeding episodes		(n= 757)
Median dose per injection (IU/kg) to treat a bleeding episode (IQR)		27.35 (22.73, 32.71)
Median total dose (IU/kg) to treat a bleeding episode (IQR)		28.23 (23.26, 46.88)
Response to first injection		(n= 745)
	Excellent or good	78.1%
	Moderate	21.2%
	No response	0.7%

Study 2 (< 12 Years)

A total of 86 new bleeding events were observed during the study. Assessment of response to each injection was recorded by subjects at 8 to 12 hours post-treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Bleeding episodes are summarised in Table 13.

The haemostatic efficacy in treatment of bleeds was rated as excellent or good in 89.4% of all evaluable injections and 92.6% for all evaluable first injections.

Table 13 - Summary of Efficacy in Control of Bleeding in Paediatric Subjects < 12 Years of Age

		<6 Years (n=35)	**6 to <12 Years (n=34)**	**Total (< 12 Years) (n=69)**
New bleeding episodes		(n=38)	(n=48)	(n=86)
# of Injections to treat bleeding episodes				
	1 injection	29 (76.3%)	41 (85.4%)	70 (81.4%)
	2 injections	7 (18.4%)	3 (6.3%)	10 (11.6%)
	3 injections	1 (2.6%)	2 (4.2%)	3 (3.5%)
	≥4 injections	1 (2.6%)	2 (4.2%)	3 (3.5%)
Median dose per injection (IU/kg) to treat a bleeding episode (IQR)		51.35 (29.94, 59.52)	48.15 (29.08, 55.97)	49.69 (29.41, 56.82)
Median total dose (IU/kg) to treat a bleeding episode (IQR)		56.40 (29.94, 72.46)	53.49 (29.08, 66.80)	54.90 (29.41, 71.09)
Response to first injection		(n=35)	(n=46)	(n=81)
	Excellent or good	32 (91.4%)	43 (93.5%)	75 (92.6%)
	Moderate	3 (8.6%)	1 (2.2%)	4 (4.9%)
	No response	0 (0.0%)	2 (4.3%)	2 (2.5%)

	<6 Years (n=35)	6 to <12 Years (n=34)	Total (< 12 Years) (n=69)

Study 3

Adult and adolescent study (12 to 71 years)

A total of 757 bleeding events were observed in 106 subjects. The majority of the bleeding episodes were spontaneous and localised in joints. The median total dose to treat a bleeding episode was 27.35 IU/kg (interquartile range: 22.73 – 32.71). Assessment of response to each injection was recorded by subjects at 8-12 hours after treatment. Efficacy in control of bleeding episodes in subjects over 12 is summarised in Table 14.

Table 14 - Efficacy in Control of Bleeding in Adults and Adolescents

Bleeding episodes	(N=757)
Number of injections to treat bleeding episodes	
1 injection	661 (87.3%)
2 injections	79 (10.4%)
3 injections	17 (2.2%)
Response* to first injection	(N=745)
Excellent or good	78.1%
Moderate	21.2%
None	0.7 %

*Excellent: abrupt pain relief and/or improvement in signs of bleeding; Good: definite pain relief and/or improvement in signs of bleeding but possibly requiring another injection in 1-2 days; Moderate: probable or slight beneficial effect and requiring more than one injection; None: no improvement, or worsening. Response evaluated at approximately 8 hours after treatment.

Paediatric study (1 to 11 years)

A total of 86 bleeding events were observed by 69 subjects during the study. Assessment of response to each injection was recorded by subjects at 8 to12 hours post treatment. Efficacy in control of bleeding episodes in subjects < 12 years old is summarised in Table 15.

Table 15 Efficacy in Control of Bleeding in Paediatric Subjects

	1 to 5 Years (n=35)	6 to 11 Years (n=34)	Total (<12 Years) (n=69)
New Bleeding episodes	(n=38)	(n=48)	(n=86)

		1 to 5 Years (n=35)	6 to 11 Years (n=34)	Total (<12 Years) (n=69)
Number of injections to treat bleeding episodes	1 injection	29 (76.3%)	41 (85.4%)	70 (81.4%)
	2 injections	7 (18.4%)	3 (6.3%)	10 (11.6%)
	>2 injections	2 (5.3%)	4 (8.3%)	6 (7.0%)
Median dose per injection (IU/kg) to treat a bleeding episode (IQR)		51.35 (29.94 – 59.52)	48.15 (29.08 – 55.97)	49.69 (29.41 – 56.82)
Median total dose (IU/kg) to treat a bleeding episode (IQR)		56.40 (29.94 – 72.46)	53.49 (29.08 – 66.80)	54.90 (29.41 – 71.09)
Response* to first injection		n=35	n=46	n=81
	Excellent or good	32 (91.4%)	43 (93.5%)	75 (92.6%)
	Moderate	3 0 (8.6%)	1 (2.2%)	4 (4.9%)
	None	0 (0.0%)	2 (4.3%)	2 (2.5%)

Study 4

A summary of efficacy in control of bleeding in PUPs is presented in **Table 16**

Table 16: Summary of Efficacy in Control of Bleeding in PUPs <6 Years of Age

		Prophylaxis (N=89)
Bleeding episodes		215
# of Injections to treat bleeding episodes	1 injection	172 (80.0%)
	2 injections	29 (13.5)
	3 injections	7 (3.3%)
	4 injections	3 (1.4%)
	>4 injections	4 (1.9%)
Median dose per injection (IU/kg) to treat a bleeding episode (IQR)		48.08 (38.76, 64.10)
Median total dose (IU/kg) to treat a bleeding episode (IQR)		55.56 (43.10, 75.0)
Subject/caregiver assessment of response to first injection1, 2	Excellent or good	130 (83.9%)
	Moderate	12 (7.7%)
	None	13 (8.4%)

IQR=interquartile range, 25th and 75th percentiles

[1]Responses are based on number of first injections for a bleeding episode with an evaluation

[2]Excellent: abrupt pain relief and/or improvement in signs of bleeding; Good: definite pain relief and/or improvement in signs of bleeding but possibly requiring another injection in 1-2 days; Moderate: probable or slight beneficial effect

and requiring more than 1 injection; None: no improvement, or condition worsening. Response evaluated at approximately 8 hours after treatment.

Efficacy in Perioperative Management (Surgical Prophylaxis)

Major Surgeries

Haemostasis was evaluated in forty-eight (48) surgeries in thirty-four (34) subjects from Study 1 and Study 3. There was 1 major surgery evaluated in the paediatric study (Study 2) and 2 major surgeries evaluated during the pharmacokinetic studies. Thirty-nine (39) surgeries (81.3%) required a single injection of rFVIIIFc to maintain haemostasis.

Haemostatic response was assessed in forty-four (44) major surgical procedures in thirty-one (31) subjects. Nine (9) major surgical procedures were performed in nine subjects in Study 1. In an extension study, a total of 35 major surgical procedures were assessed for haemostatic response in 23 subjects. The investigators post-operatively assessed haemostasis using a 4-point scale of excellent, good, fair, and poor/none. The haemostatic response was rated as excellent or good in 100% of major surgeries.

Haemostatic response to dosing during surgery and post-operatively for Study 1 and Study 3 is summarised in Table 17.

Table 17 Summary of Haemostatic Response During Surgery and Post-Operatively*

		Response			
		Excellent	**Good**	**Fair**	**Poor/None**
	Number of Procedures (Number of Subjects)				
Major Surgery	44 (31)	41	3		
Amputation	1 (1)		1		
Ankle Fusion	4 (4)	4			
Appendectomy	1 (1)	1			
Arm Fracture Open Reduction Internal Fixation	1 (1)	1			
Arthroscopy	2 (2)	2			
Bilateral Knee Replacement	1 (1)	1			
Cholecystectomy	1 (1)	1			
Cranioplasty	1 (1)	1			
Dental Extraction	1 (1)	1			
Endoscopic Third Ventriculostomy	1 (1)	1			
Laparoscopic Inguinal Hernia Repair	2 (2)	1	1		
Nasal Cauterisation	1 (1)	1			

Spinal Surgery	2 (1)	2	
Thoracotomy	2 (1)	2	
Unilateral Elbow Replacement	4 (2)	4	
Unilateral Hip Replacement	1 (1)	1	
Unilateral Knee Replacement or Revision	14 (13)	13	1
Unilateral Shoulder Replacement	1 (1)	1	
Ureteroscopy	2 (1)	2	

*24 hours following surgery

Minor Surgeries

A haemostatic assessment of 69 minor surgical procedures in 58 subjects was conducted with a 100% excellent or good response in Study 1, Study 2, and Study 3.

In Study 2, a total of 7 minor surgeries were performed in 7 paediatric subjects (2 surgeries in the <6 years of age cohort and 5 in the 6 to <12 years of age cohort). Minor surgeries included port removal, port placement, dental extraction, colonoscopy, and endoscopy. An investigator's assessment of haemostasis was collected at least 24 hours following surgery. Haemostasis was rated as excellent for 5 minor surgeries and as good for 2 minor surgeries.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of ELOCTATE (rFVIIIFc) versus ADVATE (octocog alfa) (rFVIII) was evaluated following a 10-minute IV infusion in 28 evaluable subjects (≥15 years) in Study 1. The subjects underwent a washout period of at least 96 hours (4 days) prior to receiving a single dose of 50 IU/kg of ADVATE. PK sampling was conducted pre-dose followed by assessments at 6 time points up to 72 hours (3 days) post-dose. Following a washout period of 96 hours (4 days), the subjects received a single dose of 50 IU/kg of ELOCTATE. PK samples were collected pre-dose and then subsequently at 7 time points up to 120 hours (5 days) post-dose. A repeat PK evaluation of ELOCTATE was conducted at Week 14.

Pharmacokinetic parameters for ELOCTATE were estimated based on the plasma FVIII activity over the time profile (see Figure 1) based on a one-stage clotting assay. For ELOCTATE, the maximum activity (C_{max}) was observed following the end of the infusion. The geometric mean increase in circulating FVIII activity from pre-infusion level was 2.24 IU/dL per IU/kg and the elimination half-life was 19 hours. The 1.5-fold prolongation of half- life for ELOCTATE relative to ADVATE was consistent across subjects over the range of half-lives. The ELOCTATE PK profile was stable over repeated dosing as shown by comparable PK parameters at Week 14.

A summary of PK parameters after a 50 IU/kg dose for ELOCTATE and ADVATE are presented in Table 18.

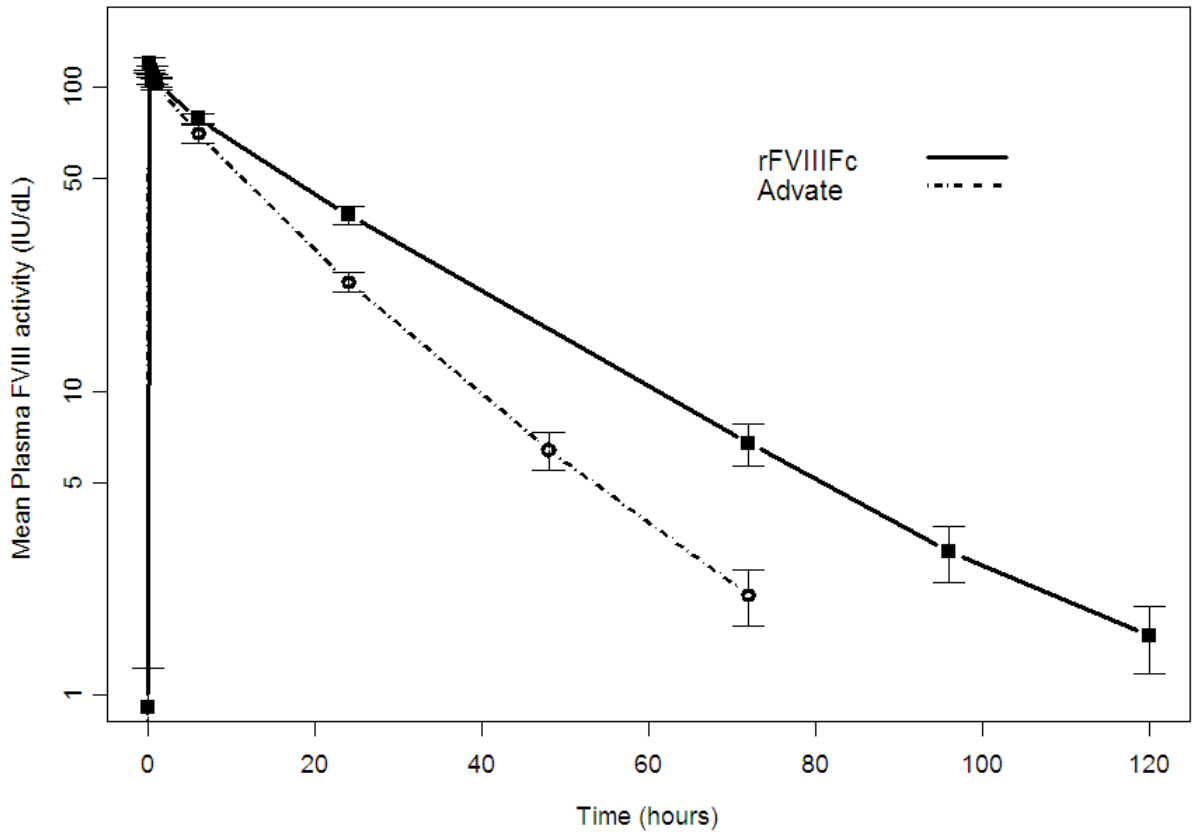
Table 18 - Pharmacokinetic Parameters of ELOCTATE (rFVIIIFc) and ADVATE (rFVIII)

PK Parameters[1]	ELOCTATE (95% CI)	ADVATE (95% CI)	Ratio of ELOCTATE to ADVATE (95% CI)
	N=28	N=28	N=28
Cmax (IU/dL)	108 (101, 115)	120 (111, 128)	0.90 (0.86, 0.95)
AUC/Dose (IU*h/dL per IU/kg)	51.2 (45.0, 58.4)	32.9 (29.3, 36.9)	1.56 (1.46, 1.67)
t1/2 (h)	19.0 (17.0, 21.1)	12.4 (11.1, 13.9)	1.53 (1.36, 1.71)
CL (mL/h/kg)	1. 95 (1.71, 2.22)	3.04 (2.71, 3.41)	0.64 (0.60, 0.69)
MRT (h)	25.2 (22.7, 27.9)	16.8 (15.2, 18.6)	1.49 (1.41, 1.58)
Vss (mL/kg)	49.1 (46.6, 51.7)	51.2 (47.2, 55.5)	0.96 (0.90, 1.02)
Incremental Recovery (IU/dL per IU/kg)	2.24 (2.11, 2.38)	2.35 (2.21, 2.50)	0.95 (0.91, 0.99)
Time to 1% (days)	4.92 (4.43, 5.46)	3.30 (2.99, 3.65)	1.49 (1.41, 1.57)

[1]PK parameters are presented in Geometric Mean (95% CI)

Abbreviations: CI = confidence interval; Cmax = maximum activity; AUC = area under the FVIII activity time curve; t1/2 = terminal half-life; CL = clearance; MRT = mean residence time; Vss = volume of distribution at steady-state

Figure 1 - *Mean (+/- SE*) Observed Activity Profile for ELOCTATE (rFVIIIFc) and ADVATE (rFVIII)*



*Standard error

Paediatric Pharmacokinetics

Pharmacokinetic (PK) parameters of ELOCTATE (rFVIIIFc) were determined for adolescents 12 to less than 18 years of age in Study 1 and for children less than 12 years of age in Study 2 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric Use).

PK parameters were evaluated following a 10-minute IV infusion in 11 evaluable adolescents who received a single dose of ELOCTATE. PK samples were collected pre-dose and then at multiple time points up to 120 hours (5 days) post-dose. In a separate study, PK parameters were evaluated following a 5-minute IV infusion in 54 evaluable children (less than 12 years of age) who received a single dose of ELOCTATE. PK samples were collected pre-dose and then at multiple time points up to 72 hours (3 days) post-dose. PK parameters for ELOCTATE were estimated based on the plasma FVIII activity over time profile. A post hoc analysis in paediatric subjects on previous ADVATE therapy (n=15) demonstrated that half-life prolongation of ELOCTATE relative to ADVATE (approximately 1.5-fold) is consistent with adult and adolescent subjects.

Table 19 presents the PK parameters calculated from the paediatric data of 65 subjects less than 18 years of age. Compared to adults and adolescents clearance appeared to be higher and half-life

appeared to be shorter in children less than 12 years of age. This may result in a need for dose adjustments in children less than 12 years of age (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric Use).

Table 19 - Comparison of PK Parameters of ELOCTATE (rFVIIIFc) by Age Category

PK Parameters[1]	Study 2		Study 1
	<6 Years (1, 5) N = 23	6 to <12 Years (6, 11) N = 31	12 to < 18 Years (12, 17) N = 11
IR (IU/dL per IU/kg)	1.90 (1.79, 2.02)	2.30 (2.04, 2.59)	1.81 (1.56, 2.09)
AUC/Dose (IU*h/dL per IU/kg)	28.9 (25.6, 32.7)	38.4 (33.2, 44.4)	38.2 (34.0, 42.9)
t½ (h)	12.3 (11.0, 13.7)	13.5 (11.4, 15.8)	16.0 (13.9, 18.5)
MRT (h)	16.8 (15.1, 18.6)	19.0 (16.2, 22.3)	22. 7 (19.7, 26.1)
CL (mL/h/kg)	3.46 (3.06, 3.91)	2.61 (2.26, 3.01)	2.62 (2.33, 2.95)
Vss (mL/kg)	57.9 (54.1, 62.0)	49.5 (44.1, 55.6)	59.4 (52.7, 67.0)

[1]PK parameters are presented in Geometric Mean (95% CI)
Abbreviations: IR=incremental recovery; CI = confidence interval; AUC = area under the FVIII activity time curve; $t_{1/2}$ = terminal half-life; CL = clearance; MRT = mean residence time; Vss = volume of distribution at steady-state

Population Pharmacokinetics

A population PK model was developed based on FVIII activity data from 249 subjects of all ages (≤65 years of age) and weighing between 13.4 kg and 132.4 kg in three clinical studies (16 subjects in a Phase 1/2a study, 164 subjects in Study 1, and 69 subjects in Study 2). The population estimate for the typical CL and steady-state volume of distribution of ELOCTATE are 1.56 dL/h and 35.7 dL, respectively. The model was used to predict the activity time profile following a single dose of ELOCTATE in patients with severe haemophilia A (see Table 20, see Table 21, see Table 22). In addition the model was used to predict trough activity for three different prophylaxis regimens (see Table 23).

Table 20 - Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE in Subjects ≥ 12 Years of Age[1]

Dose (IU/kg)	Time (h)							
	EOI[2]	12	18	24	36	48	72	96
	Median (5th, 95th Prediction Interval)							
20	39.7 (28.8, 54.4)	21.9 (13.2, 31.8)	16.5 (8.42, 26.0)	12.6 (5.33, 21.6)	7.59 (2.23, 15.4)	4.62 (0.981, 11.4)	1.78 (<0.5*, 6.44)	0.732 (<0.5*, 3.76)
30	59.5 (43.2, 81.6)	32.9 (19.9, 47.8)	24.8 (12.6, 39.0)	18.9 (7.99, 32.4)	11.4 (3.35. 23.1)	6.93 (1.47, 17.2)	2.68 (<0.5*, 9.66)	1.10 (<0.5*, 5.64)
40	79.4 (57.5, 109)	43.9 (26.5, 63.7)	33.1 (16.8, 51.9)	25.2 (10.7, 43.2)	15.2 (4.46, 30.8)	9.24 (1.96, 22.9)	3.57 (<0.5*, 12.9)	1.46 (<0.5*, 7.52)
50	99.2 (71.9, 136)	54.8 (33.1, 79.6)	41.4 (21.0, 64.9)	31.5 (13.3, 54.0)	19.0 (5.58, 38.6)	11.6 (2.45, 28.6)	4.46 (0.589, 16.1)	1.83 (<0.5*, 9.40)
60	119 (86.3, 163)	65.8 (39.7, 95.5)	49.6 (25.3, 77.9)	37.8 (16.0, 64.8)	22.8 (6.69, 46.3)	13.9 (2.94, 34.3)	5.35 (0.707, 19.3)	2.20 (<0.5* , 11.3)
65	129 (93.5, 177)	71.3 (43.0, 104)	53.8 (27.4, 84.4)	41.0 (17.3, 70.2)	24.7 (7.25, 50.1)	15.0 (3.19, 37.2)	5.80 (0.766, 20.9)	2.38 (<0.5*, 12.2)

[1] See Dosage and Administration, [2] End of Infusion, * Below the level of quantitation of 0.5 IU/dL

Table 21 - Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE in Subjects 6 to <12 Years[1]

Dose (IU/kg)	Time (h)							
	EOI[2]	12	18	24	36	48	72	96
	Median (5th, 95th Prediction Interval)							
20	37.8 (27.2, 52.2)	18.6 (11.2, 27.9)	13.3 (6.74, 21.7)	9.62 (4.11, 17.4)	5.18 (1.60, 11.5)	2.90 (0.666, 7.79)	0.961 (<0.5*, 3.72)	<0.5* (<0.5*, 1.85)
30	56.7 (40.8, 78.2)	27.9 (16.9, 41.9)	20.0 (10.1, 32.6)	14.4 (6.16, 26.1)	7.77 (2.40, 17.2)	4.35 (1.00, 11.7)	1.44 (<0.5*, 5.58)	0.499 (<0.5*, 2.77)
40	75.6 (54.4, 104)	37.2 (22.5, 55.8)	26.6 (13.5, 43.4)	19.2 (8.22, 34.8)	10.4 (3.20, 23.0)	5.80 (1.33, 15.6)	1.92 (<0.5*, 7.45)	0.665 (<0.5*, 3.70)
50	94.5 (68.0, 130)	46.5 (28.1, 69.8)	33.3 (16.9, 54.3)	24.0 (10.3, 43.6)	12.9 (4.00, 28.7)	7.25 (1.67, 19.5)	2.40 (<0.5*, 9.31)	0.832 (<0.5*, 4.62)
60	113 (81.7, 156)	55.8 (33.7, 83.8)	40.0 (20.2, 65.1)	28.9 (12.3, 52.3)	15.5 (4.79, 34.4)	8.70 (2.00, 23.4)	2.88 (<0.5*, 11.2)	1.00 (<0.5*, 5.55)
65	123 (88.5, 170)	60.5 (36.5, 90.7)	43.3 (21.9, 70.6)	31.3 (13.4, 56.6)	16.8 (5.19, 37.3)	9.42 (2.17, 25.3)	3.12 (<0.5*, 12.1)	1.08 (<0.5*, 6.01)
80	151 (109, 209)	74.5 (45.0, 112)	53.3 (27.0, 86.9)	38.5 (16.4, 69.7)	20.7 (6.39, 45.9)	11.6 (2.67, 31.2)	3.85 (0.551, 14.9)	1.33 (<0.5*, 7.40)

[1] See Dosage and Administration, [2] End of Infusion, * Below the level of quantitation of 0.5 IU/dL

Table 22 - Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE in Subjects < 6 Years[1]

Dose (IU/kg)	Time (h)							
	EOI[2]	12	18	24	36	48	72	96
	Median (5th, 95th Prediction Interval)							
20	36.5 (26.3, 50.4)	16.1 (9.44, 24.4)	10.9 (5.28, 18.4)	7.52 (2.98, 14.3)	3.73 (1.02, 9.04)	1.93 (<0.5*, 5.76)	0.545 (<0.5*, 2.45)	<0.5* (<0.5*, 1.05)
30	54.7 (39.4, 75.5)	24.1 (14.2, 36.6)	16.4 (7.92, 27.6)	11.3 (4.46, 21.4)	5.60 (1.54, 13.6)	2.90 (0.582, 8.64)	0.817 (<0.5*, 3.68)	<0.5* (<0.5*, 1.58)
40	73.0 (52.5, 101)	32.2 (18.9, 48.9)	21.9 (10.6, 36.8)	15.0 (5.95, 28.6)	7.46 (2.05, 18.1)	3.86 (0.776, 11.5)	1.09 (<0.5*, 4.91)	<0.5* (<0.5*, 2.11)
50	91.2 (65.7, 126)	40.2 (23.6, 61.1)	27.4 (13.2, 46.1)	18.8 (7.44, 35.7)	9.33 (2.56, 22.6)	4.83 (0.971, 14.4)	1.36 (<0.5*, 6.13)	<0.5* (<0.5*, 2.64)
60	109 (78.8, 151)	48.2 (28.3, 73.3)	32.8 (15.8, 55.3)	22.6 (8.93, 42.8)	11.2 (3.07, 27.1)	5.79 (1.17, 17.3)	1.63 (<0.5*, 7.36)	<0.5* (<0.5*, 3.16)
65	119 (85.4, 164)	52.3 (30.7, 79.4)	35.6 (17.2, 59.9)	24.4 (9.67, 46.4)	12.1 (3.33, 29.4)	6.27 (1.26, 18.7)	1.77 (<0.5*, 7.97)	0.521 (<0.5*, 3.43)
80	146 (105, 201)	64.3 (37.7, 97.7)	43.8 (21.1, 73.7)	30.1 (11.9, 57.1)	14.9 (4.10, 36.2)	7.72 (1.55, 23.0)	2.18 (<0.5*, 9.81)	0.641 (<0.5*, 4.22)

[1] See Dosage and Administration, [2] End of Infusion, * Below the level of quantitation of 0.5 IU/dL

Table 23 - Predicted steady state troughs [IU/dL] of ELOCTATE activity with 50 IU/kg administered every 3, 4, or 5 days by Age Category

	<6 Years	6 to <12 Years	≥ 12 Years of Age
Dosing Frequency	Median (5th, 95th Prediction Interval)		
Every 3 Days	1.40 (<0.5*, 6.26)	2.49 (<0.5*, 10.1)	4.78 (0.654, 21.1)
Every 4 Days	<0.5* (<0.5*, 2.84)	0.797 (<0.5*, 4.86)	1.84 (<0.5*, 11.0)
Every 5 Days	<0.5* (<0.5*, 1.17)	<0.5* (<0.5*, 2.31)	0.766 (<0.5*, 5.59)

* Below the level of quantitation of 0.5 IU/dL

A dosing regimen of 50 IU/kg every 5 days is predicted to yield troughs above 1 IU/dL in 42.6% of individuals ≥12 years of age.

ELOCTATE has been evaluated in 249 male haemophilia A PTPs ≤65 years of age and weighing between 13.4 kg and 132.4 kg. Body weight, a surrogate for age, affected clearance and volume of distribution. After accounting for weight, age did not impact PK.

No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on ELOCTATE disposition.

Race and ethnicity have no observed effect on the pharmacokinetics of ELOCTATE.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Efmoroctocog alfa has not been evaluated in mutagenicity or chromosomal aberration assays since it is a replacement protein factor for coagulation.

Carcinogenicity

No animal studies investigating carcinogenicity effects of efmoroctocog alfa have been conducted since it is a replacement factor for coagulation activity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder

Sucrose

Sodium chloride

Histidine

Calcium chloride dihydrate

Polysorbate 20

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

5 years. The expiry date can be found on the packaging.

Reconstituted solution

The reconstituted product can be stored at room temperature (up to 30°C) for 6 hours. Protect product from direct sunlight. If product is not used within 6 hours, it must be discarded. The appearance of the reconstituted product should be clear to slightly opalescent and colourless.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light. Unopened vials should be stored under controlled refrigeration (2°C - 8°C). Do not freeze.

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. The product must be used or discarded before the end of this period.

ELOCTATE does not contain any preservative or antimicrobial agent and is for use in one patient on one occasion only.

Dispose of all the materials in accordance with local requirements.

For storage conditions of the reconstituted medicinal product, see Section 6.3 SHELF LIFE.

6.5 NATURE AND CONTENTS OF CONTAINER

A powder vial (type 1 glass) with a stopper (butyl) and a flip-off seal (aluminium), 3 mL solvent in a pre-filled syringe (type 1 glass) with a plunger stopper (butyl), a tip-cap (butyl), and a sterile vial adapter reconstitution device. ELOCTATE is available in 5 vial sizes - 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU. Actual factor VIII activity in International Units is stated on the label of each ELOCTATE carton and vial.

3 mL diluent in a pre-filled syringe (type I glass) with a plunger stopper (butyl), a tipcap (butyl), and a sterile vial adaptor reconstitution device.

Pack size

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine should be disposed of by taking to your local pharmacy. The syringe and needle cap should be disposed of in a sharps container.

6.7 PHYSICOCHEMICAL PROPERTIES

ELOCTATE (efmoroctocog alfa) (rhu) is a long-acting, fully recombinant fusion protein consisting of a human coagulation factor VIII (FVIII) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1). The factor VIII portion of efmoroctocog alfa has a primary amino acid sequence and post-translational modifications that are comparable to the 90 + 80 kDa form of factor VIII (i.e. B-domain deleted). The Fc domain of efmoroctocog alfa contains the

hinge, CH2 and CH3 regions of IgG1. Efmoroctocog alfa contains 1890 amino acids with an apparent molecular weight of approximately 220 kilodaltons.

CAS number

1270012-79-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

27 June 2014

10 DATE OF REVISION

07 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address updated