

## NEW ZEALAND DATA SHEET

### 1 ELOCTATE (POWDER FOR INFUSION)

Eloctate 250 International Units (IU) powder for infusion

Eloctate 500 IU powder for infusion

Eloctate 750 IU powder for infusion

Eloctate 1000 IU powder for infusion

Eloctate 1500 IU powder for infusion

Eloctate 2000 IU powder for infusion

Eloctate 3000 IU powder for infusion

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains nominally 250, 500, 750, 1000, 1500, 2000, or 3000 International Units (IU) of efmoctocog alfa (rhu).

Each pre-filled syringe contains 3 mL of solvent.

Efmoctocog 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 efmoctocog 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.

Excipient with known effect: 0.6 mmol (14 mg) sodium per vial. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

### 3 PHARMACEUTICAL FORM

Powder for infusion.

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

The liquid diluent, sterilised water for injections (sWFI) 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:

$$IU/dL \text{ (or \% of normal)} = [Total \text{ Dose (IU)}/body \text{ weight (kg)}] \times 2 \text{ (IU/dL per IU/kg)}$$

OR

$$Dose \text{ (IU)} = body \text{ weight (kg)} \times Desired \text{ Factor VIII Rise (IU/dL or \% of normal)} \times 0.5 \text{ (IU/kg per IU/dL)}$$

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)
<b>Minor and Moderate</b> For example: joint, superficial muscle/no neurovascular compromise (except iliopsoas), deep laceration and renal, superficial soft tissue, mucous membranes	40-60	<b>20-30 IU/kg</b> Repeat every 24-48 hours (12-24 hours for patients less than 12 years of age) until bleeding is resolved
<b>Major</b> For example: iliopsoas and deep muscle with neurovascular injury, or substantial blood loss, retroperitoneum, CNS, throat and neck, gastrointestinal.	80-100	<b>40-50 IU/kg</b> 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 (*see – 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)
<b>Minor</b> Minor operations including uncomplicated dental extraction	<b>50-80</b>	<b>25-40 IU/kg</b> 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.
<b>Major</b> Major operations including intra-abdominal, joint replacement surgery.	<b>80-120</b>	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 (rFVIIIc) 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.

### **Use in Patients with Renal Impairment**

ELOCTATE has not been studied in patients with renal impairment.

### **Use in patients with hepatic impairment**

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

### **Effects on Ability to Drive and Use Machines**

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

## **4.3 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 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. 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*).

##### **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 patients with renal impairment**

ELOCTATE has not been studied in patients with renal impairment.

##### **Use in patients with 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 (*see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Efficacy and Safety*). 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*).

## **Effect on Laboratory Tests**

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

## **4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

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 efmoctocog alfa. It is not known whether efmoctocog alfa 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 efmoctocog alfa.

### **Pregnancy**

Category C

Animal reproductive studies have not been conducted with efmoctocog alfa, however ELOCTATE 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

efmoroctocog alfa 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.

### **Breast-feeding**

Lactation studies have not been conducted with ELOCTATE. It is not known whether

ELOCTATE 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 UNDESIRABLE EFFECTS**

The adverse drug reactions with an incidence  $\geq 0.5\%$  for ELOCTATE were arthralgia, malaise, myalgia, headache and rash.

No serious adverse drug reactions were reported in subjects who received ELOCTATE.

ELOCTATE has been evaluated in five completed studies (Study 1, 2, 3 and two pharmacokinetic studies) in previously treated patients (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. 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) were reported in 11 of 233 (4.7%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. Adverse drug reactions are considered adverse events assessed as related to treatment with ELOCTATE. No age-specific differences in ADRs were observed between paediatric and adult subjects. Adverse drug reactions 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**

MedDRA <sup>2</sup> System Organ Class	MedDRA Preferred Term	N=276*	
		Number of Subjects n (%)	Frequency Category <sup>3</sup> 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 <sup>1</sup>	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.

<sup>1</sup> Investigator term: *vascular pain after injection of study drug*

<sup>2</sup> MedDRA version 15.0

<sup>3</sup>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)

## Post Marketing Experience

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

- FVIII inhibitor
- Hypersensitivity



## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare professionals are asked to report any suspected adverse reactions  
<https://nzphvc.otago.ac.nz/reporting/>

### 4.9 OVERDOSE

No symptoms of overdose have been reported. For information on the management of overdose, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

## 5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Recombinant antihaemophilic factor, Fc fusion protein.

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 registry number: 1270012-79-7

### 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 cofactor 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 efficacy and safety**

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

#### **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 (PTPs) 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  $\geq 6$  months on study, approximately 30% achieved a mean dosing interval of  $\geq 5$  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 individualized 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 previously treated patients 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 4: Treatment groups, dose and dosage intervals for subjects from Study 1 who participated in Study 3**

	<b>Individualised prophylaxis</b>	<b>Weekly prophylaxis</b>	<b>Personalised prophylaxis</b>	<b>Episodic treatment</b>
Number of subjects in Study 3	190	34	26	13
Average <sup>1</sup> 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
Average <sup>1</sup> 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)

<sup>1</sup>Median (interquartile range)

**Table 5: Treatment groups, dose and dosage intervals for subjects from Study 2 who participated in Study 3**

	<b>Individualised prophylaxis</b>	<b>Personalised prophylaxis</b>
Number of subjects from Study 2	59	3
<b>Subjects &lt;6 years</b>		
Number of subjects	29	2
Average <sup>1</sup> 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)
<b>Subjects 6 - &lt;12 years</b>		
Number of subjects	30	1
Average <sup>1</sup> 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 (4.52 - , 84.52 IU/kg)

<sup>1</sup>Median (interquartile range)

### ***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 6.

**Table 6: Summary of Median (IQR)<sup>1</sup> Annualised Bleeding Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age**

<b>Bleeding Aetiology</b>	<b>Episode</b>	<b>Individualised Prophylaxis (N=117)</b>	<b>Weekly Prophylaxis (N=23)</b>	<b>Episodic (On-Demand) (N=23)</b>
<b>Overall ABR</b>		1.60 (0.0, 4.69)	3.59 (1.86, 8.36)	33.57 (21.14, 48.69)
<b>Spontaneous ABR</b>		0.00 (0.0, 2.03)	1.93 (0.0, 4.78)	20.24 (12.21, 36.81)

<b>Bleeding Aetiology</b>	<b>Episode</b>	<b>Individualised Prophylaxis (N=117)</b>	<b>Weekly Prophylaxis (N=23)</b>	<b>Episodic (On-Demand) (N=23)</b>
	<b>Traumatic ABR</b>	0.00 (0.0, 1.83)	1.69 (0.00, 3.27)	9.25 (1.74, 11.92)
	<b>Joint ABR</b>	0.00 (0.00, 3.11)	1.93 (0.00, 7.62)	22.76 (15.07, 39.02)

<sup>1</sup> Median (interquartile range, 25<sup>th</sup> and 75<sup>th</sup> 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 7.

**Table 7: Summary of Median (IQR) 1 Annualized Bleeding Rate (ABR) in Paediatric Subjects < 12 Years of Age**

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

<sup>1</sup> Median (interquartile range, 25<sup>th</sup> and 75<sup>th</sup> 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 8.

**Table 8: Summary of Median (IQR)<sup>1</sup> Annualized Bleeding Rate (ABR) by Treatment Arm in Subjects ≥ 12 Years of Age<sup>2</sup>**

<b>Bleeding Episode Aetiology</b>	<b>Individualised Prophylaxis (N=110)</b>	<b>Personalised Prophylaxis (N=21)</b>	<b>Prophylaxis (N=27)</b>	<b>On-Demand (N=13)</b>
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)

<sup>1</sup> Median (interquartile range, 25th and 75th percentiles)

<sup>2</sup> 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 9.

**Table 9: Summary of Median (IQR)<sup>1</sup> Annualized Bleeding Rate (ABR) by Treatment Arm in Subjects < 12 Years of Age<sup>2</sup>**

<b>Bleeding Episode Aetiology</b>	<b>Individualised Prophylaxis</b>	<b>Personalised Prophylaxis</b>
<b>&lt; 6 Years</b>	<b>(N=29)</b>	<b>(N=2)</b>
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)
<b>6-12 Years</b>	<b>(N=30)</b>	<b>(N=1)</b>
Overall ABR	1.59 (0.55, 3.55)	1.01
Spontaneous ABR	0.30 (0.00, 0.89)	0.00

<b>Bleeding Episode Aetiology</b>	<b>Individualised Prophylaxis</b>	<b>Personalised Prophylaxis</b>
Traumatic ABR	1.00 (0.00, 2.06)	1.01
Spontaneous Joint ABR	0.00 (0.00, 0.55)	0.00

<sup>1</sup> Median (interquartile range, 25th and 75th percentiles)

<sup>2</sup> Study subjects could change treatment groups during the study

### ***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 10.

**Table 10: Summary of Efficacy in Control of Bleeding in Subjects ≥ 12 Years of Age**

<b>New bleeding episodes</b>	<b>(n= 757)</b>	
<b># of Injections to treat bleeding episodes</b>	<b>1 injection</b>	661 (87.3%)
	<b>2 injections</b>	79 (10.4%)
	<b>3 injections</b>	13 (1.7%)
	<b>≥4 injections</b>	4 (0.5%)
	(n=755)	
<b>Median dose per injection (IU/kg) to treat a bleeding episode (IQR)</b>	27.35 (22.73, 32.71)	
<b>Median total dose (IU/kg) to treat a bleeding episode (IQR)</b>	28.23 (23.26, 46.88)	
<b>Response to first injection</b>	(n= 745)	
	<b>Excellent or good</b>	78.1%
	<b>Moderate</b>	21.2%
	<b>No response</b>	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 summarized in Table 11.



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 11: Summary of Efficacy in Control of Bleeding in Paediatric Subjects < 12 Years of Age**

	<b>&lt;6 Years (n=35)</b>	<b>6 to &lt;12 Years (n=34)</b>	<b>Total (&lt; 12 Years) (n=69)</b>
<b>New bleeding episodes</b>	(n=38)	(n=48)	(n=86)
<b># of Injections to treat bleeding episodes</b>			
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%)
<b>Median dose per injection (IU/kg) to treat a bleeding episode (IQR)</b>	51.35 (29.94, 59.52)	48.15 (29.08, 55.97)	49.69 (29.41, 56.82)
<b>Median total dose (IU/kg) to treat a bleeding episode (IQR)</b>	56.40 (29.94, 72.46)	53.49 (29.08, 66.80)	54.90 (29.41, 71.09)
<b>Response to first injection</b>	(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%)

### 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 12.

**Table 12: Efficacy in Control of Bleeding in Adults and Adolescents**

<b>Bleeding episodes</b>	<b>(N=757)</b>
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)

<b>Bleeding episodes</b>	<b>(N=757)</b>
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 to 12 hours post treatment. Efficacy in control of bleeding episodes in subjects < 12 years old is summarised in Table 13.

**Table 13: Efficacy in Control of Bleeding in Paediatric Subjects**

		<b>1 to 5 Years (n=35)</b>	<b>6 to 11 Years (n=34)</b>	<b>Total (&lt;12 Years) (n=69)</b>
New Bleeding episodes		(n=38)	(n=48)	(n=86)
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 (8.6%)	1 (2.2%)	4 (4.9%)
	None	0 (0.0%)	2 (4.3%)	2 (2.5%)

### 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 rFVIII<sup>FC</sup> 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 14.

**Table 14: Summary of Haemostatic Response During Surgery and Post-Operatively\***

	Number of Procedures (Number of Subjects)	Response			
		Excellent	Good	Fair	Poor/None
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 (rFVIII<sub>Fc</sub>) 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 15.

**Table 15: Pharmacokinetic Parameters of ELOCTATE (rFVIII<sub>Fc</sub>) and ADVATE (rFVIII)**

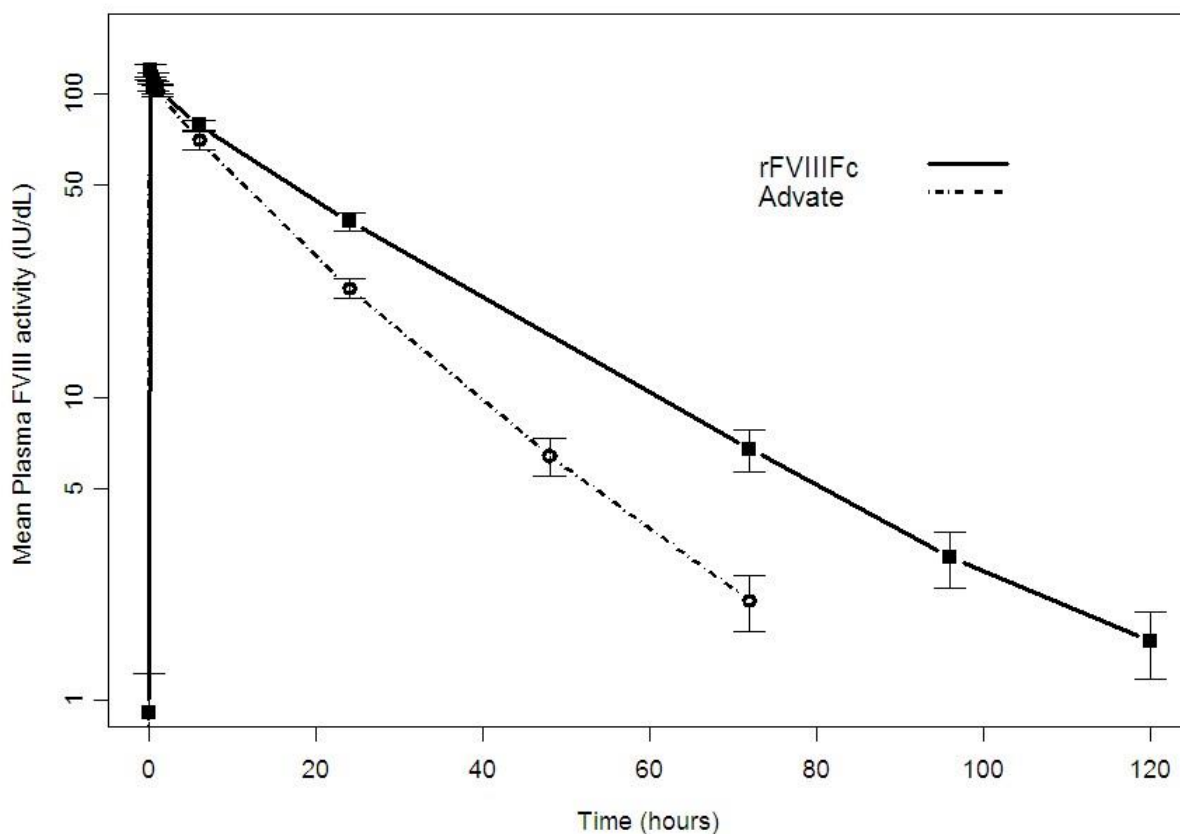
PK Parameters <sup>1</sup>	ELOCTATE (95% CI)	ADVATE (95% CI)	Ratio of ELOCTATE to ADVATE (95% CI)
	N=28	N=28	N=28
$C_{max}$ (IU/dL)	108 (101, 115)	120 (111, 128)	0.90 (0.86, 0.95)
AUC/Dose (IU*h/dL per IU/kg)	51.2 (45.0, 58.4)	32.9 (29.3, 36.9)	1.56 (1.46, 1.67)
$t_{1/2}$ (h)	19.0 (17.0, 21.1)	12.4 (11.1, 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)

PK Parameters <sup>1</sup>	ELOCTATE (95% CI)	ADVATE (95% CI)	Ratio of ELOCTATE to ADVATE (95% CI)
MRT (h)	25.2 (22.7, 27.9)	16.8 (15.2, 18.6)	1.49 (1.41, 1.58)
V <sub>ss</sub> (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)

<sup>1</sup>PK parameters are presented in Geometric Mean (95% CI)

Abbreviations: CI = confidence interval; C<sub>max</sub> = maximum activity; AUC = area under the FVIII activity time curve; t<sub>1/2</sub> = terminal half-life; CL = clearance; MRT = mean residence time; V<sub>ss</sub> = volume of distribution at steady-state

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



\*Standard error

## Paediatric Pharmacokinetics

Pharmacokinetic (PK) parameters of ELOCTATE (rFVIII<sup>h</sup>) 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 16 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 16: Comparison of PK Parameters of ELOCTATE (rFVIII<sup>h</sup>) by Age Category**

PK Parameters <sup>1</sup>	Study 2		Study 1
	<6 Years (1, 5)	6 to <12 Years (6, 11)	12 to < 18 Years (12, 17)
	N = 23	N = 31	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)
t <sub>1/2</sub> (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)
V <sub>ss</sub> (mL/kg)	57.9 (54.1, 62.0)	49.5 (44.1, 55.6)	59.4 (52.7, 67.0)

<sup>1</sup>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 ( $\leq 65$  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 17, Table 18, and Table 19). In addition, the model was used to predict trough activity for three different prophylaxis regimens (see Table 20).

**Table 17: Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE in Subjects  $\geq 12$  Years of Age<sup>1</sup>**

Dose (IU/kg)	Time (h)							
	EOI <sup>2</sup>	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)

<sup>1</sup> See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, <sup>2</sup> End of Infusion, \* Below the level of quantitation of 0.5 IU/dL

**Table 18: Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE in Subjects 6 to <12 Years<sup>1</sup>**

Dose (IU/kg)	Time (h)							
	EOI <sup>2</sup>	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)

<sup>1</sup> See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, <sup>2</sup> End of Infusion \* Below the level of quantitation of 0.5 IU/dL

**Table 19: Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE in Subjects < 6 Years<sup>1</sup>**

Dose (IU/kg)	Time (h)							
	EOI <sup>2</sup>	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)

<sup>1</sup> See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, <sup>2</sup> End of Infusion, \* Below the level of quantitation of 0.5 IU/dL



**Table 20: Predicted steady state troughs [IU/dL] of ELOCTATE activity with 50 IU/kg administered every 3, 4, or 5 days by Age Category**

	<b>&lt;6 Years</b>	<b>6 to &lt;12 Years</b>	<b>≥ 12 Years of Age</b>
<b>Dosing Frequency</b>	Median (5th, 95th Prediction Interval)		
<b>Every 3 Days</b>	1.40 (<0.5*, 6.26)	2.49 (<0.5*, 10.1)	4.78 (0.654, 21.1)
<b>Every 4 Days</b>	<0.5* (<0.5*, 2.84)	0.797 (<0.5*, 4.86)	1.84 (<0.5*, 11.0)
<b>Every 5 Days</b>	<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 patients ≤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**

Sodium chloride

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**

4 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 after reconstitution of the medicine, see *Section 6.3 SHELF LIFE*.

## **6.5 NATURE AND CONTENTS OF CONTAINER AND SPECIAL EQUIPMENT FOR USE, ADMINISTRATION OR IMPLANTATION**

### **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 7 vial sizes - 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU. Actual factor VIII activity in International Units is stated on the label of each ELOCTATE carton and vial.

### **Solvent**

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 AND OTHER HANDLING**

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.

## **7 MEDICINE SCHEDULE**

General sale

## **8 SPONSOR**

sanofi-aventis new zealand limited

Level 8, 56 Cawley Street

Ellerslie

Auckland

New Zealand

Phone: 0800 283 684

## 9 DATE OF FIRST APPROVAL

27 August 2015

## 10 DATE OF REVISION OF THE TEXT

22 September 2020

### SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Added excipient with known effect
4.8	Adverse reactions from Study 3 were included in the section
5.1	Clinical Trials – Results from Study 3 were included in the section
10	Date of revision changed

# ELOCTATE® (E-lok-tate)

## efmoroctocog alfa (rhu)

*Recombinant coagulation factor VIII Fc fusion protein 250, 500, 750, 1000, 1500, 2000, 3000 IU/vial for IV infusion*

### Directions for Use

Read all the instructions before you start. If you have any questions about this guide, ask your doctor or pharmacist. Your healthcare provider should show you or your caregiver how to reconstitute and administer ELOCTATE the first time ELOCTATE is used.

There are 5 steps, explained in this guide:

- A. Setting up**
- B. Reconstituting the injection**
- C. Pooling**
- D. Giving the injection**
- E. Post-Infusion Care & Disposal**

Take time to read through each section and keep this leaflet with your medicine as a reminder of what to do.

#### A. Setting up

**A1.** First ensure that your work area is clean.

**A2.** Collect everything you will need. Check the expiry date on the ELOCTATE kit. If it is out of date, do not use it and contact your pharmacy immediately. If refrigerated, allow the vial of ELOCTATE and the pre-filled diluent syringe to warm to room temperature (15°C to 30°C) for approximately 30 minutes. Do not use heat sources (for example, hot water or a heater) to warm the contents.

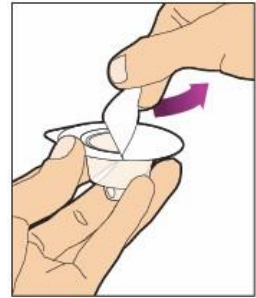
**A3.** Wash your hands thoroughly with soap and water before performing the following procedures.

**A4.** Use aseptic technique (clean and germ-free) and a flat work surface during the reconstitution procedure.

**A5.** Remove the plastic cap from the ELOCTATE vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.



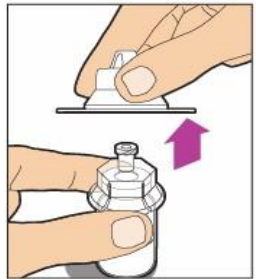
**A6.** Completely remove the backing from the vial adapter package by peeling back the lid. **Do not remove the vial adapter from the package or touch the inside of the package or the adapter.**



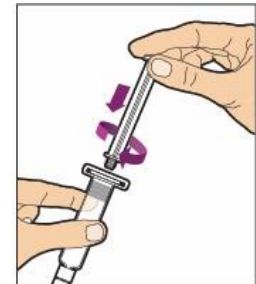
**A7.** Keep the vial on a flat surface. Hold the vial adapter package with one hand and using the other hand, place the vial adapter over the vial. The spike should be placed directly above the centre of the rubber stopper. Push the vial adapter straight down until the adapter spike punctures the centre of the vial stopper and is fully inserted.



**A8.** Lift the package cover away from the vial adapter and discard the cover.

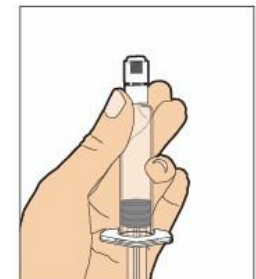


**A9.** Take the plunger rod and syringe out of the package. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn in a clockwise direction until it is securely attached. Only use the diluent syringe provided to reconstitute the drug product.

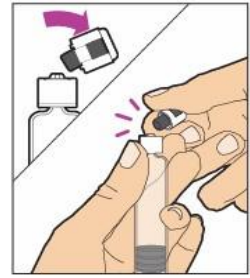


## **B. Reconstituting the injection**

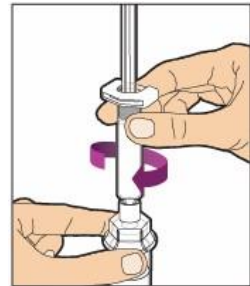
**B1.** With one hand, hold the diluent syringe right under the cap, and with the cap pointing up. Make sure you are holding the diluent syringe by the ridged part directly under the cap. **Do not use if the cap has been removed or is not securely attached.**



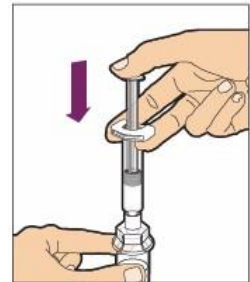
**B2.** With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe. **Do not touch the glass tip of the syringe or the inside of the cap.**



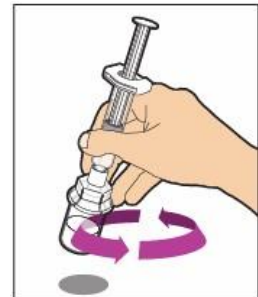
**B3.** Be sure the vial is sitting on a flat surface. Insert the tip of the syringe into the adapter opening. Turn the syringe in a clockwise direction until it is securely attached to the adapter.



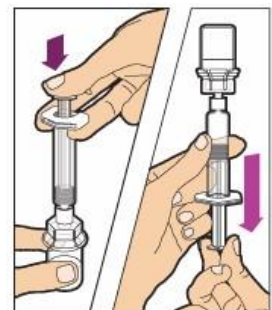
**B4.** Slowly depress the plunger rod to inject all of the diluent into the vial. The plunger rod may rise slightly after this process. This is normal.



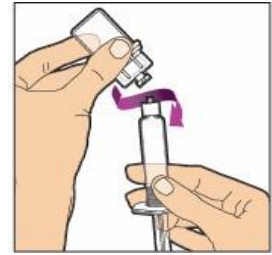
**B5.** With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. The appearance of the solution should be clear to slightly opalescent and colourless. **Do not shake. Do not use the reconstituted ELOCTATE if it contains visible particles or is cloudy.**



**B6.** Make sure the plunger rod is completely depressed. Turn the vial upside-down. Slowly pull on the plunger rod to draw the solution into the syringe. **Be careful not to pull the plunger rod completely out of the syringe.**



**B7.** Gently unscrew the syringe from the vial adapter and dispose of the vial with the adapter still attached. **Do not touch the syringe tip or the inside of the cap.**



**B8.** Your ELOCTATE is now ready to be connected to your infusion tubing set. See section D below. Reconstituted ELOCTATE should be administered as soon as possible.

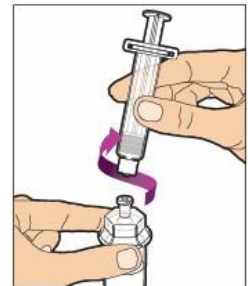
## C. Pooling

If you are using two or more reconstituted vials of ELOCTATE, you can follow these pooling steps.

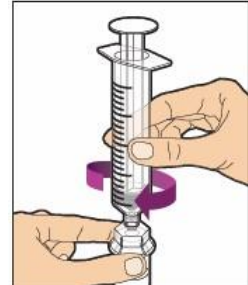
**C1.** Be sure to leave the vial adapter attached to the vial, as you will need it for attaching a large luer lock syringe.

**C2.** Do not detach the diluent syringe or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial (with vial adapter attached).

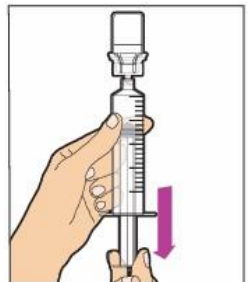
**C3.** Remove the diluent syringe from the vial adapter by turning it counter-clockwise until it is completely detached



**C4.** Attach a separate large luer lock syringe by turning clockwise until it is securely attached.



**C5.** Slowly pull on the plunger rod to draw the solution into the syringe. Repeat this pooling procedure with each vial you will be using. Once you have pooled the required dose, proceed to administration using the large luer lock syringe.



## D. Giving the injection

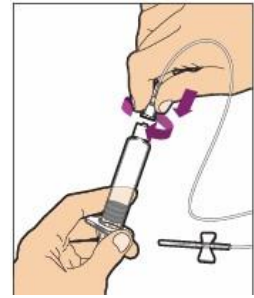
### For Intravenous Use only after Reconstitution

ELOCTATE is administered by intravenous (IV) infusion after reconstitution of the drug powder with the diluent.

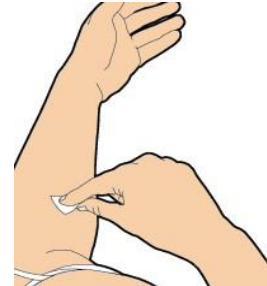
**Do not administer reconstituted ELOCTATE if it contains visible particles, is discoloured, or is cloudy.**



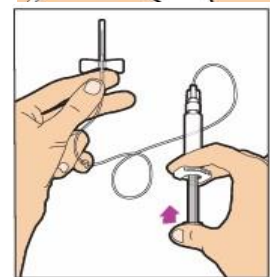
**D1.** Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. **Do not administer reconstituted ELOCTATE in the same tubing or container with other medicinal products. Do not remove the protective needle cover until you are ready to insert the needle** (see section D4 below)



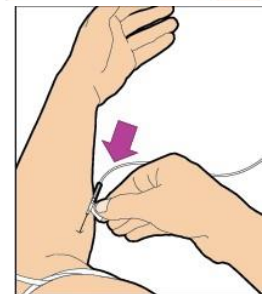
**D2.** Apply a tourniquet and clean the skin area where you will perform the infusion using an alcohol wipe.



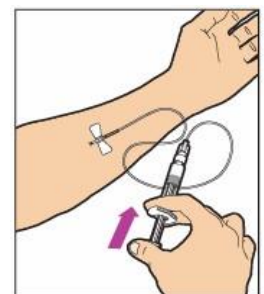
**D3.** Depress the plunger until all air is removed from the syringe and ELOCTATE has reached the end of the infusion set tubing. Do not push ELOCTATE through the needle.



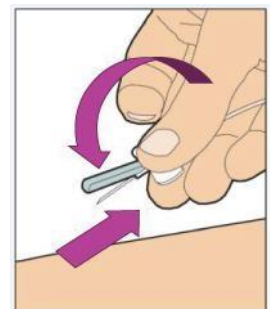
**D4.** Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.



**D5.** Slowly depress the plunger on the syringe to administer ELOCTATE. ELOCTATE should be injected intravenously over several minutes. The rate of administration should be determined by your comfort level. The small amount of drug product left in the infusion set will not affect treatment.



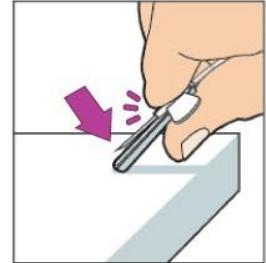
**D6.** After infusing ELOCTATE, flip the safety shield towards the needle. Remove the infusion set.



## E. Post-Infusion Care & Disposal

**E1.** Place the wing and the safety shield between your thumb and index finger.

Press the safety shield against a hard surface until an audible click is heard.



**E2.** Use a sterile gauze to put pressure on the infusion site for several minutes. Apply an adhesive bandage if necessary.



**E3.** A sharps bin should be used for disposal of all unused solution, empty vials and used needles and syringes.