PRODUCT INFORMATION

ELOCTATE (efraloctocog alfa) (rhu) powder and solvent for solution for injection.

NAME OF THE MEDICINE

ELOCTATE (efraloctocog 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 efraloctocog 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 efraloctocog alfa contains the hinge, CH2 and CH3 regions of IgG1. Efraloctocog alfa contains 1890 amino acids with an apparent molecular weight of approximately 220 kilodaltons.

Efraloctocog 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 efraloctocog 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.

CAS registry number: 1270012-79-7

DESCRIPTION

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 (sWFI) is in a pre-filled syringe.

Each single-use vial contains nominally 250, 500, 750, 1000, 1500, 2000, or 3000 International Units (IU) of ELOCTATE. When reconstituted with sWFI, the product contains the following excipients: sucrose, sodium chloride, histidine, calcium chloride, and polysorbate 20.

For intravenous administration only after reconstitution.

PHARMACOLOGY

ELOCTATE (efraloctocog 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 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 efraloctocog alfa is a glycoprotein comparable to the 90+80 kDa form of endogenous FVIII that is found in human plasma. When injected, efraloctocog alfa binds to von Willebrand factor in an individual's circulation, and replaces all functions of the missing FVIII.

The other portion of efraloctocog 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 efraloctocog alfa than endogenous FVIII.

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.

Pharmacodynamics

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.

Pharmacokinetics

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) from a clinical study. The subjects underwent a washout period of at least 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 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*). For ELOCTATE, the maximum activity (Cmax) 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.

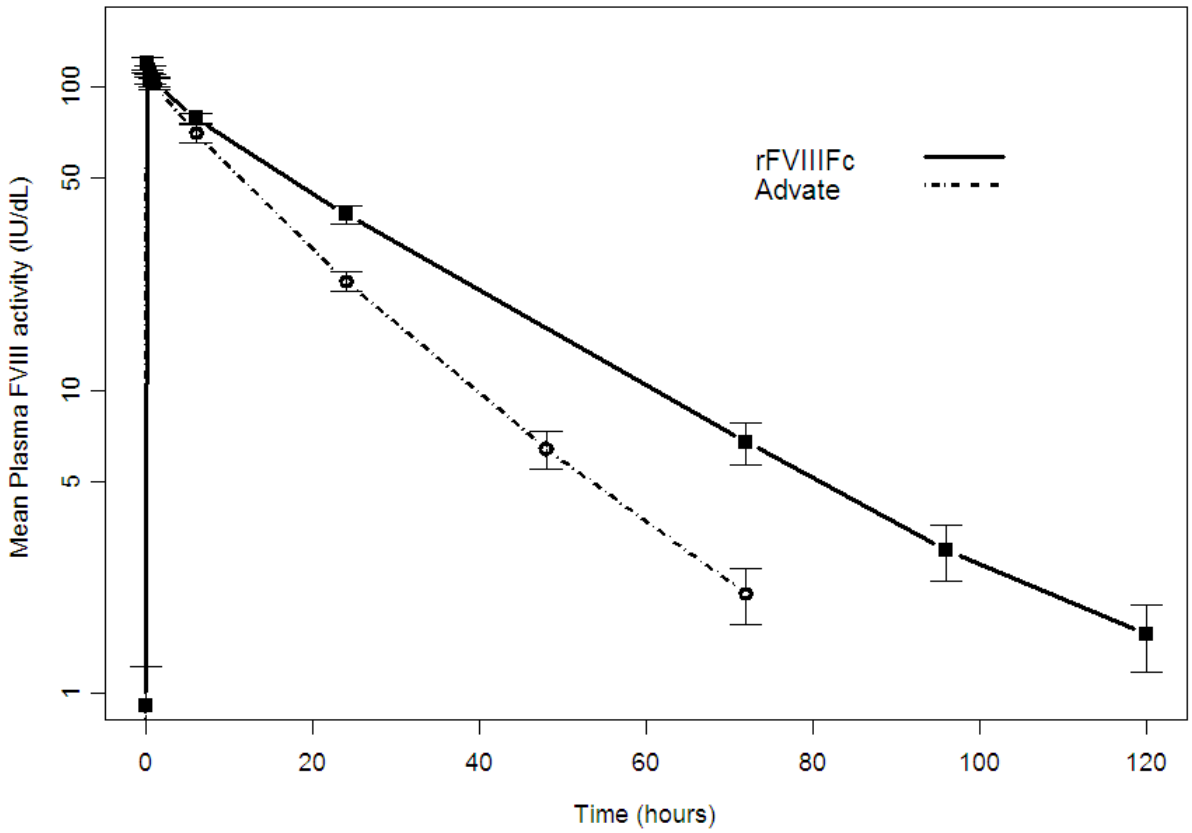
A summary of PK parameters after a 50 IU/kg dose for ELOCTATE and Advate are presented in Table 1.

Table 1: 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**
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)
Terminal half-life [$t_{1/2}$ (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)
MRT (h)	**25.2** (22.7, 27.9)	**16.8** (15.2, 18.6)	**1.49** (1.41, 1.58)
V_{ss} (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)	**4.918** (4.434, 5.455)	**3.298** (2.985, 3.645)	**1.49** (1.41, 1.57)

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

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



*Standard error

A summary of the PK parameters for adolescent (age 12-17 years, N=11) and adult (age ≥18 years, N=144) subjects is given in Table 2.

Table 2: Comparison of PK Parameters of ELOCTATE by Age Category

	12-17 years (N=11)	**≥18 years** (N=144)
Geometric Mean (95% CI)		
Incremental Recovery (IU/dL per IU/kg)	1.81 (1.56, 2.09)	1.92 (1.85, 2.00)
AUC/Dose (IU*h/dL per IU/kg)	39.7 (35.2, 44.8)	45.0 (42.5, 47.8)
Terminal half-life [t1/2 (h)]	16.1 (13.9, 18.5)	17.2 (16.4, 18.0)
MRT (h)	22.6 (19.7, 26.0)	24.3 (23.2, 25.5)

CL (mL/h/kg)	2.52 (2.23, 2.84)	2.22 (2.09, 2.36)
Vss (mL/kg)	57.0 (50.2, 64.7)	54.0 (52.1, 56.0)

A population pharmacokinetic model was developed based on pharmacokinetic data from 180 subjects, from 12 to 65 years old and weighing between 41 kg and 127.4 kg, in two clinical studies (16 subjects in a Phase 1/2a study and 164 subjects in a Phase 3 study). The population estimate for the typical CL of ELOCTATE is 1.65 dL/h, and V_{ss} is 44.4 dL. The model was used to predict the activity time profile following a single dose of ELOCTATE in patients with severe haemophilia A (*see* Table 3). In addition the model was used to predict trough activity for three different prophylaxis regimens (*see* Table 4).

Table 3: Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE[1]

Dose (IU/kg)	**Time (h)**						
	EOI[2]	**12**	**24**	**36**	**48**	**72**	**96**
	Median (5th, 95th Prediction Interval)						
20	38.7 (27.3, 54.5)	22.7 (13.5, 35.0)	13.4 (5.79, 23.8)	7.92 (2.44, 16.7)	4.72 (1.06, 12.0)	1.79 (<0.5*, 6.52)	0.763 (<0.5*, 3.63)
25	48.4 (34.2, 68.1)	28.3 (16.9, 43.7)	16.8 (7.24, 29.8)	9.90 (3.05, 20.8)	5.90 (1.32, 15.0)	2.24 (<0.5*, 8.15)	0.953 (<0.5*, 4.54)
30	58.1 (41.0, 81.7)	34.0 (20.2, 52.5)	20.2 (8.69, 35.8)	11.9 (3.66. 25.0)	7.07 (1.59, 18.0)	2.69 (<0.5*, 9.78)	1.14 (<0.5*, 5.44)
40	77.5 (54.7, 109)	45.3 (27.0, 70.0)	26.9 (11.6, 47.7)	15.8 (4.88, 33.3)	9.43 (2.11, 24.0)	3.58 (<0.5*, 13.0)	1.53 (<0.5*, 7.26)
50	96.8 (68.3, 136)	56.6 (33.7, 87.5)	33.6 (14.5, 59.6)	19.8 (6.10, 41.7)	11.8 (2.64, 30.0)	4.48 (0.615, 16.3)	1.91 (<0.5*, 9.07)
65	126 (88.9, 177)	73.6 (43.8, 114)	43.7 (18.8, 77.5)	25.7 (7.94, 54.2)	15.3 (3.44, 38.9)	5.82 (0.800, 21.2)	2.48 (<0.5*, 11.8)

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

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

Dosing Frequency		
Every 3 Days	**Every 4 Days**	**Every 5 Days**
Median (5th, 95th Prediction Interval)		
5.27 (0.774, 20.4)	2.32 (<0.5*, 11.4)	1.10 (<0.5*, 6.17)

* 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 53.4% of individuals and a dosing regimen of 65 IU/kg administered weekly is predicted to yield troughs above 1 IU/dL in 26.7 % of the individuals treated.

ELOCTATE has been evaluated in 180 male haemophilia A patients from 12 to 65 years old and weighing between 41 kg and 127.4 kg. Age had no effect on the pharmacokinetics of ELOCTATE and body weight had a minor impact.

The pharmacokinetics of ELOCTATE have not been evaluated in paediatric patients with haemophilia A below the age of 12.

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.

CLINICAL TRIALS

The safety, efficacy, and pharmacokinetics of ELOCTATE was evaluated in a multinational, open-label, Phase 3 study that 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 ≥ 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).

A total of nine subjects received ELOCTATE for perioperative management (surgical prophylaxis) in nine major surgical procedures and a total of 12 subjects received ELOCTATE for perioperative management (surgical prophylaxis) in 14 minor surgical procedures.

Efficacy in Routine Prophylaxis

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 based on a negative binomial model.

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 5.

Table 5: Summary of Median (IQR) [1] Annualised Bleeding Rate (ABR) by Treatment Arm

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)*

Efficacy in Control of Bleeding

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 6.

Table 6: Summary of Efficacy in Control of Bleeding

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)
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%

Efficacy in Perioperative Management (Surgical Prophylaxis)

Nine (9) major surgical procedures were performed in nine subjects. Haemostasis was assessed post-operatively by the investigator 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. All subjects received a single pre-operative dose to maintain haemostasis during surgery. The median dose was 51.4 IU/kg (range 50-77). On the day of surgery, most subjects got a second injection. The total dose on the day of surgery

ranged from 65.8-115.4 IU/kg. Three days following surgery, subjects received in the range of 15.3-79.1 IU/kg/day.

Haemostatic response to dosing during surgery and post-operatively is summarised in Table 7.

Table 7: Summary of Haemostatic Response During Surgery and Post-Operatively

	Number of Procedures (Number of Subjects)	Response			
		Excellent	Good	Fair	Poor/None
Major Surgery					
Total Knee Replacement	3 (3)	3			
Knee Joint Replacement – Bilateral	1 (1)	1			
Total Knee Revision	1 (1)	1			
Laproscopic Inguinal Hernia Repair	2 (2)	1	1		
Arthroscopy	1 (1)	1			
Appendectomy	1 (1)	1			
Minor surgery[1]	14 (12)[2]	11	1		

[1] Including 6 tooth extractions, 1 surgical extraction of complete bony impacted tooth, 1 surgical removal of wisdom teeth, 1 dental procedure with deep injection, 3 cystoscopies, 1 gastroscopy and colonoscopy, and 1 wound closure.
[2] Assessment of response not available for 2 minor surgeries

INDICATIONS

ELOCTATE is a long-acting antihaemophilic factor (recombinant) indicated in adults and children (≥12 years) 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.

CONTRAINDICATIONS

ELOCTATE is contraindicated in patients who have manifested severe hypersensitivity reactions, including anaphylaxis, to the product or its components. Severe hypersensitivity reactions were not observed in clinical trials; however, these have been known to occur with use of other factor VIII replacement factors.

PRECAUTIONS

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 PRECAUTIONS - Monitoring Laboratory Tests).*

Anaphylaxis and Severe Hypersensitivity Reactions

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

Neutralising Antibodies (Inhibitors)

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 factor replacement therapy in the treatment of haemophilia A. 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 PRECAUTIONS - 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 DOSAGE AND 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).

Effects on fertility

No fertility studies have been conducted in animals with efraloctocog alfa. It is not known whether efraloctocog 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 efraloctocog alfa.

Use in Pregnancy (Category C)

Animal reproductive studies have not been conducted with efraloctocog alfa. 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 efraloctocog alfa can affect reproductive capacity. Fc fusion products, including efraloctocog 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 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.

Paediatric use

Safety, efficacy, and pharmacokinetics of ELOCTATE have been evaluated in previously treated paediatric patients aged 12 years and older. No dose adjustment is required.

No data are available for patients below the age of 12 years.

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 DOSAGE AND ADMINISTRATION)*.

Genotoxicity

Efraloctocog 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 efraloctocog alfa have been conducted since it is a replacement factor for coagulation activity.

Effect on Laboratory Tests

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

INTERACTIONS WITH OTHER MEDICINES

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

ADVERSE EFFECTS

The most common adverse drug reactions observed in the multinational, open label, Phase 3 clinical study (incidence ≥1%) for ELOCTATE were arthralgia and malaise.

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

In the multinational, open-label, Phase 3 clinical study with ELOCTATE, 164 subjects were evaluated, with 146 subjects treated for at least 26 weeks and 23 subjects treated for at least 39 weeks.

Adverse drug reactions (ADRs) were reported in 9 of 164 (5.5%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. Adverse drug reactions are considered adverse events assessed as related to treatment with ELOCTATE. Adverse drug reactions are summarised in Table 9.

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

Table 9: Adverse Drug Reactions reported for ELOCTATE

MedDRA[2] System Organ Class	MedDRA Preferred Term	N=164[*]		
		Number of Subjects n (%)	Frequency Category[3]	
			Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
General disorders and administration site conditions	Malaise	2 (1.2)	Common	
	Chest pain	1 (0.6)		Uncommon
	Feeling cold	1 (0.6)		Uncommon
	Feeling hot	1 (0.6)		Uncommon
Nervous system disorders	Dizziness	1 (0.6)		Uncommon
	Dysgeusia	1 (0.6)		Uncommon
	Headache	1 (0.6)		Uncommon
Musculoskeletal disorders	Arthralgia	2 (1.2)	Common	
	Joint swelling	1 (0.6)		Uncommon
	Myalgia	1 (0.6)		Uncommon
Gastrointestinal disorders	Abdominal pain, lower	1 (0.6)		Uncommon
	Abdominal pain, upper	1 (0.6)		Uncommon
Vascular disorders	Angiopathy[1]	1 (0.6)		Uncommon
	Hypertension	1 (0.6)		Uncommon
Cardiac disorders	Bradycardia	1 (0.6)		Uncommon
Injury, poisoning, and procedural complications	Procedural hypotension	1 (0.6)		Uncommon

Respiratory, thoracic, and mediastinal disorders	Cough	1 (0.6)		Uncommon
Skin and subcutaneous tissue disorders	Rash	1 (0.6)		Uncommon

[*]164 previously treated patients (PTPs) on routine prophylaxis or episodic (on-demand) therapy
[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)

DOSAGE AND 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.

Careful control of replacement therapy is especially important in cases of life-threatening bleeding episodes or major surgery *(see Table 10 and Table 11).*

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 PRECAUTIONS and PHARMACOLOGY - Pharmacokinetics).*

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)

Control and Prevention of Bleeding Episodes

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

Table 10: 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 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 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 PHARMACOLOGY - Pharmacokinetics).*

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 and perioperative management (surgical prophylaxis):

Table 11: Guide to ELOCTATE Dosing for Perioperative Management (Surgical Prophylaxis)

Type of Surgery	target Factor VIII Level (IU/dL or % of normal)mal)	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 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 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 PHARMACOLOGY - Pharmacokinetics]*

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 PHARMACOLOGY – Pharmacokinetics).*

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.

OVERDOSAGE

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

PRESENTATION AND STORAGE CONDITIONS

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

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

The reconstituted product can be stored at room temperature (up to 30°C) for 6 hours. 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.

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.

NAME AND ADDRESS OF THE SPONSOR

Biogen Idec Australia Pty Ltd
ABN 30 095 760 115
Suite 1, Level 5, 123 Epping Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION ON THE ARTG

27 June 2014

ELOCTATE® (E-lok-tate)

efraloctocog 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.

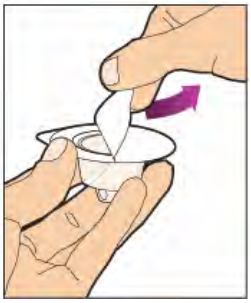
A2. Collect everything you will need. Check the expiry date on the ELOCTATE kit. If it is out of date, do not use it and contact your pharmacy immediately. Allow the vial of ELOCTATE and the pre-filled diluent syringe to warm to room temperature (15°C to 30ºC) for approximately 30 minutes. Do not use 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.

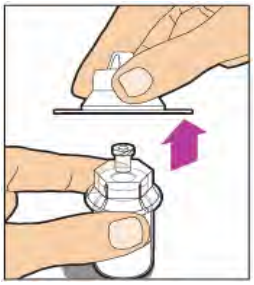
A5. Remove the plastic cap from the ELOCTATE vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.

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.



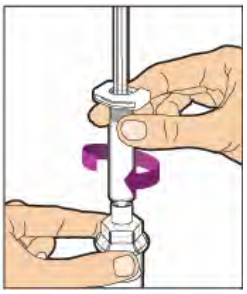
A9. Take the plunger rod and syringe out of the package. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn in a clockwise direction until it is securely attached. Only use the diluent syringe provided to reconstitute the drug product.

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.**

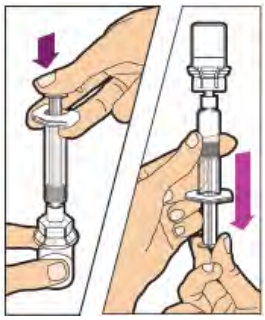
B3. Be sure the vial is sitting on a flat surface. Insert the tip of the syringe into the adapter opening. Turn the syringe in a clockwise direction until it is securely attached to the adapter.



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.

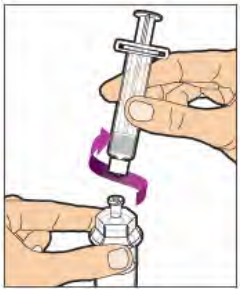
C. Pooling

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.

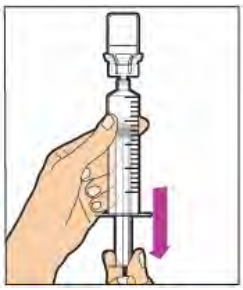
C2. Do not detach the diluent syringe or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial (with vial adapter attached).

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.

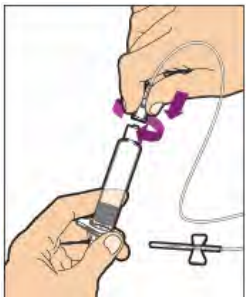


D. Giving the injection

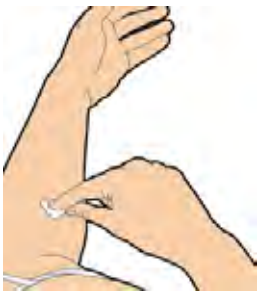
For Intravenous Use only after Reconstitution
ELOCTATE is administered by intravenous (IV) infusion after reconstitution of the drug powder with the diluent.

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

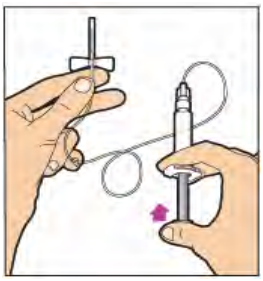
D1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. **Do not administer reconstituted ELOCTATE in the same tubing or container with other medicinal products. Do not remove the protective needle cover until you are ready to insert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

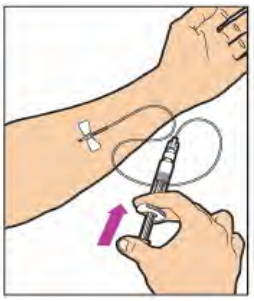


D3. Depress the plunger until all air is removed from the syringe and ELOCTATE has reached the end of the infusion set tubing. Do not push ELOCTATE through the needle.

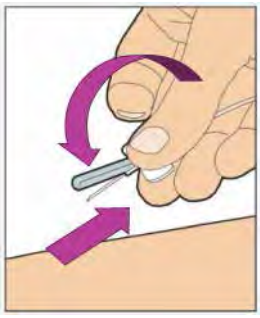


D4. Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.

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.

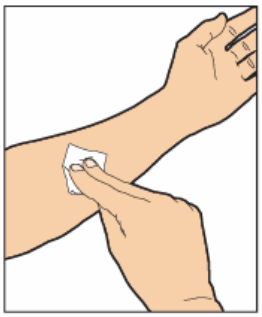


E. Post-Infusion Care & Disposal

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.