PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrELOCTATE®

Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein

Lyophilized Powder for Solution

250, 500, 750, 1000, 1500, 2000 and 3000 IU/vial

Antihemorrhagic Blood Coagulation Factor VIII

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	October 2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Eloctate (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) is an anti-hemophilic factor (recombinant) indicated in adults and children with hemophilia A (congenital factor VIII deficiency) for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes.
- Control and prevention 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.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Eloctate in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see WARNINGS AND PRECAUTIONS, Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized (see DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For intravenous use only after reconstitution

- Treatment with Eloctate (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) should be initiated under the supervision of a healthcare professional experienced in the treatment of hemophilia A.
- Each vial of Eloctate has the FVIII potency in International Units (IU) stated on the label. The potency assignment of Eloctate is determined using a chromogenic substrate assay.
- Dose and duration of treatment depend on the severity of the Factor VIII deficiency, the location and extent of bleeding, and the clinical condition of the patient. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.

4.2 Recommended Dose and Dosage Adjustment

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 WARNINGS AND PRECAUTIONS and 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).

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:

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

OR

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

Dose adjustment may be necessary in pediatric patients <12 years of age (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics and CLINICAL PHARMACOLOGY, Pharmacokinetics, Pediatrics and Adolescents). For patients ≥12 years of age, dose adjustment is not usually required.

Dosing for Routine Prophylaxis:

For individualized prophylaxis, the recommended regimen is 50 IU/kg every 3 to 5 days.
The dose may be adjusted based on patient response in the range of 25 to 65 IU/kg (see Pharmacokinetics). More frequent or higher doses up to 80 IU/kg may be required in pediatric patients <12 years of age.

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

Dosing for Control and Prevention of Bleeding Episodes:

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

Table 1: Bleeding Episode Dosing Guide

Severity of Bleed	Desired Peak Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)	Frequency of Doses	
			Age Group	Repeat Dose
Minor and Moderate For example: Joint, superficial muscle/ no neurovascular compromise (except iliopsoas), deep laceration and renal, superficial soft tissue, mucous membranes	**40 to 60**	**20 to 30 IU/kg**	≥12 years	Every 24-48 hours until bleeding is resolved
			<12 years	Every 12-24 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 to 100**	**40 to 50 IU/kg**	≥12 years	Every 12-24 hours until bleeding is resolved
			<12 years	Every 8-24 hours until bleeding is resolved

Adapted from: WFH 2012

Subsequent doses 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 Pharmacokinetics).

Dosing for Perioperative Management (Surgical Prophylaxis):

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.

Table 2: Perioperative Management Dosing Guide

Type of Surgery	Target Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)	Frequency of Doses (hrs)	
			Age Group	Repeat Dose
Minor Minor operations including uncomplicated dental extraction	**50 to 80**	**25-40 IU/kg**	≥12 years	A single infusion may be sufficient Repeat every 24 hours as needed to control bleeding
			<12 years	A single infusion may be sufficient Repeat every 12-24 hours as needed to control bleeding

Type of Surgery	Target Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)	Frequency of Doses (hrs)	
			Age Group	Repeat Dose
Major Major operations including intra-abdominal, joint replacement surgery	**80 to 120**	**Preoperative: 40-60 IU/kg** **Repeat dose: 40-50 IU/kg**	≥12 years	Repeat dose of 40-50 IU/kg after 8-24 hours and then every 24 hours to maintain FVIII activity within the target range.
			<12 years	Repeat dose of 40-50 IU/kg after 6-24 hours and then every 24 hours to maintain FVIII activity within the target range.

4.4 Administration

Eloctate is administered by intravenous (IV) injection after reconstitution with sterile Water for Injection.

Eloctate should be administered using the infusion set provided with the drug product, and the pre-filled diluent syringe provided. In addition, the solution should be withdrawn from the vial using the vial adapter.

Detailed instructions for preparation and administration are included in PART III: PATIENT MEDICATION INFORMATION.

Reconstitute lyophilized Eloctate powder for injection with the supplied diluent (sterile Water for Injection) from the pre-filled syringe provided. Gently rotate the vial until all of the powder is dissolved.

After reconstitution, the solution is drawn back into the syringe. The solution should be clear to slightly opalescent and colourless.

Dispose of all unused solution, empty vials, and used needles and syringes in an appropriate container and dispose of according to local requirements.

5 OVERDOSAGE

No symptoms of overdose have been reported.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: **Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Intravenous injection	Lyophilized powder nominally containing 250, 500, 750, 1000, 1500, 2000, and 3000 IU/vial. The reconstituted product contains: 83, 167, 250, 333, 500, 667 and 1000 IU/mL, respectively.	When reconstituted with provided diluent, the product contains calcium chloride dihydrate, L-histidine, polysorbate 20, sodium chloride, sucrose

Eloctate is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, white to off-white powder to cake, for intravenous administration in a single use vial. Liquid diluent (Sterile Water for Injection) for reconstitution is provided in a pre-filled syringe.

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

The diluent (sterile Water for Injection) is provided in a pre-filled syringe.

When reconstituted with provided diluent, the product contains sucrose, sodium chloride, L-histidine, calcium chloride dihydrate, and polysorbate 20.

Each carton of Eloctate contains a powder vial with a stopper and a flip-off seal, 3 mL diluent in a pre-filled syringe with a plunger stopper, a tip-cap and a sterile vial adapter reconstitution device.

A carton containing 1 butterfly infusion set, 2 alcohol pads, 1 gauze pad, and 2 bandages is provided along with the drug product carton.

Dispose of all the materials of the packaging in accordance with local requirements.

7 WARNINGS AND PRECAUTIONS

General

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 (neutralizing antibodies) should be suspected, and appropriate testing performed (see Monitoring and Laboratory Tests).

Catheter-Related Complications

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

Carcinogenesis and Mutagenesis

No animal studies investigating carcinogenic effects of Eloctate have been conducted.

Eloctate has not been evaluated in mutagenicity or chromosomal aberration assays.

Cardiovascular

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

Hepatic/Biliary/Pancreatic

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

Immune

Neutralizing Antibodies (Inhibitors)
Inhibitors have been reported with factor replacement therapy in the treatment of hemophilia 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 hemophilia 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 (neutralizing antibodies) should be suspected, and appropriate testing performed (see Monitoring and 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.

Monitoring and Laboratory Tests

Monitor plasma factor VIII activity levels by performing a suitable test (one-stage clotting assay or chromogenic substrate assay) to confirm adequate factor VIII levels have been achieved and maintained, when clinically indicated (see DOSAGE AND ADMINISTRATION). The potency assignment of Eloctate is determined using a chromogenic substrate assay.

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 titer inhibitors).

Renal

Eloctate has not been studied in patients with renal impairment.

Reproductive Health: Female and Male Potential

Eloctate has not been evaluated in animal fertility studies. It is not known whether Eloctate can affect fertility or sperm development in hemophilia A patients.

7.1 Special Populations

7.1.1 Pregnant Women

Eloctate should be used during pregnancy only if the potential benefit justifies the potential risk. Animal reproductive studies have not been conducted with Eloctate; however, Eloctate has been shown to cross the placenta in mice. Experience regarding the use of factor VIII during pregnancy is not available. It is not known whether Eloctate can affect reproductive capacity or cause fetal harm when given to pregnant women.

7.1.2 Breast-feeding

Experience regarding the use of factor VIII during breast-feeding is not available. Eloctate should only be administered to nursing mothers if clinically indicated. 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.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Safety and efficacy of Eloctate have been evaluated in 13 previously treated adolescents aged between 12 to 17 years old in one clinical trial (Study 1). Eleven (11) of them received Eloctate as routine prophylaxis and 2 of them received Eloctate for control of bleeding episodes. No dose adjustment is required. Safety and efficacy of Eloctate have been evaluated in previously untreated pediatric patients (PUPs) <6 years of age (median 0.58 year; range: 0.02-4.00 years) in Study 4 (see ADVERSE REACTIONS and CLINICAL TRIALS).

Study 2 evaluated the safety and efficacy of Eloctate in 71 previously treated patients <12 years of age. All patients received Eloctate as routine prophylaxis. In comparison with adolescents and adults, patients <12 years of age may have a higher clearance and a shorter half-life of Eloctate. These differences should be taken into account when dosing. More frequent or higher dosing may be needed in patients <12 years of age (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of Eloctate did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized (see DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Hypersensitivity or allergic reactions have been reported with Eloctate and may in some cases progress to anaphylaxis (including shock).

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Eloctate. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be

contacted.

8.2 Clinical Trial Adverse Reactions

Previously treated patients (PTPs)

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Eloctate has been evaluated in 276 subjects in five completed studies (Study 1, 2, 3 and two pharmacokinetic studies) in previously treated patients (PTPs) with severe hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe hemophilia A). Sixty-nine (25%) were pediatric 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). There were 200 subjects treated for at least 104 weeks (2 years), 151 subjects treated for at least 156 weeks (3 years) and 107 subjects treated for at least 208 weeks (4 years). The total number of exposure days (EDs) was 80,848 with a median of 294 (range 1-735) EDs per subject. Adverse events (AEs) were monitored for a total of 893.72 subject-years. A total of 255 subjects had ≥50 EDs; 66 of these were <12 years of age. The subjects received a total of 82,024 injections with a median of 303.5 injections of Eloctate (range 1-755) per subject.

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

ADRs were reported in 11 of 276 (4.0%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. The ADRs with an incidence ≥0.5% for Eloctate were arthralgia, malaise, myalgia, headache, and rash. No serious ADRs were reported in subjects who received Eloctate. Adverse drug reactions are considered adverse events assessed as related to treatment with Eloctate. No age-specific differences in adverse drug reactions were observed between pediatric and adult subjects. All adverse drug reactions were uncommon (≥1/1,000 to 1/100) and most were mild or moderate in severity. ADRs in PTPs are summarized in Table 4.

One 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 4: Adverse Drug Reactions reported for Eloctate in PTPs

MedDRA[2] System Organ Class	MedDRA Preferred Term	Number of Patients N=276* n (%)
Nervous system disorders	Headache	2 (0.7)
	Dizziness	1 (0.4)
	Dysgeusia	1 (0.4)
Cardiac disorders	Bradycardia	1 (0.4)
Vascular disorders	Hypertension	1 (0.4)
	Hot flush	1 (0.4)
	Angiopathy[1]	1 (0.4)

Respiratory, thoracic and mediastinal disorders	Cough	1 (0.4)
Gastrointestinal disorders	Abdominal pain, lower	1 (0.4)
Skin and subcutaneous tissue disorders	Rash	2 (0.7)
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Back pain Joint swelling	2 (0.7) 2 (0.7) 1 (0.4) 1 (0.4)
General disorders and administration site conditions	Malaise Chest pain Feeling cold Feeling hot	2 (0.7) 1 (0.4) 1 (0.4) 1 (0.4)
Injury, poisoning and procedural complications	Procedural hypotension	1 (0.4)

*The Eloctate clinical program included 276 previously treated patient (PTPs) on routine prophylaxis or episodic (on-demand) therapy from 5 completed studies
[1]Investigator term: *vascular pain after injection of study drug*
[2]MedDRA Version 15.0

Previously untreated patients (PUPs)

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

Adverse drug reactions (ADRs) were reported in 29 of 103 (28.2%) subjects treated with Eloctate. ADRs in PUPs are summarized in Table 5.

Table 5: Adverse Drug Reactions Reported for Eloctate in PUPs

MedDRA[1] System Organ Class	**MedDRA Preferred Term**	**N=103[2]**
		Number of Subjects n (%)
Blood and lymphatic system disorders	**Factor VIII inhibition**	**28 (27.2)**
General disorders and administration site conditions	**Device related thrombosis[3]**	**2 (1.9)**
Skin and subcutaneous tissues disorders	**Rash papular**	**1 (1.0)**

[1]MedDRA version 22.0
[2]The Eloctate clinical program included 103 previously untreated patients (PUPs) on routine prophylaxis or episodic (on-demand) therapy from 1 study
[3]Includes device related thrombosis and deep vein thrombosis, each event occurred in 1 subject with an indwelling central venous catheter

Immunogenicity

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

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

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

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

The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease. Therefore, it may be misleading to compare of the incidence of antibodies to Eloctate with the incidence of antibodies to other products.

8.5 Post-Market Adverse Reactions

During post-approval use, the following adverse reactions have been reported: FVIII inhibitor development and hypersensitivity reactions.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

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

9.5 Drug-Food Interactions

There is no known effect of food on exposure of Eloctate. Therefore, Eloctate may be taken with or without food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Eloctate (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) is a fully recombinant fusion protein comprised of recombinant B domain-deleted human Factor VIII (BDD FVIII) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1) and produced by recombinant DNA technology.

The FVIII portion of Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein is a glycoprotein

comparable to the 90+80 kDa form of endogenous FVIII that is found in human plasma.

The other portion of Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) is the Fc region of human immunoglobulin G1 (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. Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein binds to FcRn thereby utilizing this same naturally occurring pathway to delay lysosomal degradation and allow for longer plasma half-life 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.

10.2 Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional clotting factor VIII (FVIII), which leads to prolonged clotting time in the activate partial thromboplastin time (aPTT) assay, a conventional *in vitro* test for the biological activity of FVIII. Treatment with Eloctate normalizes the clotting time over the effective dosing period.

10.3 Pharmacokinetics

The pharmacokinetics of ELO Eloctate CTATE compared with Advate® (Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method) 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 4 days prior to receiving 50 IU/kg of Advate. Pharmacokinetic 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. Pharmacokinetic samples were collected pre-dose and then subsequently at 7 time points up to 120 hours (5 days) post-dose. A repeat pharmacokinetic evaluation of Eloctate was conducted at week 14.

The pharmacokinetic parameter results (Table 6) were based on plasma FVIII activity measured by the one-stage clotting assay. The pharmacokinetic profiles of 27 patients were obtained at week 14, after repeat dosing, and were comparable with the pharmacokinetic profiles obtained after the first dose. The pharmacokinetic data demonstrate that Eloctate has a prolonged circulating half-life.

Table 6: Summary of Pharmacokinetic Parameters of Eloctate and Advate

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)
$t_{1/2}$ (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[1]	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_{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)	4.92 (4.434. 5.46)	3.30 (2.99, 3.65)	1.49 (1.41, 1.57)

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

Abbreviations: CI = confidence interval; 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

Pediatrics (<18 years)

Pharmacokinetic (PK) parameters of Eloctate were determined for adolescents 12 to <18 years of age in Study 1 and for children <12 years of age in Study 2 (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

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 (Study 2), PK parameters were evaluated following a 5-minute IV infusion in 54 evaluable children <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. In pediatric subjects <12 years of age on previous Advate therapy (n=15), half-life prolongation of Eloctate relative to Advate (approximately 1.5 fold) is consistent with adult and adolescent subjects.

Table 7 presents the PK parameters calculated from the data of 65 subjects <18 years of age. Compared to adults and adolescents clearance appeared to be higher and half-life appeared to be shorter in children <12 years of age. This may result in a need for dose adjustments in children <12 years of age (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Table 7: Comparison of PK Parameters of Eloctate by Age

PK Parameters[1]	Study 2		Study 1
	<6 Years	6 to <12 Years	12 to <18 Years
	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)
$t_{½}$ (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_{SS} (mL/kg)	57.9 (54.1, 62.0)	49.5 (44.1, 55.6)	59.4 (52.7, 67.0)

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

Abbreviations: IR = incremental recovery; CI = confidence interval; 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

Special Populations and Conditions

- **Geriatrics**
  Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized (see DOSAGE AND ADMINISTRATION).
- **Hepatic Insufficiency**
  No formal pharmacokinetic studies have been conducted to examine the effects of hepatic impairment on Eloctate disposition.
- **Renal Insufficiency**
  No formal pharmacokinetic studies have been conducted to examine the effects of renal impairment on Eloctate disposition

11 STORAGE, STABILITY AND DISPOSAL

Store unopened vials at 2°C to 8°C. The product may be stored at room temperature (15°C to 30°C) for a single 6-month period. The date that the product is removed from refrigeration should be noted on the carton. Do not use Eloctate (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) after the expiry date printed on the label or 6 months after removing the carton from refrigeration, whichever is earlier.

Protect from light.

Do not freeze the pre-filled syringe.

Product after reconstitution: The reconstituted product can be stored at room temperature (15-30◦C) for 6 hours. Protect from direct sunlight. After reconstitution, if the product is not used within 6 hours, it must be discarded.

12 SPECIAL HANDLING INSTRUCTIONS

Reconstituted Solutions

Detailed instructions for preparation and administration are included in PART III: PATIENT MEDICATION INFORMATION. Patients should follow the specific reconstitution and administration procedures provided by their physicians.

Always wash your hands before performing the procedures. Aseptic technique should be used during

the reconstitution procedure.

Eloctate (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) will be administered by intravenous (IV) injection after reconstitution with sterile Water for Injection (diluent).

Parenteral Products (for reconstitution before use)

Vial Size	Volume of Diluent to be added to vial	Nominal Concentration Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein* per mL
250 IU	3 mL	83 IU
500 IU	3 mL	167 IU
750 IU	3 mL	250 IU
1000 IU	3 mL	333 IU
1500 IU	3 mL	500 IU
2000 IU	3 mL	667 IU
3000 IU	3 mL	1000 IU

* The potency (IU) is determined using the European Pharmacopoeia chromogenic assay against an in-house standard that is referenced to the WHO standard. The specific activity of Eloctate is 4000-10200 IU/mg protein.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper name: Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein)

Chemical name: Blood coagulation factor VIII (synthetic human) fusion protein with immunoglobulin G1 (synthetic human Fc domain fragment), (1444->6'), (1447 ->9')-bis(disulfide) with immunoglobulin G1 (synthetic human Fc domain fragment)

Molecular formula and molecular mass: The theoretical molecular weight based on the amino acid sequence of Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein single chain without post-translational modifications is approximately 26 kDa.

Product Characteristics:

Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein is a fully recombinant fusion protein consisting of human coagulation factor VIII (FVIII) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1). The factor VIII portion of Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein has a primary amino acid sequence and post-translational modifications that are comparable to the 90 + 80 kDa form of factor VIII (i.e., BDD). The Fc domain of Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein contains the hinge, CH2 and CH3 regions of IgG1. Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein contains 1890 amino acids with an apparent molecular weight of approximately 220 kilodaltons.

Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterized. The HEK cell line expresses Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein into a defined cell culture medium that does not contain any proteins derived from animal or human sources. The purification process utilizes a series of chromatography steps that does not require use of a monoclonal antibody.

Viral Inactivation

The process also includes a detergent viral inactivation step and multiple viral clearance steps, including an affinity chromatography step and a 15 nm virus-retaining nano-filtration step. No human or animal derived additives are used in the purification and formulation processes.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Prophylaxis and Bleeding Control in Previously Treated Patients

The safety, efficacy and pharmacokinetics of Eloctate was evaluated in 2 multicentre, open-label, pivotal studies in previously treated patients (PTPs): a Phase 3 study (Study 1), and a Phase 3

pediatric study (Study 2). Patients from these studies could subsequently enroll in the long-term extension study (Study 3).

Study 1 designed to assess the efficacy of Eloctate in the treatment of bleeding episodes and in the prevention of bleeding episodes in each of two prophylactic treatment regimens (fixed weekly and individualized interval), as well as in the efficacy during perioperative management in subjects undergoing major surgical procedures. A total of 164 previously treated male patients (PTPs) with severe hemophilia A (≤1% endogenous FVIII activity or a genetic mutation consistent with severe hemophilia A) received at least one dose of Eloctate in the study. Subjects were aged 12 to 65 years, including 13 adolescent subjects aged 12 to 17 years.

Subjects on prophylaxis regimens prior to entering the study were assigned to the individualized prophylaxis arm. Those subjects on episodic (on-demand) therapy prior to entering the study either entered the individualized prophylaxis arm or were randomized 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.

Study 2 was designed to assess the efficacy, safety and pharmacokinetics of Eloctate. A total of 69 previously treated male pediatric patients with severe hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe hemophilia A) received at least 1 dose of Eloctate. Subjects were <12 years of age (35 were <6 years of age and 34 were 6 to <12 years of age).

Study 3 was an open-label, multicentre, long-term study in previously treated patients (PTPs) with hemophilia A who had completed Study 1, Study 2, or the pharmacokinetic studies. The primary objective of Study 3 was to assess the long-term safety of Eloctate in PTPs with hemophilia A. During the study, subjects could change treatment groups (individualized prophylaxis, personalized prophylaxis, weekly prophylaxis, or on-demand regimen). 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. Of the 240 subjects enrolled in Study 3 (aged 2-66 years), 61 subjects entered from Study 2. In this group, 30 were in the <6 years of age cohort, and 31 were in the 6 to <12 years of age cohort.

Table 8: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Median age (Range) (Years)	Gender
Study 1	Open-label, multicentre	Arm 1: Individualized prophylaxis 25 IU/kg IV on Day 1 and 50 IU/kg IV on Day 4 initially, then individualized regimen	117	29.0 (12, 65)	Male
		Arm 2: Weekly prophylaxis 65 IU/kg IV once weekly	24	31.5 (18, 59)	
		Arm 3: Episodic dosing 10-50 IU/kg IV as required for treatment of bleeding episodes	23	34.0 (13, 62)	
Study 2	Open-label, multicentre	25 IU/kg on Day 1, followed by 50 IU/kg twice weekly starting on Day 4, then individualized prophylaxis	71	5.0 (1,11)	Male
Study 3	Open-label, multicentre, long-term extension	Individualized prophylaxis 25-65 IU/kg IV every 3-5 days or approximately 20-65 IU/kg IV on Day 1 and 40-65 IU/kg IV on Day 4. up to 80 IU/kg IV every 2 days in pediatric subjects	190	(2, 66)	Male
		Weekly prophylaxis 65 IU/kg IV once weekly	34		
		Personalized prophylaxis	26		
		Episodic treatment	13		

Study 1 (≥12 Years)

A total of 140 subjects received prophylactic Eloctate and were evaluable for efficacy: 117 subjects in the individualized interval arm and 23 subjects in the weekly interval arm. The observed median annualized bleeding rate (ABR) was 1.60 for the subjects in the individualized interval arm, and 3.59 for the subjects in the weekly interval arm (Table 9).

Table 9: Annualized Bleed Rate (ABR) by Prophylaxis Arm

	Individualized Prophylaxis (N=117)	Weekly Prophylaxis (N=23)
Median Overall ABR (range)	1.60 (0.0, 18.2)	3.59 (0.00, 58.0)

Median Spontaneous ABR (range)	0.00 (0.0, 16.7)	1.93 (0.0, 32.8)
Median Traumatic ABR (range)	0.00 (0.0, 8.1)	1.69 (0.0, 25.1)
Median Joint ABR (range)	0.00 (0.00, 16.7)	1.93 (0.00, 50.2)

A comparison of the estimated number of bleeding episodes per subject in the 12 months prior to study start, which was based on subject-reported historical data, to the estimated annualized number of on study bleeding episodes per subject for subjects on a prior prophylaxis regimen is shown in Table 10.

Table 10: Estimated Number of Bleeding Episodes per Subject in the Prior 12 Months as Compared to the Estimated Annualized Number of Bleeding Episodes per Subject On-study

	Prophylaxis (Arm 1) Individualized Interval
Number of subjects on prophylactic regimen prior study	85
Estimated annualized number of bleeding episodes per subject: Mean ± SD; Median (range)	
Prior 12 months	12.62 ± 18.498 6.00 (0.00, 105.0)
On-study	3.51 ± 4.281 2.32 (0.00, 18.2)

A total of 757 bleeding events were observed during the study in the prophylactic arms and episodic (on-demand) arm. The response to each injection for a bleeding episode was evaluated and recorded by subjects at 8 to 12 hours post-treatment using a 4-point rating scale of excellent, good, moderate and no response. The number of injections used to treat bleeding episodes, the dose and the response to the first injection are summarized in **Error! Reference source not found.**.

Table 11: Summary of Bleeding Episodes in Arm 1, 2, 3 Combined

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%)
Median dose per injection (IU/kg) to treat a bleeding episode (range)	(n=755) 27.35 (2.7, 69.8)
Median total dose (IU/kg) to treat a bleeding episode (range)	(n=755)

		28.23 (2.7, 223.1)
Response to first injection		n=745
	Excellent or good	582 (78.1%)
	Moderate	158 (21.2%)
	No response	5 (0.7%)

In the episodic (on-demand) arm, the observed median annualized bleed rate was 33.57. The median spontaneous annualized bleed rate was 20.24 and the median traumatic annualized bleed rate was 9.25.

A total of 880 injections have been administered for 757 bleeding episodes; 860 of these were evaluated (**Error! Reference source not found.**) by subjects.

Table 12: Subject's Assessment of Response to Eloctate Injections by Type of Bleeds and Location of Bleeds (Arms 1, 2 and 3 Combined)

Type / Location of Bleeds	Number of Injections	Excellent	Good	Moderate	No response
Spontaneous bleeding episodes	576	164 (28.5%)	292 (50.7%)	116 (20.1%)	4 (0.7%)
Traumatic bleeding episodes	277	76 (27.4%)	130 (46.9%)	69 (24.9%)	2 (0.7%)
Unknown Type bleeding episodes	7	2 (28.6%)	3 (42.9%)	2 (28.6%)	0 (0.0%)
Joint bleeds	671	186 (27.7%)	332 (49.5%)	149 (22.2%)	4 (0.6%)
Muscle bleeds	156	40 (25.6%)	83 (53.2%)	31 (19.9%)	2 (1.3%)
Internal bleeds	11	3 (27.3%)	3 (27.3%)	5 (45.5%)	0 (0.0%)
Soft tissue bleeds	64	15 (23.4%)	34 (53.1%)	14 (21.9%)	1 (1.6%)
Skin/mucosa bleeds	28	11 (39.3%)	14 (50.0%)	3 (10.7%)	0 (0.0%)

Quality of Life was measured in Study 1 using the HAEM-A-QOL, a quality of life instrument specific to hemophilia. HAEM-A-QOL was performed in adults (aged 18 and older) in the individualized prophylactic regimen. Lower scores represent better quality of life; therefore, a negative change from baseline represents improvement during the course of the study. Changes from baseline to week 28 are summarized in Table 13.

Table 13: Median Change from Baseline for the Haem-A-QOL Questionnaire (Individualized Prophylaxis)

	Pre-Study Regimen					
	Prophylaxis			Episodic (On-demand)		
	N	Change from baseline		N	Change from baseline	
Total Score	34	-1.03	(-26.7, 11.5)	12	-4.31	(-35.6, 13.9)
Domains, during the past month						
1. Physical Health	40	0.00	(-31.3, 60.0)	17	-25.00	(-65.0, 25.0)
2. Feeling	40	-3.13	(-50.0, 25.0)	17	-6.25	(-50.0, 18.8)
3. View of Yourself	42	0.00	(-40.0, 35.0)	17	0.00	(-40.0, 20.0)
4. Sports and leisure	29	0.00	(-68.8, 45.0)	10	-5.00	(-50.0, 5.0)
5. Work and school	34	0.00	(-50.0, 37.5)	15	-6.25	(-56.3, 25.0)
6. Dealing with hemophilia	40	0.00	(-33.3, 33.3)	17	0.00	(-25.0, 58.3)
7. Treatment	42	0.00	(-28.1, 18.8)	14	-4.69	(-43.8, 12.5)
Domains, recently						
8. Future	40	0.00	(-45.0, 35.0)	17	-5.00	(-45.0, 60.0)
9. Family Planning	19	0.00	(-25.0, 16.7)	10	0.00	(-18.8, 33.3)
10. Partnership and sexuality	37	0.00	(-25.0, 66.7)	14	0.00	(-25.0, 91.7)

NOTE: summary statistics are median (minimum, maximum)

Study 2 (<12 Years)

Sixty-nine subjects received Eloctate on an individualized prophylactic dose regimen. The observed median annualized bleeding rate (ABR) was 0.00 for subjects <6 years of age, 2.01 for subjects 6 to <12 years of age and 1.96 for the overall group of <12 years of age (Table 14).

Table 14: Annualized Bleed Rate (ABR) in Pediatric Subjects <12 Years of Age

	<6 Years (n=35)	6 to <12 Years (n=34)	Total (<12 Years) (n=69)
Median Overall ABR (range)	0.00 (0.0, 10.5)	2.01 (0.00, 27.2)	1.96 (0.00, 27.2)
Median Spontaneous ABR (range)	0.00 (0.0, 7.9)	0.00 (0.0, 19.8)	0.00 (0.0, 19.8)
Median Traumatic ABR (range)	0.00 (0.0, 6.5)	0.00 (0.00, 7.9)	0.00 (0.00, 7.9)
Median Joint ABR (range)	0.00 (0.0, 6.3)	0.00 (0.0, 17.3)	0.00 (0.00, 17.3)

A comparison of the estimated number of bleeding episodes per subject in the 12 months prior to study start, which was based on subject-reported historical data, to the estimated annualized number of on study bleeding episodes per subject for subjects on a prior prophylaxis regimen is shown in Table 15.

Table 15: Estimated Number of Bleeding Episodes per Subject in the Prior 12 Months as Compared to the Estimated Annualized Number of Bleeding Episodes per Subject On-study

	<6 Years	6 to <12 Years	Total
Number of subjects on prophylactic regimen prior study	32	30	62
Estimated annualized number of bleeding episodes per subject: Mean ± SD; Median (range)			
Prior 12 months	2.16 ± 2.216	5.97 ± 8.168	4.00 ± 6.156
	1.50 (0.0, 8.0)	2.50 (0.0, 36.0)	2.00 (0.0, 36.0)
On-study	1.95 ± 2.765	3.32 ± 5.256	2.62 ± 4.183
	0.0 (0.0, 10.5)	2.01 (0.0, 27.2)	(1.96 (0.0, 27.2)

A total of 86 bleeding events were observed during the study. The response to each injection for a bleeding episode was evaluated and recorded by subjects at 8 to 12 hours post-treatment using a 4-point rating scale of excellent, good, moderate and no response. One hundred and four (104) injections were evaluated for response (45 injections in the < 6 years of age group and 59 in the 6 to <12 years of age group). Hemostatic efficacy was rated as excellent or good in 89.4% of all evaluable injections and in 92.6% of all evaluable first injections.

The number of injections used to treat bleeding episodes, the dose and the response to the first injection are summarized in Table 16.

Table 16: Summary of Bleeding Episodes in Pediatric Subjects <12 Years of Age

	<6 Years n=35	6 to <12 Years n=34	Total (<12 Years) n=69
New bleeding episodes	38	48	86
Injections to treat bleeding episodes			
1 injection	29 (76.3%)	41 (85.4%)	70 (81.4%)
2 injections	7 (18.4%)	3 (6.3%)	10 (11.6%)
3 injections	1 (2.6%)	2 (4.2%)	3 (3.5%)
≥4 injections	1 (2.6%)	2 (4.2%)	3 (3.5%)
Median dose per injection (IU/kg) to treat a bleeding episode (range)	51.35 (13.9, 91.3)	48.15 (14.0, 77.0)	49.69 (13.9, 91.3)
Median total dose (IU/kg) to treat a bleeding episode (range)	56.40 (13.9, 200.0)	53.49 (14.0, 196.6)	54.90 (13.9, 200.0)
Response to first injection	n=35	n=46	n=81
Excellent or good	32 (91.4%)	43 (93.5%)	75 (92.6%)
Moderate	3 (8.6%)	1 (2.2%)	4 (4.9%)
No response	0 (0.0%)	2 (4.3%)	2 (2.5%)

Study 3

The results from Study 3 for routine prophylaxis and for control of bleeding were consistent with those of Study 1 and Study 2.

Surgical Prophylaxis in Previously Treated Patients

Major Surgeries

Hemostatic efficacy was evaluated in forty-eight (48) surgeries in thirty-four (34) subjects from Study 1 and Study 3. There were no major surgeries in Study 2. A single dose was sufficient to maintain hemostasis during 39 surgeries (81.3%), and 2 injections were sufficient to maintain hemostasis during 6 surgeries (12.5%); 3 surgeries (6.3%) required no injections. The median average dose per injection to maintain hemostasis during surgery was 59.5 IU/kg (range 35-111 IU/kg). On the day of surgery, 29 out of 47 (61.7%) subjects got a second injection. The total dose on the day of surgery ranged from 37.6-157.9 IU/kg.

Hemostatic response was assessed in forty-four (44) major surgical procedures in thirty-one (31) subjects. Nine (9) major surgical procedures were performed in 9 subjects in Study 1. In an extension Study 3, a total of 35 major surgical procedures were assessed for hemostatic response in 23 subjects. The investigators post-operatively assessed hemostasis using a 4-point scale of excellent, good, fair and poor/none. The hemostatic response was rated as excellent or good in 100% of major surgeries.

Table 17 summarizes the hemostatic response to dosing during surgery and post-operatively for Study

1 and Study 3.

Table 17: Summary of Hemostatic Response during Surgery and Post-Operatively*

	# of Procedures (# of Subjects)	Response	
		Excellent	Good
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	3 (3)	3	
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 Cauterization	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 hemostatic 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 pediatric 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 hemostasis was collected at least 24 hours following surgery. Hemostasis was rated as excellent for 5 minor surgeries and as good for 2 minor surgeries.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Results of repeat-dose studies in two animal species, rats and monkeys, using IV administration, revealed no safety findings relevant to use in humans. Rats were dosed for 4 weeks while monkeys were dosed for 4 weeks in 2 separate studies. The highest dose, 1000 IU/kg, provides a safety margin of 20-fold relative to a starting dose of 50 IU/kg for patients and a 10-fold relative to a starting dose of 100 IU/kg for patients.

Study Number and Title	Species	Dose and Frequency	Key Findings
Repeat-Dose Toxicology Studies			
Four-Week IV Dose Toxicity and PK Study of FVIIIFc in Rats Followed by a 4-Week Recovery Period	Sprague Dawley Rats	0, 50, 250 and 1000 IU/kg (liquid formulation) IV every 2 days for 4 weeks (14 doses)	Repeat doses were well tolerated. Antibodies to Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein (~80% to 90% at all dose levels). ~25% increase in aPTT on SD29. NOAEL was 1000 IU/kg.
Four-Week IV Dose Toxicity and PK Study of FVIIIFc in Cynomolgus Monkeys Followed by a 4-Week Recovery Period	Cynomolgus Monkeys	0, 50, 250 and 1000 IU/kg (liquid formulation) IV every 2 days for 4 weeks (14 doses)	Dose-related increases in antibodies to Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein and dose-related increases in aPTT. Dose-related increases in bruising and SC hemorrhage following blood collection. 3 moribund sacrifices at 1000 IU/kg (after the last dose). NOAEL was 1000 IU/kg for direct toxicological effects.
Four-Week IV Dose Toxicity and PK Study of FVIIIFc Lyophilized DP in Cynomolgus Monkeys Followed by a 4-Week Recovery Period	Cynomolgus Monkeys	0, 50, 250 and 1000 IU/kg (lyophilized formulation) IV every 2 days for 4 weeks (14 doses)	Dose-related increases in antibodies to Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein and dose-related increases in aPTT. Dose-related increases in bruising and SC hemorrhage following blood collection. There were no moribund sacrifices. NOAEL was 1000 IU/kg for direct toxicological effects.

aPTT = activated partial thromboplastin time; DP = drug product; IV = intravenous; NOAEL = no observed adverse effect level; SC = subcutaneous; SD = study day

Teratogenicity:

Eloctate has not been evaluated in animal reproductive studies. No impact on male or female reproductive organs was shown in toxicology studies in rats and monkeys. In a placental transfer study, Eloctate has been shown to cross the placenta in small amounts in mice.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ELOCTATE® [pronounced ē lok tate]
Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein

Read this carefully before you start taking **Eloctate** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Eloctate**.

What is Eloctate used for?

- Eloctate is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia A (congenital factor VIII deficiency).

How does Eloctate work?

- People with hemophilia A do not have enough natural coagulation factor VIII in their blood.
- Factor VIII is a protein produced naturally in the body. It helps the blood to form clots to stop bleeding.
- When your body does not produce enough coagulation factor VIII and you become injured, your blood will not form clots and you may bleed into and damage your muscles and joints.
- Eloctate is coagulation FVIII made using recombinant technology in a laboratory, which can be given by injection to help control and prevent bleeding in people with hemophilia A.

What are the ingredients in Eloctate?
Medicinal ingredients: Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein

Non-medicinal ingredients: When reconstituted with provided diluent, the product contains sucrose, sodium chloride, L-Histidine, calcium chloride dihydrate, polysorbate 20.

Eloctate comes in the following dosage forms:
Eloctate comes as a powder in a vial. It must be reconstituted with the diluent (Sterile Water for Injection) supplied in the pre-filled syringe before use. Before reconstitution, Eloctate is available nominally in 250, 500, 750, 1000, 1500, 2000 and 3000 IU/vial.

Eloctate must be reconstituted (dissolved) before injection. After reconstitution, the actual activity level of the vial is printed in International Units on the vial and carton label. The product contains approximately 83, 167, 250, 333, 500, 667 or 1000 IU/mL, respectively.

Do not use Eloctate if:

- You are allergic to this drug or any ingredient listed above (nonmedicinal ingredients).
- The expiry date (printed on the vial) has passed. If you take this medicine after the expiry date has passed, it may not work well.

If you are not sure if you should use Eloctate, talk to your doctor.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Eloctate. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or planning to become pregnant. It is not known if Eloctate may harm your unborn baby.
- Are breastfeeding. It is not known if Eloctate passes into the milk and if it can harm your baby.
- Have any allergies to this drug or its ingredients or components of the container (see **Do not use Eloctate if**).

Other warnings you should know about:
Allergic reactions may occur with Eloctate. Call your doctor or get emergency treatment right away if you have any of the following symptoms:

- Difficulty breathing
- Chest tightness
- Swelling of the face
- Rash
- Hives

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Eloctate:

- There are no known interactions of Eloctate with other medications.
- Tell your doctor or pharmacist if you are taking any other medicines, including any you buy without a prescription, including natural health products.

How to take Eloctate:
The initial administration of Eloctate under proper medical supervision is recommended, where proper medical care for severe allergic reactions could be provided.

Usual dose:
Your doctor will prescribe the dose you should take. You should always follow the specific instructions given by your healthcare provider. The steps in the **Preparing your dose for administration** section are general guidelines for using Eloctate. If you are unsure of these procedures, please call your healthcare provider before using.

Overdose:
Talk to your doctor if you take too much Eloctate.

If you think you, or a person you are caring for, have taken too much Eloctate, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Talk to your doctor if you miss a dose.

Preparing your dose for administration:

Always wash your hands with soap and water before preparing the dose for administration.

Check the expiration date on the Eloctate package. Obtain a replacement package if the product has expired.

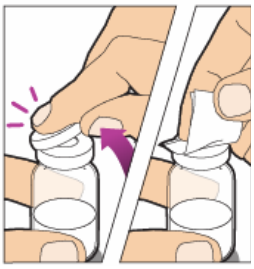
Use aseptic technique (clean and germ-free) and a flat work surface during the reconstitution procedure.

Use the diluent in the pre-filled syringe supplied in the package.

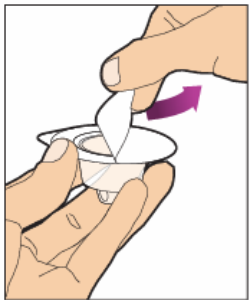
Actual factor VIII activity in International Units is stated on the label of each Eloctate carton and vial.

1. If refrigerated, allow the vial of Eloctate and pre-filled diluent syringe to reach room temperature before use.

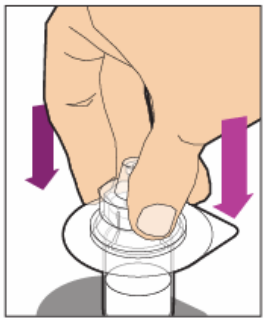
2. Remove the plastic cap from the Eloctate vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.



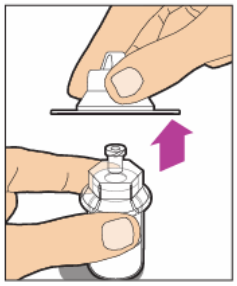
3. Completely remove the backing from the vial adapter package by peeling back the lid. Do not remove the vial adapter from the package or touch the inside of the package of the adapter.



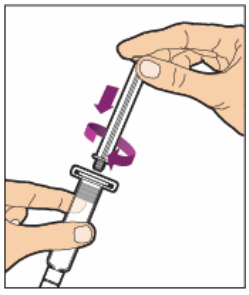
4. Keep the vial on a flat surface. Hold the vial adapter package with one hand and using the other hand, place the vial adapter over the vial. The spike should be placed directly above the centre of the rubber stopper. Push the vial adapter straight down until the adapter spike punctures the centre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



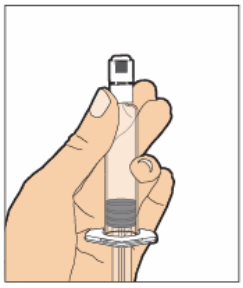
5. Lift the package cover away from the vial adapter and discard the cover.



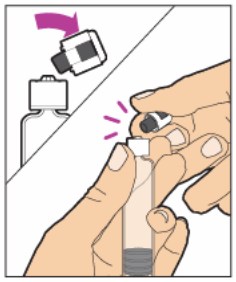
6. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn in a clockwise motion until it is securely attached. Only use the diluent syringe provided to reconstitute the drug product.



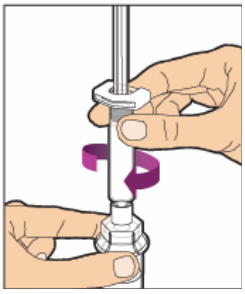
7. With one hand, hold the diluent syringe right under the cap, and with the cap pointing up. Make sure you are holding the diluent syringe by the ridged part directly under the cap. Do not use if the cap has been removed or is not securely attached.



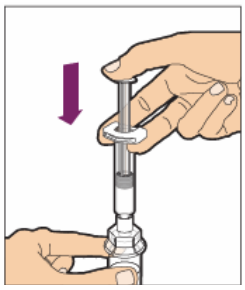
8. With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe. Do not touch the glass tip of the syringe or inside of the cap.



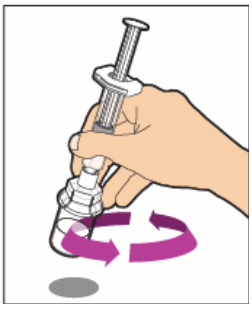
9. Be sure the vial is sitting on a flat surface. Insert the tip of the syringe into the adapter opening. Turn the syringe in a clockwise motion until it is securely attached to the adapter.



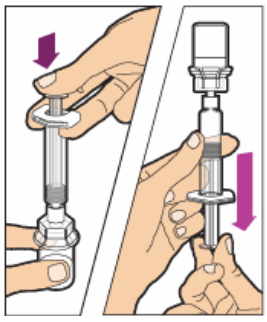
10. Slowly depress the plunger rod to inject all of the diluent into the vial. The plunger rod may rise slightly after this process. This is normal.



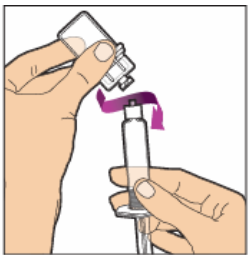
11. With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. The appearance of the solution should be clear to slightly opalescent and colorless. Do not shake. Do not use the reconstituted Eloctate if it contains visible particles or is cloudy.



12. 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.



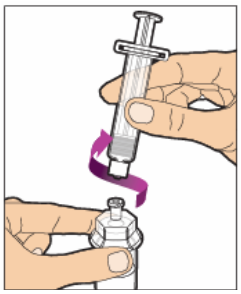
13. Gently unscrew the syringe from the vial adapter and dispose of the vial with the adapter still attached. Do not touch the syringe tip or the inside of the cap. Reconstituted Eloctate should be administered as soon as possible.



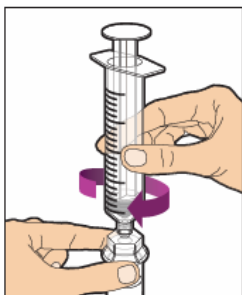
Pooling

If you are using two or more vials of Eloctate, you can follow these pooling steps. Be sure to leave the vial adapter attached to the vial, as you will need it for attaching a large luer lock syringe. Do not detach the diluent syringe or the large luer syringe until you are ready to attach the large luer lock syringe to the next vial (with vial adapter attached).

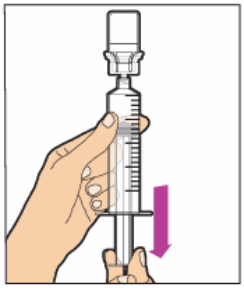
1. Remove the diluent syringe from the vial adapter by turning it counterclockwise until it is completely detached.



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



3. 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.



Administration
For Intravenous Use only after Reconstitution

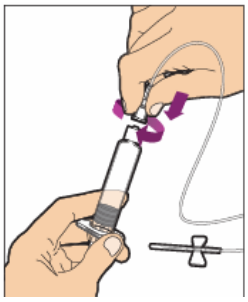
IMPORTANT: Contact your doctor or local hemophilia treatment centre if you experience any problems with this procedure.

Your doctor or hemophilia centre healthcare professional should instruct you on the proper way to self-inject the product. Please do not attempt to give yourself the injection unless you have been trained by your doctor or hemophilia centre healthcare professional.

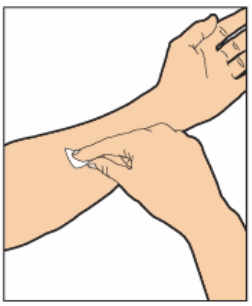
Eloctate is administered by intravenous (IV) injection after reconstitution of the drug powder with the diluent.

Do not administer reconstituted Eloctate if it contains particulate matter, is discoloured, or is cloudy.

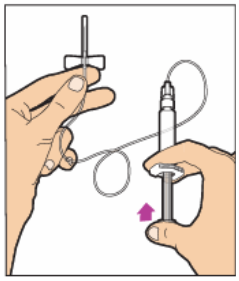
1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. Do not administer reconstituted Eloctate in the same tubing or container with other medicinal products.



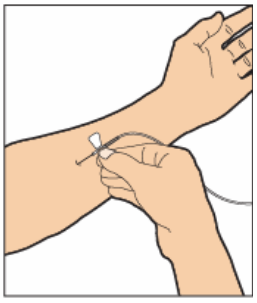
2. Apply a tourniquet and clean the skin area where you will perform the injection using an alcohol wipe.



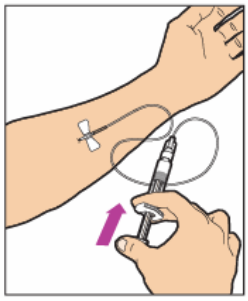
3. Depress the plunger until all air is removed from the syringe and Eloctate has reached the end of the infusion set tubing. Do not push Eloctate through the needle.



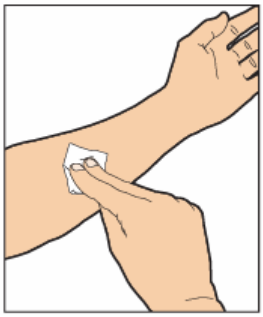
4. Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.



5. 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.



6. After infusing Eloctate, remove the infusion set and use a sterile gauze to put pressure on the infusion site for several minutes. Apply an adhesive bandage if necessary.



What are possible side effects from using Eloctate?
These are not all the possible side effects you may have when taking [Brand name]. If you experience any side effects not listed here, tell your healthcare professional.

These are not all the possible side effects you may feel when taking Eloctate. If you experience any side effects not listed here, contact your healthcare professional.

Allergic reactions may occur with Eloctate (see allergic reactions **under To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Eloctate**).
Some common side effects of Eloctate are joint pain and general discomfort, muscle pain, headache and rash.

Your body can also make antibodies called 'inhibitors' against Eloctate. These inhibitors may stop Eloctate from working properly. Talk to your doctor right away if bleeding is not controlled after using Eloctate.

Talk to your doctor about any side effect that bothers you or that does not go away.

Serious side effects and what to do about them

Symptom / effect	Stop taking Eloctate and call your doctor immediately
The following side effects could mean you are having an allergic reaction.	
Difficult breathing	√
Chest tightness	√
Swelling of the face, rash or hives.	√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep the vials of Eloctate in the refrigerator at 2°C to 8°C.

You can keep the vials of Eloctate at room temperature at 15°C to 30°C for a single 6-month period.

Write the date that you take the product out of the refrigerator on the carton to help you remember. You must either use the product or dispose of it before the end of this 6-month period.

Do not freeze the product to avoid damaging the pre-filled diluent syringe.

Protect the Eloctate vials from light.

After reconstitution, you can keep the product at room temperature at 15°C to 30°C for six (6) hours. Protect the reconstituted product from direct sunlight. If you do not use the product within 6 hours, you must not use it. Do not use Eloctate if the reconstituted solution is not clear to slightly opalescent and colourless.

Throw away any unused Eloctate.

Do not use product or diluent after the expiry date that is shown on the label of the vial and the carton.

Keep out of reach and sight of children.

If you want more information about Eloctate:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised November 8, 2021