PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ELOCTATE®

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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Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal 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.	None are clinically relevant. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

ELOCTATE® (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 the use of a monoclonal antibody. 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 nanofiltration step. No human or animal derived additives are used in the purification and formulation processes.

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

INDICATIONS AND CLINICAL USE

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.

The safety and efficacy of ELOCTATE in previously untreated patients (PUPs) have not yet been established.

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).

CONTRAINDICATIONS

ELOCTATE® (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) is contraindicated in individuals who have manifested severe hypersensitivity reactions, including anaphylaxis, to the product or its components.

WARNINGS AND PRECAUTIONS

General
The clinical response to ELOCTATE® (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) 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).

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.

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).

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.

Hepatic/Biliary/Pancreas
Specific studies of ELOCTATE in patients with hepatic impairment have not been performed.

Renal
ELOCTATE has not been studied in patients with renal impairment.

Sexual Function/Reproduction
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. No impact on male or female reproductive organs was shown in toxicology studies in rats and monkeys.

Special Populations

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.

Nursing Women: 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.

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.

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

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).

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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most common adverse drug reactions observed in the open-label clinical trials (incidence ≥ 0.5%) were arthralgia, malaise, myalgia, headache and rash. No serious adverse drug reactions were reported in subjects who received ELOCTATE® (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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) were reported in 11 of 276 (4.0%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. Adverse drug reactions are considered adverse events assessed as related to treatment with ELOCTATE. No age-specific differences in 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. Adverse drug reactions are summarized in Table 1.

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 1: Adverse Drug Reactions reported for ELOCTATE

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	2 (0.7)
	Myalgia	2 (0.7)
	Back pain	1 (0.4)
	Joint swelling	1 (0.4)
General disorders and administration site conditions	Malaise	2 (0.7)
	Chest pain	1 (0.4)
	Feeling cold	1 (0.4)
	Feeling hot	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

Abnormal Hematologic and Clinical Chemistry Findings
No clinically meaningful changes were observed in any of the hematology or chemistry parameters.

In the open-label clinical studies with ELOCTATE in previously treated patients, subjects were monitored for neutralizing antibodies to Factor VIII (inhibitor). One hundred and ten (110) out of 164 subjects in Study 1 (subjects ≥12 years of age) and 61 of 71 subjects in Study 2 (subjects <12 years of age) had a valid inhibitor test following ≥ 50 exposure days (EDs) to ELOCTATE. No subjects developed confirmed, neutralizing antibodies (inhibitors) to Factor VIII.

One subject from Study 1 had a transient positive neutralizing antibody at week 14, and had negative results on repeat testing 18 days later, and at week 28 and week 34.

Post-Market Adverse Drug Reactions
During post-approval use of 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.

DRUG INTERACTIONS

Drug-Drug Interactions
There are no known drug interactions reported with ELOCTATE® (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein). No drug interaction studies have been performed.

DOSAGE AND ADMINISTRATION

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.

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 ACTION 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:

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.

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
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.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No symptoms of overdose have been reported.

ACTION AND CLINICAL PHARMACOLOGY

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.

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.

Pharmacokinetics

The pharmacokinetics of ELOCTATE 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 2) 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 2: 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)
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 3 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 3: 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 Impairment: No formal pharmacokinetic studies have been conducted to examine the effects of renal impairment on ELOCTATE disposition

STORAGE AND STABILITY

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.

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ELOCTATE® (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) 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.

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 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.

PART II: SCIENTIFIC INFORMATION

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. 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.

CLINICAL TRIALS

Study demographics and trial design

The safety, efficacy and pharmacokinetics of ELOCTATE® (Antihemophilic Factor

(Recombinant BDD), Fc Fusion Protein) were evaluated in 2 multicentre, open-label, pivotal studies: 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 4: 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 results

Efficacy in Routine Prophylaxis

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 5).

Table 5: 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 6 .

Table 6: 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)

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 7).

Table 7: 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 8.

Table 8: 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 1.50 (0.0, 8.0)	5.97 ± 8.168 2.50 (0.0, 36.0)	4.00 ± 6.156 2.00 (0.0, 36.0)
On-study	1.95 ± 2.765 0.0 (0.0, 10.5)	3.32 ± 5.256 2.01 (0.0, 27.2)	2.62 ± 4.183 (1.96 (0.0, 27.2)

Study 3

The results from Study 3 for routine prophylaxis were consistent with those of Study 1 and Study 2. [M2.7.3.4]

Efficacy in Control of Bleeding

Study 1(≥12 Years)
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 Table 9.

Table 9: 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 (Table 10) by subjects.

Table 10: 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%)

Study 2 (<12 Years)
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 11.

Table 11: 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 control of bleeding were consistent with those of Study 1 and Study 2.

Efficacy in Perioperative Management (Surgical Prophylaxis)

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 12 summarizes the hemostatic response to dosing during surgery and post-operatively for Study 1and Study 3.

Table 12: 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 hemostatis was collected at least 24 hours following surgery. Hemostasis was rated as excellent for 5 minor surgeries and as good for 2 minor surgeries.

Impact on Quality of Life

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)

DETAILED PHARMACOLOGY

See ACTION AND CLINICAL PHARMACOLOGY

MICROBIOLOGY

Not applicable.

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® (Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein) has not been evaluated in animal reproductive studies. In a placental transfer study, ELOCTATE has been shown to cross the placenta in small amounts in mice.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

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**).

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 have taken too much ELOCTATE, contact your 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.

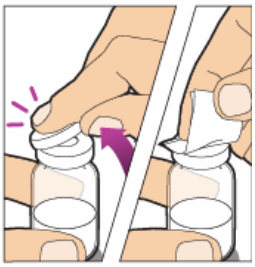
Check the expiration date on the ELOCTATE package. Obtain a replacement package if the product has expired.

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

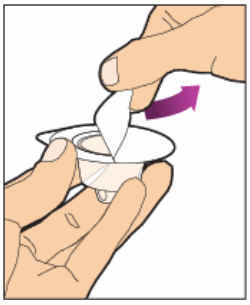
Use the diluent in the pre-filled syringe supplied in the package.

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

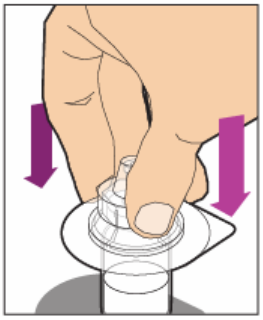
1. If refrigerated, allow the vial of ELOCTATE and pre-filled diluent syringe to reach room temperature before use.
2. Remove the plastic cap from the ELOCTATE vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.



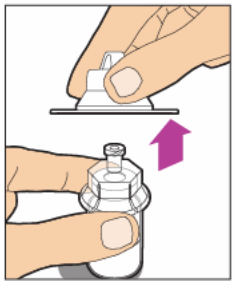
3. Completely remove the backing from the vial adapter package by peeling back the lid. Do not remove the vial adapter from the package or touch the inside of the package of the adapter.



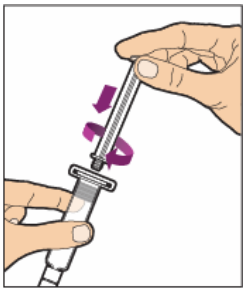
4. Keep the vial on a flat surface. Hold the vial adapter package with one hand and using the other hand, place the vial adapter over the vial. The spike should be placed directly above the centre of the rubber stopper. Push the vial adapter straight down until the adapter spike punctures the centre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



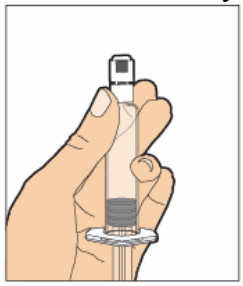
5. Lift the package cover away from the vial adapter and discard the cover.



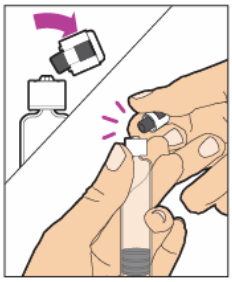
6. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn in a clockwise motion until it is securely attached. Only use the diluent syringe provided to reconstitute the drug product.



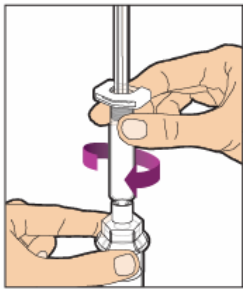
7. With one hand, hold the diluent syringe right under the cap, and with the cap pointing up. Make sure you are holding the diluent syringe by the ridged part directly under the cap. Do not use if the cap has been removed or is not securely attached.



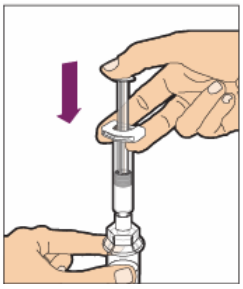
8. With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe. Do not touch the glass tip of the syringe or inside of the cap.



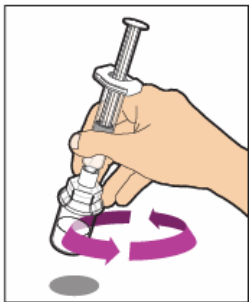
9. Be sure the vial is sitting on a flat surface. Insert the tip of the syringe into the adapter opening. Turn the syringe in a clockwise motion until it is securely attached to the adapter.



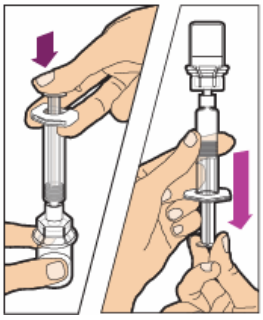
10. Slowly depress the plunger rod to inject all of the diluent into the vial. The plunger rod may rise slightly after this process. This is normal.



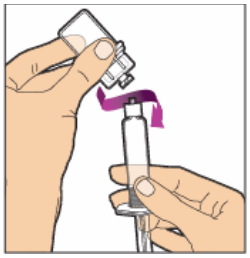
11. With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. The appearance of the solution should be clear to slightly opalescent and colorless. Do not shake. Do not use the reconstituted ELOCTATE if it contains visible particles or is cloudy.



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.



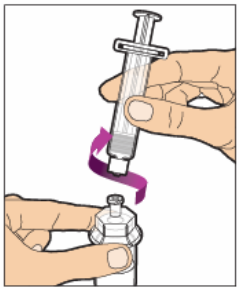
13. Gently unscrew the syringe from the vial adapter and dispose of the vial with the adapter still attached. Do not touch the syringe tip or the inside of the cap. Reconstituted ELOCTATE should be administered as soon as possible.



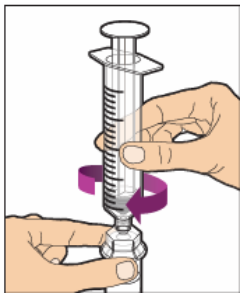
Pooling

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).

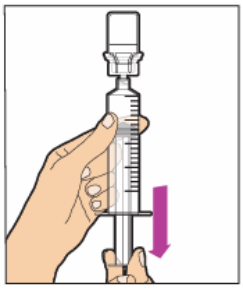
1. Remove the diluent syringe from the vial adapter by turning it counterclockwise until it is completely detached.



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.

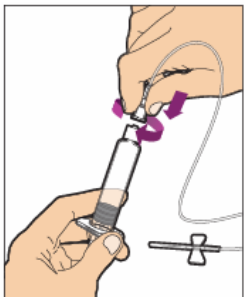
Your doctor or hemophilia centre healthcare professional should instruct you on the proper way to self-inject the product. Please do not attempt to give yourself the injection unless you have been trained by your doctor or hemophilia centre healthcare professional.

ELOCTATE is administered by intravenous (IV) injection after reconstitution of the drug

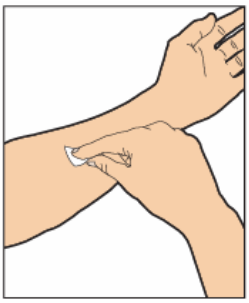
powder with the diluent.

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

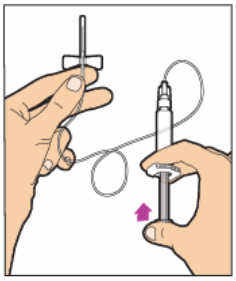
1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely attached. Do not administer reconstituted ELOCTATE in the same tubing or container with other medicinal products.



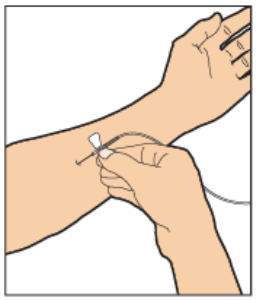
2. Apply a tourniquet and clean the skin area where you will perform the injection using an alcohol wipe.



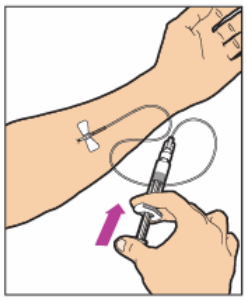
3. Depress the plunger until all air is removed from the syringe and ELOCTATE has reached the end of the infusion set tubing. Do not push ELOCTATE through the needle.



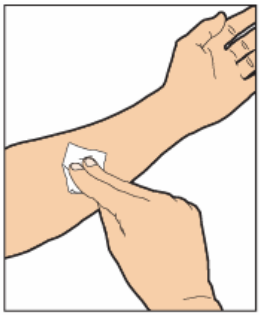
4. Remove the protective needle cover from the infusion set tubing. Insert the needle on the infusion set tubing into the vein. Remove the tourniquet. Always verify proper needle placement when performing intravenous administration.



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 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, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

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; or by calling 1-888-794-1415 or medinfo@bioverativ.com (Medical Information).

This leaflet was prepared by Bioverativ Canada Inc.

Last Revised: November 21, 2019.