HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELOCTATE® safely and effectively. See full prescribing information for ELOCTATE.

ELOCTATE® [Antihemophilic factor (recombinant), Fc fusion protein], Lyophilized powder for solution for intravenous injection
Initial U.S. Approval: 2014

INDICATIONS AND USAGE
ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes.

Limitation of Use
ELOCTATE is not indicated for the treatment of von Willebrand disease. (1)

DOSAGE AND ADMINISTRATION
For intravenous use after reconstitution only.
- Each vial of ELOCTATE is labeled with the amount of recombinant Factor VIII in international units (IU or unit)
- For on-demand treatment and control of bleeding episodes and perioperative management, calculate dose using the following formulas:
  
  Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

- For routine prophylaxis: 50 IU/kg every 4 days. Adjust dose based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals.
- For routine prophylaxis in children less than 6 years of age: 50 IU/kg twice weekly. Adjust dose based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals.

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DOSE FORMS AND STRENGTHS
For injection: nominally 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, or 6000 IU, lyophilized powder in single-dose vials for reconstitution.

CONTRAINDICATIONS
Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to ELOCTATE or excipients of ELOCTATE (sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20). (4)

WARNINGS AND PRECAUTIONS
- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, immediately discontinue ELOCTATE and initiate appropriate treatment. (5.1)
- Neutralizing antibodies (inhibitors) to Factor VIII have been reported. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. (5.2, 5.3)

ADVERSE REACTIONS
Previously Treated Patients (PTPs): The most frequently occurring adverse reactions (>$0.5% of subjects) in clinical trials were arthralgia, malaise, myalgia, headache, and rash. (6)
Previously Untreated Patients (PUPs): The most frequently occurring adverse reactions (incidence >1%) from clinical trial were Factor VIII inhibition, device-related thrombosis, and rash papular. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Bioverativ Therapeutics Inc. at 1-855-693-5628 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Pediatric: Clearance (based on per kg body weight) is higher (75%) in pediatric patients 1 to 5 years of age. Higher or more frequent dosing may be needed. (8.4)
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
Revised: 05/2023

Full Prescribing Information

1 INDICATIONS AND USAGE
ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes.

Limitation of Use
ELOCTATE is not indicated for the treatment of von Willebrand disease. (1)

2 DOSAGE AND ADMINISTRATION
For intravenous use after reconstitution only.
- Dose and duration of treatment depend on the severity of the Factor VIII deficiency, the location and extent of bleeding, and the patient’s clinical condition. Careful monitoring of replacement therapy is necessary in cases of major surgery or life-threatening bleeding episodes.
- Each vial label of ELOCTATE states the Factor VIII potency in international units (IU). One IU corresponds to the activity of Factor VIII contained in one milliliter of normal human plasma.
- Potency assignment is determined using a chromogenic substrate assay. A field study has indicated that plasma Factor VIII levels can be monitored using either a chromogenic substrate assay or a one stage clotting assay routinely used in US clinical laboratories.
- Calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU of Factor VIII per kg body weight raises the plasma Factor VIII level by 2 IU/dL. The expected in vivo peak increase in Factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula:
  
  Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

- The dose to achieve a desired in vivo peak increase in Factor VIII level may be calculated using the following formula:
  
  Dose (IU) = body weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)
The dose to achieve a desired in vivo peak increase in Factor VIII level may be calculated using the following formula:

3 USE IN SPECIFIC POPULATIONS
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Sections or subsections omitted from the full prescribing information are not listed
Table 1: Dosing for Control of Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Factor VIII Level Required (IU/dL or % of normal)</th>
<th>Dose (IU/kg)</th>
<th>Frequency of Dosing (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor and Moderate</td>
<td>40-60</td>
<td>20-30</td>
<td>Repeat every 24-48 hours (12 to 24 hours for patients less than 6 years of age)</td>
<td>Until the bleeding episode is resolved</td>
</tr>
<tr>
<td>Joint, superficial muscle/no neurovascular compromise (except iliopsoas), deep laceration and renal, superficial soft tissue, mucous membranes</td>
<td>80-100</td>
<td>40-50</td>
<td>Repeat every 12-24 hours (8 to 24 hours for patients less than 6 years of age)</td>
<td>Until bleeding is resolved (approximately 7-10 days)</td>
</tr>
<tr>
<td>Major Life or limb threatening hemorrhage, iliopsoas and deep muscle with neurovascular injury, retroperitoneum, intracranial, or gastrointestinal surgery</td>
<td>50-80</td>
<td>25-40</td>
<td>Repeat every 24 hours (12-24 hours for patients less than 6 years of age)</td>
<td>At least 1 day until healing is achieved</td>
</tr>
</tbody>
</table>

Perioperative Management

A guide for dosing ELOCTATE during surgery (perioperative management) is provided in Table 2. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 2: Dosing for Perioperative Management

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Factor VIII Level Required (IU/dL or % of normal)</th>
<th>Dose (IU/kg)</th>
<th>Frequency of Dosing (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Uncomplicated tooth extraction</td>
<td>50-80</td>
<td>25-40</td>
<td>Repeat every 24 hours (12-24 hours for patients less than 6 years of age)</td>
<td>At least 1 day until healing is achieved</td>
</tr>
<tr>
<td>Major Intracranial, intra-abdominal, or joint replacement surgery</td>
<td>80-120 (pre and postoperative)</td>
<td>Preoperative: 40-60</td>
<td>Preoperative dose of 40 to 60 IU/kg followed by a repeat dose of 40-50 IU/kg after 8-24 hours (6 to 24 for patients less than 6 years of age) and then every 24 hours to maintain FVIII activity within the target range</td>
<td>Until adequate wound healing, then continue therapy for at least 7 days to maintain a Factor VIII activity within the target range</td>
</tr>
</tbody>
</table>

Routine Prophylaxis

- The recommended starting regimen is 50 IU/kg of ELOCTATE administered every 4 days. Adjust the regimen based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals.
- For children <6 years of age, the recommended starting regimen is 50 IU/kg of ELOCTATE administered twice weekly. Adjust the regimen based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals. More frequent or higher doses up to 80 IU/kg may be required [see Use In Specific Populations (8.4), Clinical Pharmacology (12.3)].

2.2 Preparation and Reconstitution

1. Use aseptic technique (clean and germ free) and a flat work surface during the reconstitution procedure.
2. Allow the vial of ELOCTATE, containing the white to off-white lyophilized powder, and the pre-filled diluent syringe to reach room temperature before use.
3. Remove the plastic cap from the vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry.
4. 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.
5. Place the vial on a flat and solid surface and use one hand to hold the vial steady. Use the other hand to place the vial adapter over the vial. Place the adapter spike directly above the center of the rubber stopper and push the adapter straight down until the spike punctures the center of the vial stopper and is fully inserted.
6. Lift the package cover away from the vial adapter and discard the cover.
7. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn clockwise until it is securely attached. Only use the diluent syringe provided in the ELOCTATE package.
8. With one hand, hold the diluent syringe by the ridged part directly under the cap, with the cap pointing up. Do not use if the cap has been removed or is not securely attached.
9. With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe. Do not touch the glass tip of the syringe or the inside of the cap.
10. With the vial sitting on a flat surface, insert the tip of the syringe into the adapter opening. Turn the syringe clockwise until it is securely attached to the adapter.
11. 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.
12. With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. Do not shake. The reconstituted solution should be clear to slightly opalescent and colorless. Do not use the reconstituted ELOCTATE if it contains visible particles or is cloudy.
13. 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.
14. 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.
15. Use the reconstituted ELOCTATE as soon as possible, but no later than 3 hours after reconstitution. Do not touch the glass tip of the syringe if not used immediately after reconstitution. Protect from direct sunlight. Do not refrigerate after reconstitution.

To combine two or more vials of ELOCTATE, after step 12 above, follow these pooling steps:
1. Remove the diluent syringe from the vial adapter by turning it counterclockwise until it is completely detached.
2. Leave the vial adapter attached to the vial, as it is needed for attaching a large luer lock syringe (not included in kit). Do not detach the diluent syringe until ready to attach the large luer-lock syringe.
3. Attach a separate, large luer-lock syringe by turning clockwise until it is securely in place.
4. Slowly pull on the plunger rod to draw the solution into the syringe.
5. Repeat this pooling procedure with each vial that is needed to obtain the required dose. When pooling, do not detach the large luer-lock syringe until ready to attach it to the next vial (with vial adapter attached). Once you have pooled the required dose, proceed to administration using the large luer-lock syringe.

2.3 Administration

For intravenous injection only

- Inspect the reconstituted ELOCTATE solution visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.
- Do not administer reconstituted ELOCTATE in the same tubing or container with other medications.

Administration Steps:
1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely in place.
2. 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 solution through the tubing.
3. Remove the protective needle cover from the infusion set tubing.
4. Perform intravenous bolus infusion. The rate of administration should be determined by the patient's comfort level, and no faster than 10 ml per minute. After infusing ELOCTATE, remove and properly discard the infusion set.

3. DOSE FORMS AND STRENGTHS

ELOCTATE is available as a white to off-white lyophilized powder in single-dose vials containing nominally 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000 or 6000 international units (IU) per vial. The actual Factor VIII potency is labeled on each ELOCTATE vial.

4. CONTRAINDICATIONS

ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, or its excipients (sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20).

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with ELOCTATE. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with Factor VIII replacement products. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to Factor VIII or its excipients (sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20).

5.3 Cardiovascular Risk Factors

Hemophiliacs with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-hemophiliac patients when clotting has been normalized by treatment with Factor VIII.

5.4 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.

5.5 Monitoring Laboratory Tests

Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting). A deficit in Factor VIII activity may be observed in previously untreated patients (PUPs) even after normalizing the concentration of Factor VIII by treatment with ELOCTATE.

6. ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence >0.5% of subjects) reported in previously treated patients (PTPs) clinical trials were arthralgia, malaise, myalgia, headache, and rash. The most frequently occurring adverse reactions (incidence ≥1.0% of subjects) reported in previously untreated patients (PUPs) clinical trials were Factor VIII inhibition, device-related thrombosis, and rash papular.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Previously Treated Patients (PTPs)

ELOCTATE has been evaluated in 276 subjects in five completed studies in previously treated patients (PTPs) with severe Hemophilia A (<1% endogenous Factor VIII activity or a genetic mutation consistent with severe Hemophilia A) who received at least one dose of ELOCTATE as part of other clinical trials or on-demand treatment of bleed episodes or perioperative management. Sixty-nine (25.0%) were pediatric subjects <12 years of age, 25 (9.1%) were adolescents (12 to <18 years of age), and 182 (65.9%) were adults (16 years of age and older). There were 200 subjects treated for at least 104 weeks, 151 subjects treated for at least 156 weeks and 107 subjects treated for at least 208 weeks. The total number of exposure days (EDs) was 80,848 with a median of 294 (range 1-735) exposure days per subject. The subjects received a total of 82,024 injections with a median of 303.5 injections of ELOCTATE (range 1-755) per subject. Adverse events (AEs) were monitored for a total of 893.72 subject-years. Two subjects (0.7% of total 276) were withdrawn from continued treatment due to cardiovascular risk factors each experienced a serious adverse reaction of myocardial infarction during the study.

Adverse reactions (ARs) were reported for 11 of 276 (4.0%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. No age-specific differences in ARs were observed between pediatric and adult subjects. Table 3 summarizes the most frequently occurring adverse reactions in PTPs. Additional adverse reactions, each occurring in a single subject (incidence 0.4%), include dizziness, dysgeusia, bradycardia, hypertension, hot flush, angioedema (investigator term: vascular pain after injection of study drug), cough, low-grade pyrexial pain, back pain, joint swelling, chest pain, feeling cold, feeling hot, and procedural hypotension. Two subjects were withdrawn from study due to adverse reactions of rash and arthralgia. In the studies, no inhibitors were detected and no events of anaphylaxis were reported.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Adverse Reactions</th>
<th>Number of Subjects n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Malaise</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

Previously Untreated Patients (PUPs)

ELOCTATE safety was also evaluated in one completed study (PUPs study) in 103 subjects with severe hemophilia A (<1% endogenous Factor VIII activity). 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 on routine prophylaxis, episodic, and/or immune tolerance induction (ITI) therapies. ADRs in PUPs are summarized in Table 4.

Table 4: Adverse Drug Reactions Reported for ELOCTATE in PUPs Study

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Adverse Reactions</th>
<th>Number of Subjects n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor VIII inhibition</td>
<td>28 (27.2)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Device related thrombosis</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissues disorders</td>
<td>Rash papular</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

Immunogenicity

Clinical trial subjects were monitored for neutralizing antibodies to Factor VIII. No PTPs developed confirmed neutralizing antibodies to Factor VIII. One 25 year old subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter.

In PUPs Study, development of neutralizing antibodies (inhibitors) was observed in 28/86 subjects (32.6%) who had developed inhibitors (12 with high-titer inhibitors and 3 with low-titer inhibitors).

□ Two subjects who experienced events of factor VIII inhibition also experienced events of deep vein thrombosis in 1 subject and rash papular in another subject.

Includes device-related thrombosis and deep vein thrombosis, each event occurred in 1 subject with an indwelling central venous catheter.
Blood and lymphatic system disorders: Factor VIII inhibitor development
Immune system disorders: hypersensitivity

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no studies of ELOCTATE use in pregnant women to inform a drug-associated risk. The background risk of major birth defects and miscarriage in the indicated population is unknown; however, the background risk of major birth defects in the U.S. general population is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Animal reproductive and developmental toxicity studies have not been conducted with ELOCTATE. In a placental transfer study, ELOCTATE was detected in murine fetal blood samples at approximately 1% of the maternal blood levels (range, 0.2% to 1.9%), 3 to 4 hours following dosing of pregnant mice with 260 to 650 times the clinical dose of 20 to 50 IU/kg ELOCTATE. It is not known whether ELOCTATE can cause fetal harm when administered to a pregnant woman, or whether it can affect reproduction capacity. If ELOCTATE is clearly needed to treat a pregnant woman, advise the patient that the risks to the fetus are unknown.

Data
Animal data
Pregnant, genetically-modified, FVIII-deficient mice (Hem A mice) were injected intravenously with a single dose of 400 IU (approximately 13,000 IU/kg) ELOCTATE at the end of gestation on Gestation Day 19. Blood samples were collected from the maternal mice and the fetuses 3 to 4 hours after dosing, and FVIII activity was measured in both maternal and fetal plasma using a FVIII chromogenic assay. After dosing pregnant HemA mice with ELOCTATE, FVIII activity in fetal blood was approximately 1% of the maternal blood levels, suggesting that placental transfer of ELOCTATE may occur. The relevance of these data to humans is unknown.

8.2 Lactation
Risk Summary
There is no information regarding the presence of ELOCTATE in human milk, its effects on the breastfed infant, or its effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ELOCTATE and any potential adverse effects on the breastfed infant from ELOCTATE or from the underlying maternal condition.

8.4 Pediatric Use
Safety and efficacy studies have been performed in 82 previously treated, pediatric patients (PTPs) <18 years of age who received at least one dose of ELOCTATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 were enrolled in a pediatric trial. Safety and efficacy of ELOCTATE have been evaluated in 103 previously untreated pediatric patients (PUPs) <6 years of age (median = 3.5 years; range: 0.02–4.40 years) in one study (PUPs Study [see Adverse Reactions (6.8)].

Pharmacokinetic data from a pediatric study of the 84 evaluable subjects <12 years of age showed that no dose adjustment was required for patients ≥6 years old. Children aged 1 to 5 years had a shorter half-life and higher clearance (adjusted for body weight); it is not known whether ELOCTATE can cause fetal harm when administered to a pregnant woman, or whether it can affect reproduction capacity. If ELOCTATE is clearly needed to treat a pregnant woman, advise the patient that the risks to the fetus are unknown.

8.5 Geriatric Use
Clinical studies of ELOCTATE did not include sufficient numbers of subjects aged 65 and over to determine whether or not they respond differently from younger subjects.

11 DESCRIPTION
ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-dose vials containing nominal potencies of 250, 500, 750, and 1,250 IU per vial. ELOCTATE is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (SWFI) supplied in a sterile prefilled syringe for reconstitution. ELOCTATE contains no preservatives.

ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-dose vials containing nominal potencies of 250, 500, 750, and 1,250 IU per vial. ELOCTATE is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (SWFI) supplied in a sterile prefilled syringe for reconstitution. ELOCTATE contains no preservatives.

ELOCTATE is a recombinant fusion protein that temporarily replaces the missing Factor VIII component in the plasma of patients with severe hemophilia A. ELOCTATE contains the Fc region of human immunoglobulin G1 (IgG1), which binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
ELOCTATE is a recombinant fusion protein that temporarily replaces the missing Coagulation Factor VIII needed for effective hemostasis. ELOCTATE contains the Fc region of human immunoglobulin G1 (IgG1), which binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life.

12.2 Pharmacodynamics
Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation Factor VIII. ELOCTATE is a recombinant protein consisting of a B-domain deleted analogue of human Coagulation Factor VIII covalently linked to the human ingredient in ELOCTATE. BDD-rFVIIIFc is a recombinant protein consisting of a B-domain deleted recombinant Factor VIII, Fc fusion protein (BDD-rFVIIIFc) is the active polysorbate 20. ELOCTATE contains no preservatives.

The safety and efficacy of ELOCTATE was evaluated in two multicenter, prospective, open-label clinical trials in previously treated patients (PTPs) (adult and adolescent study) and in an extension study. The adult and adolescent study compared the efficacy of each of two prophylactic treatment regimens (individualized and fixed weekly) to episodic (on-demand) treatment; determined hemostatic efficacy in the treatment of bleeding episodes; and determined hemostatic efficacy during perioperative management in subjects undergoing major surgical procedures. The study enrolled a total of 165 previously treated male patients (PTPs) with severe Hemophilia A (<1% endogenous Factor VIII activity or a genetic mutation consistent with severe hemophilia A) A total of 135 subjects (91%) completed the study. The total mean (±SD) change in the percent endogenous Factor VIII activity after treatment with ELOCTATE was significant at 1 week, 4 weeks, and 12 weeks compared to baseline (p<0.001).

The pediatric study evaluated the efficacy of individualized prophylactic treatment; determined hemostatic efficacy in the treatment of bleeding episodes; and determined hemostatic efficacy during perioperative management in subjects undergoing surgical procedures. The study enrolled a total of 71 previously treated male pediatric patients with severe hemophilia A (<1% endogenous Factor VIII activity or a genetic mutation consistent with severe hemophilia A) A total of 135 subjects (91%) completed the study. The total mean (±SD) change in the percent endogenous Factor VIII activity after treatment with ELOCTATE was significant at 1 week, 4 weeks, and 12 weeks compared to baseline (p<0.001).

The safety and efficacy of ELOCTATE was evaluated in two multicenter, prospective, open-label clinical trials in previously treated patients (PTPs) (adult and adolescent study and pediatric study), and in an extension study. The adult and adolescent study compared the efficacy of each of two prophylactic treatment regimens (individualized and fixed weekly) to episodic (on-demand) treatment; determined hemostatic efficacy in the treatment of bleeding episodes; and determined hemostatic efficacy during perioperative management in subjects undergoing major surgical procedures. The study enrolled a total of 165 previously treated male patients (PTPs) with severe Hemophilia A (<1% endogenous Factor VIII activity or a genetic mutation consistent with severe hemophilia A). Of the 71 enrolled subjects, 69 received at least 1 dose of ELOCTATE and were evaluable for efficacy. All subjects were less than 12 years of age (35 were 1 to 5 years of age and 34 were 6 to 11 years of age).

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Pediatric Study</th>
<th>Adult and Adolescent Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=23</td>
<td>N=31</td>
<td>N=11</td>
</tr>
<tr>
<td>Incremental Recovery (IU/dl per IU/kg)</td>
<td>1.92 (1.80, 2.04)</td>
<td>2.44 (2.07, 2.80)</td>
</tr>
<tr>
<td>AUC/Dose (IU x h/dl per IU/kg)</td>
<td>30.0 (26.5, 33.5)</td>
<td>41.9 (34.5, 48.9)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>12.7 (11.2, 14.1)</td>
<td>14.9 (12.0, 17.8)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>17.2 (15.4, 19.1)</td>
<td>20.9 (17.1, 24.7)</td>
</tr>
<tr>
<td>CL (mL/h/kg)</td>
<td>3.60 (3.13, 4.07)</td>
<td>2.78 (2.34, 3.13)</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>58.6 (54.9, 62.3)</td>
<td>52.1 (45.3, 59.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CL = clearance interval; AUC = area under the FVIII activity time curve; T1/2 = terminal half-life; MRT = mean residence time; CL = body weight adjusted clearance; Vss = body weight adjusted volume of distribution at steady state.

PK parameters are presented in Arithmetic Mean (95% CI) ± SEM (± Standard Error of the Mean). The analysis included two adolescent subjects (15 and 16 years old).
The extension study evaluated the safety and efficacy of prophylactic treatment regimens or on-demand treatment, as well as hemostatic efficacy during perioperative management in subjects undergoing surgical procedures. The study enrolled a total of 240 previously treated male patients (aged 2 to 66 years old) with severe hemophilia A who completed the adult and adolescent study or the pediatric study.

On-demand Treatment and Control of Bleeding Episodes

In the adult and adolescent study, a total of 757 bleeding episodes in 106 subjects were treated with ELOCTATE. The majority of the bleeding episodes were spontaneous and localized in joints. The median dose per injection used to treat a bleeding episode was 27.35 (IQR 22.73, 32.71) IU/kg. Assessment of response to each injection was recorded by subjects at 8-12 hours after treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Efficacy in control of bleeding episodes in subjects ≥12 years of age is summarized in Table 6.

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In the pediatric study, a total of 86 bleeding episodes in 69 pediatric subjects were treated with ELOCTATE. Assessment of response to each injection was recorded by subjects at 8 to 12 hours post-treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Efficacy in control of bleeding episodes in subjects <12 years of age is summarized in Table 7.

The hemostatic efficacy in treatment of bleeds was rated excellent or good in 92.6% for all evaluable first injections.

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<tr>
<td>1 injection</td>
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<td>7 (18.4%)</td>
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In the pediatric study or the pharmacokinetics studies. Of the 45 major surgeries, 36 surgeries (80.0%) required a single perioperative dose to maintain hemostasis. Of the 42 major surgeries treated with at least one dose, the median average dose per injection to maintain hemostasis during surgery was 59.1 IU/kg (range 35-111). On the day of surgery, most subjects received a second injection. The total dose on the day of surgery ranged from 37.6-157.9 IU/kg.

Hemostatic response was assessed by the investigator using ordinal scales as follows:

*Excellent*: abrupt pain relief and/or improvement in bleeding; Good: definite pain relief and/or improvement in signs of bleeding but possibly requiring more than one injection; Moderate: probable beneficial effect and requiring more than one injection; No response: no improvement or condition worsens. Response evaluated at approximately 8-12 hours after treatment.

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<tr>
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*Median (interquartile range, 25th and 75th percentiles)*

Pediatric study

Sixty-nine (69) subjects received ELOCTATE on an individualized prophylactic dose regimen starting with a twice weekly regimen consisting of 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. The median total dose per injection used to treat a bleeding episode was 27.35 (IQR 22.73, 32.71) IU/kg. Assessment of response to each injection was recorded by subjects at 8-12 hours after treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess response. Efficacy in control of bleeding episodes in subjects ≥12 years of age is summarized in Table 6.

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ELOCTATE® is a registered trademark of Bioverativ Therapeutics Inc.

For patent information: https://www.sanofi.us/en/products-and-resources/patents

**Patient Information**

**ELOCTATE®** /’el’-ok’-tate /

[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

Please read this Patient Information carefully before using ELOCTATE and each time you get a refill, as there may be new information. This Patient Information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is ELOCTATE?**

ELOCTATE is an injectable medicine that is used to help control and prevent bleeding in people with Hemophilia A (congenital Factor VIII deficiency).

Your healthcare provider may give you ELOCTATE when you have surgery.

**Who should not use ELOCTATE?**

You should not use ELOCTATE if you had an allergic reaction to it in the past.

**What should I tell my healthcare provider before using ELOCTATE?**

Talk to your healthcare provider about:

- Any medical problems that you have or had.
- All prescription and non-prescription medicines that you take, including over-the-counter medicines, supplements or herbal medicines.
- Pregnancy or if you are planning to become pregnant. It is not known if ELOCTATE may harm your unborn baby.
- Breastfeeding. It is not known if ELOCTATE passes into the milk and if it can harm your baby.

**How should I use ELOCTATE?**

You get ELOCTATE as an infusion into your vein. Your healthcare provider will instruct you on how to do infusions on your own, and may watch you give yourself the first dose of ELOCTATE. Contact your healthcare provider right away if bleeding is not controlled after using ELOCTATE.

**What are the possible side effects of ELOCTATE?**

You can have an allergic reaction to ELOCTATE. Call your healthcare provider or emergency department right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash or hives.

Your body can also make antibodies called “inhibitors” against ELOCTATE. This can stop ELOCTATE from working properly. Your healthcare provider may give you blood tests to check for inhibitors. Additional common side effects of ELOCTATE are headache, rash, joint pain, muscle pain, and general discomfort.

If you have risk factors for developing abnormal blood clots in your body, such as an indwelling venous catheter, treatment with Factor VIII may increase this risk. These are not the only possible side effects of ELOCTATE. Tell your healthcare provider about any side effect that bothers you or does not go away.

**How should I store ELOCTATE?**

- Keep ELOCTATE in its original package.
- Protect it from light.
- Do not freeze.
- Store refrigerated (2°C to 8°C or 36°F to 46°F) or at room temperature [not to exceed 30°C (86°F)], for up to six months.
- When storing at room temperature:
  - Do not return the product to the refrigerator.
- Do not use ELOCTATE after the expiration date printed on the vial or, if you removed it from the refrigerator, after the date that was noted on the carton, whichever is earlier.

**Storage and Handling**

Prior to reconstitution:

- Store ELOCTATE in the original package to protect the ELOCTATE vials from light.
- Store ELOCTATE in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the pre-filled diluent syringe.
- ELOCTATE may be stored at room temperature, not to exceed 30°C (86°F), for a single period of up to 6 months, within the expiration date printed on the label.
- If stored at room temperature, record the date that ELOCTATE is removed from refrigeration on the carton in the area provided. After storage at room temperature, do not return the product to the refrigerator.
- Do not use beyond the expiration date printed on the vial or 6 months after the date that was written on the carton, whichever is earlier.

After Reconstitution:

- The reconstituted product may be stored at room temperature, not to exceed 30°C (86°F), for up to 3 hours. Protect from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded.
- Do not use ELOCTATE if the reconstituted solution is cloudy or has particulate matter.
- Discard any unused ELOCTATE.

**17 PATIENT COUNSELING INFORMATION**

Advise the patients to:

- Read the FDA approved patient labeling (Patient Information and Instructions for Use).
- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII therapy because this may be a sign of inhibitor development.

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Waltham, MA 02451
After reconstitution (mixing with the diluent):

- Do not use ELOCTATE if the reconstituted solution is not clear to slightly opalescent and colorless.
- Use reconstituted product as soon as possible.
- You may store reconstituted solution at room temperature, not to exceed 30°C (86°F), for up to three hours. Protect the reconstituted product from direct sunlight. Discard any product not used within three hours.

What else should I know about ELOCTATE?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use ELOCTATE for a condition for which it was not prescribed. Do not share ELOCTATE with other people, even if they have the same symptoms that you have.

This Patient Information has been approved by the US Food and Drug Administration.

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Waltham, MA 02451
A SANOFI COMPANY
US License Number 2078

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Revised: May 2023

ELOCTATE®
Antihemophilic Factor (Recombinant), Fc Fusion Protein

INSTRUCTIONS FOR USE

Read the Instructions for Use before you start using ELOCTATE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider should show you or your caregiver how to reconstitute and administer ELOCTATE the first time ELOCTATE is used.

Check the expiration date on the ELOCTATE kit.

**Do not use the product if past the expiration date.**

Allow the ELOCTATE vial and the diluent to come to room temperature.

**Do not use external heat sources such as putting the vial and/or diluent in hot water.**

Find a clean, flat work surface and collect all the supplies you will need to reconstitute and administer ELOCTATE.

Wash your hands with soap and water. **Aseptic technique** (clean and germ free) should be used.

**YOUR KIT CONTAINS:**

- Vial adapter with package
- Vial with powdered drug
- Prefilled diluent syringe
- Plunger rod

**RECONSTITUTION**

**Step 1**
Remove the plastic cap from the ELOCTATE vial.

Wipe the rubber stopper of the vial with an alcohol wipe and allow it to dry.

After cleaning, **do not touch the rubber stopper with your hand or allow it to touch any surface.**

**Step 2**
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 vial adapter.**

**Step 3**
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 center of the rubber stopper.**

Push the vial adapter straight down until the adapter spike punctures the center of the vial stopper and is fully inserted.

**Step 4**
Lift the package cover away from the vial adapter and discard the cover.

**Step 5**
**Only use the diluent syringe provided to reconstitute the drug product.**

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.

**Step 6**
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.**

**Step 7**
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.**
Step 8
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.

Step 9
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.

Step 10
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.

Step 11
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.

Step 12
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.

ADMINISTRATION (Intravenous Injection)
ELOCTATE is administered by intravenous infusion after reconstitution of the drug powder with the diluent.
Your healthcare provider should teach you how to infuse ELOCTATE.
Once you have been taught to self-infuse, you can follow these instructions.
Do not administer reconstituted ELOCTATE if it contains particulate matter, is discolored, or is cloudy.

Step 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.

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

Step 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.

POOLING
POOLING is the process of combining two or more reconstituted vials into a larger syringe (not into the diluent syringe) prior to intravenous administration.
If you are using two or more vials, follow these pooling steps.

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

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

Step 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.

Reconstituted ELOCTATE should be administered as soon as possible.

If you are using more than one vial, stop here and proceed to the Administration instructions on the back.
**Step 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.*

**Step 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._

**Step 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.

_Dispose of all unused solution, empty vial(s), and other used medical supplies in an appropriate medical waste container._

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**STORAGE CONDITIONS - PRODUCT KIT**
Keep refrigerated until use.
Keep away from direct sunlight.

**STORAGE CONDITIONS - RECONSTITUTED**
ELOCTATE should be administered within 3 hours after reconstitution.
Do not refrigerate after reconstitution.
Keep away from direct sunlight.

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For more information go to www.ELOCTATE.com or call 1-855-693-5628

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