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). One unit per kilogram body weight will raise the Factor VIII level by 2% (IU/dL). (2.1)
• 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)

Required Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)
• 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. More frequent or higher doses up to 80 IU/kg may be required. (2.1)

DOSAGE FORMS AND STRENGTHS
For injection: nominally 250, 500, 750, 1500, 2000, 3000, 4000, 5000, or 6000 IU, lyophilized powder in single-use vials for reconstitution. (3)

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)
• Development of Factor VIII neutralizing antibodies (inhibitors) may occur. 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
The most frequently occurring adverse reactions (>0.3% of subjects) in clinical trials were arthralgia, myalgia, headache, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bioverativ Therapeutics Inc. at 1-855-993-5628 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: 09/2019
Perioperative Management

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

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>Every 24-48 hours</td>
<td>Until bleeding episode is resolved</td>
</tr>
<tr>
<td>Joint, superficial muscle/no neurovascular compromise (except iliospss), deep laceration and renal, superficial soft tissue, mucous membranes</td>
<td></td>
<td></td>
<td>12 to 24 hours for patients less than 6 years of age</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>80-100</td>
<td>40-50</td>
<td>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>Life or limb threatening hemorrhage, iliospss and deep muscle with neurovascular injury, retropitoneum, intracranial, or gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Dosing for Perioperative Management

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Factor VIII Level Required (IU/kg 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</td>
<td>50-80</td>
<td>25-40</td>
<td>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>Uncomplicated tooth extraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>80-120 (pre- and post-operative)</td>
<td>Preoperative: 40-60</td>
<td>Repeat: 40-50</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>
<tr>
<td>Intracranial, intra-abdominal, or joint replacement surgery</td>
<td></td>
<td></td>
<td></td>
<td></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 or ELOCTATE administered twice weekly. Adjust the regimen based on patient response with dosing in the range of 25-85 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. Point 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.

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.
ELOCTATE is available as a white to off-white lyophilized powder in single use 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.

2 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 has been reported following administration of ELOCTATE, including in previously untreated patients. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after ELOCTATE administration, confirm that adequate Factor VIII levels have been achieved and maintained. [See Dosage and Administration (2.2).]

5.3 Monitoring Laboratory Tests

Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained. [See Dosage and Administration (2).]

Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of ELOCTATE. Use Bethesda Units (BU) to report inhibitor levels.

6 Adverse Reactions

The most frequently occurring adverse reactions (incidence >5.0% of subjects) reported in clinical trials were arthralgia, malaise, myalgia, headache, and rash.

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. 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 routine prophylaxis, or episodic treatment of bleeding 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 (18 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 80,846 with a median of 294 (range 1-735) exposure days per subject. The subjects received a total of 62,924 injections with a median of 203 (range 1-785) injections of ELOCTATE (range 1-756) per subject. Adverse events (AEs) were monitored for a total of 893.72 subject-years. Two subjects (0.7% of total 276) with cardiovascular risk factors each had a single cardiovascular event (myocardial infarction). Each of the cardiovascular events was fatal. The median age at the time of the myocardial infarction was 57 years (range 51-62 years). The adverse reaction profile has been consistent across all trials involving previously treated patients. The majority of the adverse events reported in previously treated patients were arthralgia, malaise, myalgia, headache, and rash.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the post-approval use of ELOCTATE.

- Arthralgia
- Malaise

In clinical trials of one drug cannot be directly compared to rates in clinical trials of another drug. The background risk of major birth defects and miscarriage in the indicated population is unknown, however, the background risk of major birth defects to 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 1.3%). 3 to 4 h following dosing of pregnant mice with 260 to 650 times the clinical dose of 20 to 51 IU/kg ELOCTATE [see Data]. 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 mother and to the fetus are unknown.

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.

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 the use of ELOCTATE or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy studies have been performed in 276 previously treated, pediatric patients <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. Pharmacokinetic data from a pediatric study of the 54 evaluable subjects <12 years of age showed that no dose adjustment was required for patients >6 years old. Children 1 to 5 years had a shorter half-life and higher clearance, adjusted for body weight; therefore, a higher dose or more frequent dosing may be needed in this age group. [See Clinical Pharmacology (12.3).]

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, Antithrombin Factor (Recombinant), Fc Fusion Protein, is a sterile, pyrogen-free, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single use vials containing nominal quantities of 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, 6000 IU of ELOCTATE. Each vial of ELOCTATE contains 1890 amino acids with an apparent molecular weight of 220 kDa. The majority of the expressed protein is proteolytically processed to a two chain molecule; however ELOCTATE may also contain up to 93% of a single chain, non-processed form. Both molecules have been shown to have comparable Factor VIII activity.

BDD-FvIIIcC is produced by recombinant DNA technology from a human embryonic kidney (HEK) cell line, which has been extensively characterized. The HEK cell line expresses BDD-FvIIIcC into a defined, cell culture medium that does not contain any proteins derived from animal or human sources. The FvIIIcC-FvIIIcC is purified using a series of chromatography steps, including affinity capture with a recombinant, single chain antibody fragment produced in a yeast expression system. No human or animal derived proteins are used in the purification or formulation steps. The production process also incorporates two dedicated viral clearance steps - a detergent treatment step for inactivation and a 15 nm filtration step for removal of viruses.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ELOCTATE is a recombinant fusion protein that temporarily replaces the missing Coagulation Factor VIII, BDD-FvIIIcC. BDD-rFVIIIFc is a recombinant Factor VIII, Fc fusion protein consisting of a B-domain deleted analogue of human Factor VIII (FVIII) covalently linked to the human immunoglobulin G (IgG) Fc domain sequence. The FVIII portion of the molecule has a 10 kDa heavy chain and an 83 kDa light chain (similar to endogenous Factor VIII), which are linked by 14 (of 908) amino acids from the B-domain of the FvIIIcC. The Fc portion contains the hinge, CH2, and CH3 regions of IgG. BDD-FvIIIcC contains 1890 amino acids with an apparent molecular weight of 220 kDa. The majority of the expressed protein is proteolytically processed to a two chain molecule; however ELOCTATE may also contain up to 93% of a single chain, non-processed form. Both molecules have been shown to have comparable Factor VIII activity.

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12.2 Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation Factor VIII, resulting in a prolonged, patient plasma clotting time as measured by the activated partial thromboplastin time (aPTT) assay. Treatment with ELOCTATE normalizes the aPTT over the effective dosing period.

Table 3: Adverse Reactions Reported for ELOCTATE (N=276)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Adverse Reaction</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>

#MedDRA version 15.0

Immunogenicity

Clinical trial subjects were monitored for neutralizing antibodies to Factor VIII. No subjects developed robust 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. The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease. Therefore, it may be misleading to compare the incidence of antibodies to ELOCTATE with the incidence of antibodies to other products.
The Pharmacokinetics (PK) of ELOCTATE (FVIIIc) were evaluated in 28 subjects following a 10-minute intravenous infusion of a single dose of 50 IU/kg. The PK parameters were based on plasma FVIII activity measured by the one-stage clotting assay. The PK profile obtained at week 14, after repeated dosing, was comparable with the PK profile obtained after the first dose. The PK data demonstrated that ELOCTATE has a prolonged circulating half-life. Time to T1/2 was 5.10 days (95% CI: 4.54, 5.65). The terminal plasma half-life of ELOCTATE when compared against a currently marketed recombinant Factor VIII (ADVATE®) was 1.5 fold longer.

Pediatric and Adolescent Pharmacokinetics

Pharmacokinetic (PK) parameters of ELOCTATE were determined for adolescents (ages 12 to 17 years) in the adult and adolescent study and for children (ages 1 to 5 years and 6 to 11 years) in the pediatric study. Table 4 presents the PK parameters calculated from the pediatric data of 65 subjects, less than 12 years of age, after receiving a single 50 IU/kg dose. Compared to adults and adolescents, body weight adjusted clearance was 75% higher in children 1 to 5 years of age. These results indicate a need for dose adjustments in children 1 to 5 years of age.

The PK evaluation of pediatric subjects, ages 6 to 17 years, showed that their PK profiles and arithmetic means of PK parameters are similar to those of adults. Therefore, for subjects 6 years and older, an age-based dose adjustment is not required.

Table 4: Comparison of PK Parameters of ELOCTATE by Age

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Pediatric Study</th>
<th>Adult and Adolescent Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental Recovery (IU x h/dL per IU/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 23</td>
<td>N = 31</td>
<td>N = 11</td>
</tr>
<tr>
<td>1.92 (1.80, 2.04)</td>
<td>2.44 (2.07, 2.80)</td>
<td>1.85 (1.58, 2.12)</td>
</tr>
<tr>
<td>AU/C dose (IU x h/dL per IU/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.00 (26.5, 33.6)</td>
<td>41.9 (34.0, 49.8)</td>
<td>36.7 (34.3, 43.1)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.7 (11.2, 14.1)</td>
<td>14.9 (12.0, 17.8)</td>
<td>16.4 (14.1, 18.6)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.2 (15.4, 19.1)</td>
<td>20.2 (17.1, 24.7)</td>
<td>23.1 (19.3, 26.4)</td>
</tr>
<tr>
<td>CL (mL/h/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.60 (3.13, 4.07)</td>
<td>2.78 (2.44, 3.13)</td>
<td>2.66 (2.34, 2.98)</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58.6 (54.9, 62.3)</td>
<td>52.1 (45.3, 59.0)</td>
<td>60.3 (53.3, 67.3)</td>
</tr>
</tbody>
</table>

*PK parameters are presented in Arithmetic Mean (95% CI)

**The analysis included two adolescent subjects (15 and 16 years old)

**Abbreviations: AU/C = 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

12.3 Pharmacokinetics

The pharmacokinetics of ELOCTATE were assessed in clinical trials (adult and adolescent study and pediatric study), and in an extension study. A total of 86 bleeds were rated excellent or good in 92.6% for all evaluable first injections.

### Table 5: ELOCTATE Efficacy in Control of Bleeding in Subjects ≥12 Years of Age

<table>
<thead>
<tr>
<th># of injections to treat bleeding episodes</th>
<th>(n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 injection</td>
<td>661 (67.3%)</td>
</tr>
<tr>
<td>2 injections</td>
<td>79 (10.4%)</td>
</tr>
<tr>
<td>≥2 injections</td>
<td>17 (2.2%)</td>
</tr>
</tbody>
</table>

Response to first injection

| Excellent or good | 78.1% |
| Moderate | 21.2% |
| No response | 0.7% |

*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.

### Table 6: ELOCTATE Efficacy in Control of Bleeding in Pediatric Subjects <12 Years of Age

<table>
<thead>
<tr>
<th>New bleeding episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=35)</td>
</tr>
<tr>
<td>1 injection</td>
</tr>
<tr>
<td>2 injections</td>
</tr>
<tr>
<td>≥2 injections</td>
</tr>
</tbody>
</table>

**Median dose per injection (IU/kg) to treat a bleeding episode (IGR)**

| (n=35) | (n=46) |
|-----------------------|
| Median total dose (IU/kg) to treat a bleeding episode (IGR) | 51.35 (28.5, 59.52) | 48.15 (28.08, 55.97) | 49.66 (28.40, 86.28) |
| Median dose per injection (IU/kg) to treat a bleeding episode (IGR) | 56.49 (29.14, 72.48) | 53.39 (28.13, 66.80) | 54.96 (29.41, 71.09) |

Response to first injection

| Excellent or good | 32 (91.4%) | 43 (93.5%) | 75 (92.6%) |
| Excellent | 3 (8.6%) | 1 (2.2%) | 4 (4.9%) |
| Moderate | 0 (0.0%) | 2 (4.3%) | 2 (2.5%) |

*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.

### Table 7: ELOCTATE Efficacy in Control of Bleeding in Subjects ≥12 Years of Age

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For forty-one (41) major surgeries in twenty-nine (29) subjects, hemostatic response was assessed and rated as excellent in 38 (93%) surgeries and good in 3 (7%) surgeries. Types of surgeries assessed include major orthopedic procedures such as joint replacements (bilateral knee, as well as unilateral elbow, hip and knee replacements), ankle fusion and amputation. Other major surgeries include appendectomy, arthroscopy, spinal surgery, and inguinal hernia repair.

Minor Surgeries

A hemostatic assessment of 72 minor surgical procedures in 59 subjects from all three studies was conducted with all (100%) having excellent or good response (excellent response [61 of 72, 84.7%] and good response [11 of 72, 15.3%]).

Routine Prophylaxis

**Adult and Adolescent Study**

The efficacy of routine prophylaxis was evaluated against on-demand treatment. A total of 117 subjects received an individualized, twice weekly regimen, which started with 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. The dose and interval were adjusted within the range of 25-65 IU/kg every 3-5 days to maintain trough levels between 1% and 3% above baseline, or higher, as clinically indicated to prevent bleeding. The median dosing interval was 3.5 days. Among the 112 subjects treated for at least 6 months, 111 (99%) achieved a dosing interval of three days or longer, 39 (35%) achieved a dosing interval of 4 days or longer, and 23 (21%) achieved a dosing interval of 5 days or longer during the last 3 months on study. Twenty-three subjects received 65 IU/kg of ELOCTATE once weekly for a median period of 28 weeks. An additional 23 subjects received episodic (on-demand) doses of ELOCTATE for the treatment of bleeding episodes and were on study for a median period of 29 weeks. Using a negative binomial model to analyze the annualized bleeding rate (ABR), there was a statistically significant reduction in ABR of 92% (p < 0.001) for subjects in the individualized prophylaxis arm and a statistically significant reduction of 76% (p < 0.001) for subjects in the weekly prophylaxis arm compared to the episodic (on-demand) arm. Fifty-three (53) of 117 (45%) subjects experienced no bleeding episodes while on individualized prophylaxis and 4 of 23 (17%) subjects experienced no bleeding episodes while on weekly prophylaxis.

Median ABRS in subjects evaluable for efficacy is summarized in Table 7.

**Spontaneous ABR**

<table>
<thead>
<tr>
<th>Bleeding Episode Etiology</th>
<th>Individualized Prophylaxis (N=117)</th>
<th>Episodic (On-Demand) (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ABR</td>
<td>1.6</td>
<td>33.6</td>
</tr>
<tr>
<td></td>
<td>(0.0, 4.7)</td>
<td>(21.1, 48.7)</td>
</tr>
<tr>
<td>Spontaneous ABR</td>
<td>0.0</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>(0.0, 2.0)</td>
<td>(12.2, 36.8)</td>
</tr>
<tr>
<td>Joint ABR</td>
<td>0.0</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>(0.0, 3.1)</td>
<td>(15.9, 39.0)</td>
</tr>
</tbody>
</table>

1. 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 dose could be adjusted within the range of 25-80 IU/kg for every 2 days to maintain trough levels of 1% above baseline or as clinically indicated to prevent bleeding. The median dosing interval was 3.49 days (interquartile range, 3.46 to 3.51 days) with no difference in the median dosing interval between age cohorts. 89.9% of subjects remained on a twice weekly interval. The median weekly dose of ELOCTATE for subjects 1-5 years of age was 91.63 IU/kg (interquartile range, 84.72 to 104.58 IU/kg). For subjects in the 6 to 11 years of age cohort, the median weekly dose was 86.88 IU/kg (IQR, 79.12 to 103.08 IU/kg). Of all subjects, 32 (46.4%) experienced no bleeding episodes (18 subjects [51.4%] 1-5 years of age and 14 subjects [41.2%] 6 to 11 years of age). A presentation of the median ABRS evaluable for efficacy is summarized in Table 8.

<table>
<thead>
<tr>
<th>Bleeding Episode Etiology</th>
<th>1-5 Years (N=35)</th>
<th>6 to 11 Years (N=34)</th>
<th>Total (&lt;12 Years of Age) (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ABR</td>
<td>0.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(0.0, 4.0)</td>
<td>(0.0, 4.0)</td>
<td>(0.0, 4.0)</td>
</tr>
<tr>
<td>Spontaneous ABR</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>(0.0, 0.0)</td>
<td>(0.0, 0.0)</td>
<td>(0.0, 0.0)</td>
</tr>
<tr>
<td>Joint ABR</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>(0.0, 1.9)</td>
<td>(0.0, 2.0)</td>
<td>(0.0, 2.0)</td>
</tr>
</tbody>
</table>

1. Median (interquartile range, 25th and 75th percentiles)

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

**How Supplied**

ELOCTATE® is supplied in kits comprising a single use vial containing nominally, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000 or 6000 international units (IU) of Factor VIII potency; a pre-filled syringe with 3 mL sterile water for injection, and a sterile vial adapter (reconstitution device). The actual amount of ELOCTATE in IU is stated on the label and carton of each vial. Not made with natural rubber latex.

**Strength** | **Potency Color Code** | **Kit NDC Number**
---|---|---
250 IU | Yellow | 71104-801-01
500 IU | Red | 71104-802-01
750 IU | Garnet | 71104-803-01
1000 IU | Green | 71104-804-01
1500 IU | Dark Green | 71104-805-01
2000 IU | Royal Blue | 71104-806-01
3000 IU | Mist Grey | 71104-807-01
4000 IU | Orange | 71104-808-01
5000 IU | Mist Brown | 71104-809-01
6000 IU | Purple | 71104-810-01

**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

Advises 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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**FDA-Approved Patient Labeling Patient Information**

ELOCTATE® /el’ ok’ tate / [Antithemophilic Factor (Recombiant), 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.

Common side effects of ELOCTATE are headache, rash, joint pain, muscle pain and general discomfort.

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:
  - Note on the carton the date on which the product is removed from refrigeration.
  - Use the product before the end of this 6 month period or discard it.
  - 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.

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.

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Revised: December 2017
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.

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

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.

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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:

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).

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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.
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.

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.

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.
Revised September 2017

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

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