ADVATE® is FDA approved for prophylaxis in both adults & children (0-16 years)¹

You should be trained on how to do infusions by your hemophilia treatment center or your healthcare provider.

Please see ADVATE Indications and Detailed Important Risk Information on page 3. Please see accompanying ADVATE full Prescribing Information.

ADVATE [Antihemophilic Factor (Recombinant)]
There's more to life.
<table>
<thead>
<tr>
<th>INFUSION RECORDS</th>
<th>VIAL INFORMATION</th>
<th>INFUSION RECORDS</th>
<th>VIAL INFORMATION</th>
<th>INFUSION RECORDS</th>
<th>VIAL INFORMATION</th>
</tr>
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<tbody>
<tr>
<td>(combine all vials used)</td>
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<td>(combine all vials used)</td>
<td>Expiration date: <em><strong>/</strong></em>/___</td>
<td>(combine all vials used)</td>
<td>Expiration date: <em><strong>/</strong></em>/___</td>
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<td>Lot number: ________</td>
<td>Time: ❑ AM ❑ PM</td>
<td>Lot number: ________</td>
<td>Time: ❑ AM ❑ PM</td>
<td>Lot number: ________</td>
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<td>Units: ________ IU</td>
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<td>Total units: ________ IU</td>
<td>Units: ________ IU</td>
</tr>
<tr>
<td>Reason: ❑ Prophylaxis</td>
<td>❑ Spontaneous</td>
<td>❑ Injury</td>
<td>❑ Surgery/Dental</td>
<td>❑ Other</td>
<td>❑ Prophylaxis</td>
</tr>
</tbody>
</table>

Please see ADVATE Detailed Important Risk Information on page 3.

You should be trained on how to do infusions by your hemophilia treatment center or your healthcare provider.
ADVATE [Antihemophilic Factor (Recombinant)] Important Information

Indications

ADVATE is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called “classic” hemophilia).

ADVATE is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A.

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

ADVATE can reduce the number of bleeding episodes in adults and children (0-16 years) when used regularly (prophylaxis).

ADVATE is not used to treat von Willebrand disease.

DETAILED IMPORTANT RISK INFORMATION

You should not use ADVATE if you:

• Are allergic to mice or hamsters.
• Are allergic to any ingredients in ADVATE.

Tell your healthcare provider if you are pregnant or breastfeeding because ADVATE may not be right for you.

You should tell your healthcare provider if you:

• Have or have had any medical problems.
• Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
• Have any allergies, including allergies to mice or hamsters.
• Have been told that you have inhibitors to factor VIII (because ADVATE may not work for you).

Your body may form inhibitors to factor VIII. An inhibitor is part of the body's normal defense system. If you form inhibitors, it may stop ADVATE from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

You can have an allergic reaction to ADVATE.

Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea or fainting.

Side effects that have been reported with ADVATE include: cough, headache, joint swelling/aching, sore throat, fever, itching, dizziness, hematoma, abdominal pain, hot flashes, swelling of legs, diarrhea, chills, runny nose/congestion, nausea/vomiting, sweating, and rash.

Tell your healthcare provider about any side effects that bother you or do not go away or if your bleeding does not stop after taking ADVATE.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see accompanying ADVATE full Prescribing Information.

Reference

1. ADVATE Prescribing Information.

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CONTRAINDICATIONS
Do not use in patients who have life-threatening hypersensitivity reactions, including anaphylaxis, to mouse or hamster protein or other constituents of the product (mannitol, trehalose, sodium chloride, histidine, Tris, calcium chloride, polysorbate 80, and/or glutathione). (4)

WARNINGS AND PRECAUTIONS
• Hypersensitivity reactions, including anaphylaxis, may occur. Patients may develop hypersensitivity to mouse or hamster protein, which is present in trace amounts in the product. Should symptoms occur, discontinue treatment with ADVATE and administer appropriate treatment. (5.1)
• Development of activity-neutralizing antibodies 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
• Serious adverse drug reactions reported are hypersensitivity and factor VIII inhibitors. (6.1)
• The most common adverse drug reactions observed in greater than 5% of patients are pyrexia, headache, cough, nasopharyngitis, arthralgia, vomiting, upper respiratory tract infection, limb injury, nasal congestion, and diarrhea. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Baxalta US Inc. at 1-800-999-1785 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS
• Pregnancy: No human or animal data. Use only if clearly needed. (8.1)
• Pediatric Use: Clearance (based on per kg body weight) is higher in the pediatric population. Dose adjustment may be needed. (8.4)
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
1 INDICATIONS AND USAGE

ADVATE [Antihemophilic Factor (Recombinant)] is a recombinant antihemophilic factor indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency) for:

- Control and prevention of bleeding episodes.
- Perioperative management.
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ADVATE is not indicated for the treatment of von Willebrand disease.

2 DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only.

2.1 Dose

- Dosage and duration of treatment depend on the severity of factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.

- Each vial of ADVATE has the recombinant factor VIII potency in International Units (IU) stated on the label. The expected in vivo peak increase in factor VIII level expressed as IU/dL of plasma or percent of normal can be estimated using the following formulas:
  
  \[ \text{IU/dL or % of normal} = \left( \frac{\text{total dose} \times \text{body weight (kg)}}{2 \times \text{IU/UdL}} \right) \]

  **OR**

  \[ \text{Required dose (International Units) = body weight (kg) \times desired factor VIII rise (IU/UdL or % of normal) \times 0.5 (IU/kg per IU/dL)} \]

Examples (assuming patient’s baseline factor VIII level is <1% of normal):

1. A dose of 1750 IU ADVATE administered to a 70 kg patient should be expected to result in a peak post-infusion factor VIII increase of: 1750 IU \times \left( \frac{2 \times \text{IU/UdL}}{70 \text{ kg}} \right) = 50 IU/dL.

2. A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be 40 kg \times 70 \text{ IU/dL} \times \left( \frac{2 \times \text{IU/UdL}}{70 \text{ kg}} \right) = 1400 IU.

- Base the dose and frequency on the individual clinical response. Patients may vary in their pharmacokinetics (e.g., half-life, in vivo recovery) and clinical responses to ADVATE. Although the dose can be estimated by the calculations above, whenever possible, perform appropriate laboratory tests including serial factor VIII activity assays. [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Control and Prevention of Bleeding Episodes

A guide for dosing ADVATE for the control and prevention of bleeding episodes is provided in Table 1. The goal of treatment is to maintain a plasma factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Type of Bleeding Episode</th>
<th>Factor VIII Level Required (% of normal or IU/dL)</th>
<th>Dosea (IU/kg)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>Early hemorrhage, mild muscle bleeding, or mild oral bleeding episode.</td>
<td>20-40</td>
<td>10-20</td>
<td>12-24 (Every 8 to 24 hours for patients under the age of 6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Muscle bleeding, bleeding into the oral cavity, definite hemorrhages, and known trauma.</td>
<td>30-60</td>
<td>15-30</td>
<td>12-24 (Every 8 to 24 hours for patients under the age of 6)</td>
</tr>
<tr>
<td>Major</td>
<td>Significant gastrointestinal bleeding, intracranial, intra-abdominal or intra-articular bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or illoposis sheath, fractures, head trauma.</td>
<td>60-100</td>
<td>30-50</td>
<td>8-24 (Every 6 to 12 hours for patients under the age of 6)</td>
</tr>
</tbody>
</table>

*aDose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) \times 0.5 (IU/kg per IU/dL)"

Table 2: Dosing for Perioperative Management

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Factor VIII Level Required (% of normal or IU/dL)</th>
<th>Dosea (IU/kg)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>Including tooth extraction</td>
<td>60-100</td>
<td>30-50</td>
<td>Single dose within one hour of the operation. 12-24 (as needed to control bleeding)</td>
</tr>
<tr>
<td>Major</td>
<td>Intracranial, intra-abdominal, or intra-articular bleeding, joint replacement surgery</td>
<td>80-120 (pre- and post-operative)</td>
<td>40-60</td>
<td>One dose preoperative to achieve 100% activity. Every 9-24 to keep factor VIII activity in desired range. (Every 6 to 24 hours for patients under the age of 6)</td>
</tr>
</tbody>
</table>

*aDose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) \times 0.5 (IU/kg per IU/dL)"

Routine Prophylaxis

- Use dose of 20 to 40 International Units of factor VIII per kg body weight every other day (3 to 4 times weekly).
- Alternatively, use every third day dosing regimen targeted to maintain FVIII trough levels ≥1%.
- Adjust dose based on the patient’s clinical response.12

2.2 Preparation and Reconstitution

Preparation

- Do not remove ADVATE or diluent vials from the external housing.
- Always work on a clean surface and wash your hands before performing the procedures.
- Examine the packaging containing ADVATE to ensure no damage or peeling of the label is evident. Do not use if the lid is not completely sealed on the blister. Do not remove ADVATE or diluent vials from the external housing.

Reconstitution

1. Allow the ADVATE package to reach room temperature.

2. Open the package by peeling away the lid. Remove ADVATE from the external housing.

3. Place the ADVATE on a flat surface with the diluent vial on top (Figure A). Do not inject air into the ADVATE. For intravenous injection after reconstitution only.

4. With one hand holding the ADVATE housing, press down firmly on the ADVATE housing and diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADVATE vial (Figure B). Do not tilt the system until the transfer is complete.

5. Verify that diluent transfer is complete. Swirl gently until the powder is dissolved (Figure C). Do not shake. Do not refrigerate after reconstitution.

2.3 Administration

For intravenous injection after reconstitution only.

- Inspect parenteral drug products for discoloration and particulate matter. The ADVATE powder should be white to off-white in color and the diluent free from foreign particles. Do not use if the criteria are not met.
- Adjust dose based on the patient’s clinical condition.12

Perioperative Management

A guide for dosing ADVATE during surgery (perioperative management) is provided in Table 2. The goal of treatment is to maintain a plasma factor VIII activity level at or above the plasma level (in % of normal or in IU/dL) outlined in Table 2.
6 ADVERSE REACTIONS

Serious adverse reactions seen with ADVATE are hypersensitivity reactions, including anaphylaxis, and the development of high-titer inhibitors necessitating alternative treatments to factor VIII.

The most common adverse reactions observed in clinical trials (frequency greater than 5% of subjects) were pyrexia, headache, cough, nasopharyngitis, arthralgia, vomiting, upper respiratory tract infection, limb injury, nasal congestion, and diarrhea.

6.1 Clinical Trials Experience

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

ADVATE has been evaluated in eleven clinical trials in previously treated patients (PTPs) and one trial in previously untreated patients (PUPs) with severe to moderately severe hemophilia A (factor VIII ≤2% of normal). A total of 418 subjects have been treated with ADVATE as of January 2012. Total exposure to ADVATE was 63,188 infusions. The median duration of participation per subject was 397 (min-max: 2–1620) days and the median number of exposure days to ADVATE per subject was 97 (min-max: 1–709).

The summary of adverse reactions with a frequency >5% are shown in Table 3 below. No subject was withdrawn from a clinical trial due to an adverse reaction.

Table 3
Summary of Adverse Reactions (ARs)* with a Frequency Greater than 5% in 418 Subjects

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number of Adverse Reactions</th>
<th>Number of Subjects</th>
<th>Percent of Subjects</th>
</tr>
</thead>
</table>
| 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ADVATE. 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.
**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category C. Animal reproduction studies have not been conducted with ADVATE. It is not known whether ADVATE can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. ADVATE should be given to a pregnant woman only if clearly needed.

**8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ADVATE is administered to a nursing woman.

**8.4 Pediatric Use**

Pharmacokinetic studies in children have demonstrated higher clearance, a shorter half-life and lower recovery of factor VIII compared to adults. (see Clinical Pharmacology (12.3)). This may be explained by differences in body composition and should be taken into account when dosing or following factor VIII levels in the pediatric population. Because clearance (based on per kg body weight) has been demonstrated to be higher in the pediatric population, dose adjustment or more frequent dosing based on per kg body weight may be needed in this population. (see Clinical Pharmacology (12.3)). In the ADVATE routine prophylaxis clinical trial, 3 children aged 7 to <12 and 4 adolescents aged 12 to <16 were included in the per-protocol analysis. The reductions in annualized bleeding rate per subject per year during any prophylaxis regimen as compared to during on-demand therapy were similar among children, adolescents, and adults.

**8.5 Geriatric Use**

Clinical trials of ADVATE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Individualize dose selection for geriatric patients.

**11 DESCRIPTION**

ADVATE [Antihemophilic Factor (Recombinant)] is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line but does not contain plasma or albumin. The CHO cell line employed in the production of ADVATE is derived from that used in the biosynthesis of RECOMBINATE [Antihemophilic Factor (Recombiant)]. ADVATE has been shown to be comparable to RECOMBINATE with respect to its biochemical and physicochemical properties, as well as its non-clinical in vivo pharmacology.

In culture, the CHO cell line expresses the recombinant antihemophilic factor (rAHF) into the cell culture medium. The rAHF is purified from the culture medium using a series of chromatography columns. The purification process includes an immunoaffinity chromatography step in which a monoclonal antibody directed against factor VIII is employed to selectively isolate the rAHF from the medium. The cell culture and purification processes used in the manufacture of ADVATE employ no additives of human or animal origin. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. The rAHF synthesized by the CHO cells has a similar combination of heterogeneous heavy and light chains as in vivo recovery values for the test and control products were within the pre-established limits of 0.80 and 1.25. In addition, in vivo recoveries at the onset of treatment and after ≥75 exposure days were compared for 62 subjects. Results of this analysis indicated no significant change in the in vivo recovery at the onset of treatment and after ≥75 exposure days.

In an analysis of data from 58 subjects with 65 surgical procedures in the perioperative management trial, the target factor VIII level was met or exceeded in all cases following a single loading dose ranging from 29 to 104 IU/kg.

Pharmacokinetic parameters calculated from 98 subjects less than 16 years of age ( intent-to-treat analysis) are available for 7 infants (1 month to less than 2 years), 32 children (2 to less than 5 years), 24 older children (5 to less than 12 years), and 35 adolescents (12 to less than 16 years), as shown in Table 7. The mean clearance (based on body weight) of ADVATE in infants, children, older children, and adolescents was higher than adults (3.6 mL/kg/hr). The mean half-life of ADVATE in infants, children, older children, and adolescents was lower than adults (12 hours). The extent to which these differences may be clinically significant is not known.

Each ADVATE housing is labeled with the rAHF activity expressed in international units. Biological potency is determined by an in vitro assay, which employs a factor VIII concentrate standard that is referenced to a WHO international standard for factor VIII concentrates. One international unit, as defined by the WHO standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1 mL of fresh pooled human plasma. The specific activity of ADVATE is 4000 to 10000 International Units per milligram of protein.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

ADVATE temporarily replaces the missing coagulation factor VIII that is needed for effective hemostasis.

**12.2 Pharmacodynamics**

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia. Determination of aPTT is a conventional in vitro assay for biological activity of factor VIII. Treatment with ADVATE normalizes the aPTT over the effective dosing period.

**12.3 Pharmacokinetics**

A randomized, crossover pharmacokinetic trial of ADVATE (test) and RECOMBINE [Antihemophilic Factor (Recombiant)] (reference) was conducted in 56 non-bleeding subjects. The subjects received either of the products as an IV infusion (50 + 5 IU/kg body weight) and there was a washout period of 72 hours to 4 weeks between the two infusions. The pharmacokinetic parameters were calculated from factor VIII activity measurements in blood samples obtained up to 48 hours following each infusion. The per-protocol analysis included 30 patients (20 adults and 10 children). Pharmacokinetic parameters for the 20 adults for each trial are presented in Table 6.
A total of 837 bleeding episodes occurred in 70 of the 81 subjects. The other 11 subjects experienced no bleeding episodes. The response to treatment with ADVATE was rated as excellent or good for 80.4% of all bleeding episodes. Most (88%) bleeding episodes required only 1 or 2 infusions to obtain hemostasis. Among the 837 bleeding episodes, 2 (0.3%) did not require treatment (0 infusions), 521 (62.2%) required 1 infusion, 216 (25.8%) required 2 infusions, 23 (2.7%) required 3 infusions, and 75 (9.0%) required 4 or more infusions. By etiology, 45.3% of these bleeding events were secondary to trauma and 27.7% occurred spontaneously; the other 27% had an undetermined etiology.

In vivo recoveries at the onset of treatment and after 75 exposure days were compared for 62 subjects and there were no significant differences.

**Perioperative Management Study**

The safety and efficacy of ADVATE for perioperative management was investigated in 59 subjects with severe or moderately severe hemophilia A (factor VIII <2%). They were between the ages of 7 to 65 years of age (3 were 7 to <13, 6 were 13 to <16, and 50 were >16). Fifty-five were Caucasian, 3 were Black, and 1 was Asian. One subject elected not to undergo the planned surgery. Thus, 58 subjects underwent 65 surgical procedures, among which, 6 subjects underwent more than 1 procedure each. One subject withdrew during the postoperative period; thus, 57 subjects completed the study. Of the 65 procedures, 22 in 22 subjects were classified as major, 35 in 28 subjects were classified as minor, and 8 in 8 subjects were dental. (See Table 2 for definitions of major and minor procedures).

Prior to surgery, subjects received a pre-operational loading dose aimed at increasing the plasma factor VIII level to 60% to 100% of normal for dental procedures or 80% to 120% of normal for all other surgical procedures. During the surgery, subjects received replacement therapy by either bolus (47 procedures) or continuous infusion (18 procedures). For continuous infusion, the initial rate was 4 IU/kg/hr for subjects >12 years of age and 5 IU/kg/hr for subjects 5 to 12 years of age. After discharge, subjects received ADVATE for 2 to 28 days. (See Table 7 for the definition of continuous infusion interval).

ADVATE use in two prophylactic treatment regimens compared to that of on-demand therapy. In a multicenter, open-label, prospective, randomized, controlled postmarketing clinical trial of ADVATE use in two prophylactic treatment regimens compared to that of on-demand therapy, 53 PTPs with severe to moderately severe hemophilia A (factor VIII ≤2%) were enrolled. They were between the ages of 12 to <16 years (N = 35) or 16 years and older (N = 34) who had completed at least 75 exposure days of treatment with ADVATE. The median annual bleed rate during the on-demand therapy period was 44 bleeds per subject per year compared to 1 bleed per subject per year while on either prophylaxis regimen, which was a statistically significant difference (p<0.001). Twenty-five of 53 (42%) subjects experienced no bleeding episodes while on prophylaxis for one year. While there was no statistically significant difference in bleeding frequency observed between the two prophylaxis regimens studied, the trial was not powered to demonstrate equivalence in bleeding rate between the two prophylaxis arms.

### Table 7

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Infants (N = 7) (1 month to &lt;2 yrs)</th>
<th>Children (N = 32) (2 to &lt;5 yrs)</th>
<th>Older Children (N = 24) (5 to &lt;12 yrs)</th>
<th>Adolescents (N = 30) (12 to &lt;16 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC,0-∞ (IU/min/L)</td>
<td>1240 ± 330</td>
<td>1104 ± 424</td>
<td>1396 ± 506</td>
<td>1300 ± 469</td>
</tr>
<tr>
<td>Incremental Recovery at C∞ (IU/L per IU/kg)</td>
<td>2.1 ± 0.5</td>
<td>1.8 ± 0.4</td>
<td>2.1 ± 0.6</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>8.7 ± 1.4</td>
<td>9.5 ± 1.8</td>
<td>11.2 ± 3.5</td>
<td>12.9 ± 2.9</td>
</tr>
<tr>
<td>Maximum Plasma</td>
<td>104 ± 27</td>
<td>91 ± 19</td>
<td>105 ± 34</td>
<td>103 ± 25</td>
</tr>
<tr>
<td>Concentration Post Infusion (IU/L)</td>
<td>14.3 ± 4.3</td>
<td>14.9 ± 4.6</td>
<td>14.8 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>Mean Residence Time (hr)</td>
<td>10.4 ± 2.5</td>
<td>11.8 ± 2.8</td>
<td>14.3 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>Volume of Distribution</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>Clearance (mL/hr/kg)</td>
<td>4.3 ± 1.0</td>
<td>4.8 ± 1.5</td>
<td>4.1 ± 1.5</td>
<td>4.2 ± 1.2</td>
</tr>
</tbody>
</table>

*Incremental recovery at C∞ calculated as C∞/baseline factor VIII divided by the dose in IU/kg, where C∞ is the maximal post-infusion factor VIII measurement.

### Table 8

<table>
<thead>
<tr>
<th>Rate of New Bleeding Episodes During Prophylaxis</th>
<th>Mean (± SD)</th>
<th>New Bleeding Episodes/Subject/Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>0.34 ± 0.49</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic</td>
<td>0.39 ± 0.46</td>
<td></td>
</tr>
<tr>
<td>Unknown/Indeterminate</td>
<td>0.33 ± 0.34</td>
<td></td>
</tr>
</tbody>
</table>

The pharmacokinetic properties of ADVATE were investigated at the beginning of treatment in a multicenter trial of previously treated subjects and at the end of treatment in a subset of subjects (n = 34) who had completed at least 75 exposure days of treatment with ADVATE. [Clinical Pharmacology (12:3)]

### Table 7

**Clinical Pharmacology**

**Clinical Studies**

**Original Safety and Efficacy Study**

A safety and efficacy trial evaluated the pharmacokinetics (double-blinded, randomized, cross-over, safety, immunogenicity, and hemostatic efficacy (open-label) of ADVATE in 111 subjects. The trial was conducted in the US and Europe with 103 Caucasian, 7 Black, and 1 Asian patients (102 individuals were evaluable). Subjects with severe or moderately severe hemophilia A (factor VIII <2%) were enrolled. They were between 7 to 65 years of age. Subjects who were >10 years of age (20 were 10 to <13, 50 were >16). Fifty-five were Caucasian, 3 were Black, and 1 was Asian. Subjects initially treated for 6 months of on-demand therapy and then randomized to 12 months of either a standard prophylaxis regimen (20-40 IU/kg every 48 hours) or PK-driven prophylaxis regimen (20-80 IU/kg every 72 hours). All subjects had a history of at least 8 joint bleeding episodes per year upon entering the trial. Each subject in the per-protocol group was adherent to >90% of the prescribed number of prophylactic infusions. No subjects in the per-protocol group were enrolled in another clinical trial at the time of drain removal were rated as excellent or good for 80.4% of all bleeding episodes. Most (88%) bleeding episodes required only 1 or 2 infusions to obtain hemostasis. Among the 837 bleeding episodes, 2 (0.3%) did not require treatment (0 infusions), 521 (62.2%) required 1 infusion, 216 (25.8%) required 2 infusions, 23 (2.7%) required 3 infusions, and 75 (9.0%) required 4 or more infusions. By etiology, 45.3% of these bleeding events were secondary to trauma and 27.7% occurred spontaneously; the other 27% had an undetermined etiology.

In vivo recoveries at the onset of treatment and after 75 exposure days were compared for 62 subjects and there were no significant differences.

### Table 8

<table>
<thead>
<tr>
<th>Types of Bleeding Episode</th>
<th>Mean (± SD) New Bleeding Episodes/Subject/Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>0.34 ± 0.49</td>
</tr>
<tr>
<td>Post-traumatic</td>
<td>0.39 ± 0.46</td>
</tr>
<tr>
<td>Unknown/Indeterminate</td>
<td>0.33 ± 0.34</td>
</tr>
</tbody>
</table>

The median annual bleed rate during the on-demand therapy period was 44 bleeds per subject per year compared to 1 bleed per subject per year while on either prophylaxis regimen, which was a statistically significant difference (p<0.001). Twenty-five of 53 (42%) subjects experienced no bleeding episodes while on prophylaxis for one year. While there was no statistically significant difference in bleeding frequency observed between the two prophylaxis regimens studied, the trial was not powered to demonstrate equivalence in bleeding rate between the two prophylaxis arms.
A human factors study was performed with 44 participants to evaluate the usability of the ADVATE in the BAXJECT III reconstitution system. Participants in the study included 15 patients, 16 caregivers, and 13 healthcare providers. During the study, participants viewed an instructional video then performed the reconstitution steps utilizing the instructions for use (IFU). Objective performance data were collected and analyzed. The annualized bleed rates by age category during on-demand and either standard or PK-driven prophylaxis regimens are shown in Table 10.

As a secondary endpoint, the trial assessed all Short Form Health Survey (SF-36v1) domains. The SF-36v1 is a valid and reliable measure of health-related quality of life that is comprised of 8 domains categorized into 2 summary scores (Table 11). As a result, the content of the package insert was revised to clarify the instructions for use.

### 15 REFERENCES


### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### How Supplied

ADVATE in a BAXJECT III system is packaged with 2 mL or 5 mL of Sterile Water for Injection, one Terumo Microbore Infusion set (2 mL only), one full prescribing physician insert, and one patient insert.

ADVATE is available in single-dose vials that contain the following nominal product strengths:

<table>
<thead>
<tr>
<th>Nominal Strength</th>
<th>Factor VIII Potency Range</th>
<th>Carton NDC (Includes 2 mL sWFI Diluent)</th>
<th>Carton NDC (Includes 5 mL sWFI Diluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 IU</td>
<td>200-400 IU per vial</td>
<td>0944-3051-02</td>
<td>0944-3045-10</td>
</tr>
<tr>
<td>500 IU</td>
<td>401-800 IU per vial</td>
<td>0944-3052-02</td>
<td>0944-3046-10</td>
</tr>
<tr>
<td>1000 IU</td>
<td>801-1200 IU per vial</td>
<td>0944-3053-02</td>
<td>0944-3047-10</td>
</tr>
<tr>
<td>1500 IU</td>
<td>1201-1800 IU per vial</td>
<td>0944-3054-02</td>
<td></td>
</tr>
<tr>
<td>2000 IU</td>
<td>1801-2400 IU per vial</td>
<td>0944-3055-02</td>
<td></td>
</tr>
<tr>
<td>3000 IU</td>
<td>2401-3600 IU per vial</td>
<td>0944-3056-02</td>
<td></td>
</tr>
<tr>
<td>4000 IU</td>
<td>3001-4800 IU per vial</td>
<td>0944-3057-02</td>
<td></td>
</tr>
</tbody>
</table>

Actual factor VIII activity in International Units is stated on the label of each ADVATE housing or carton.

Not made with natural rubber latex.

#### Storage and Handling

- Refrigerate ADVATE in powder form at 2°C–8°C (36°F–46°F).
- Store at room temperature up to 30°C (86°F) for a period of up to 6 months not to exceed the expiration date.
- Record on the carton the date ADVATE is removed from refrigeration. The product must not be returned to refrigerated temperature.
- Do not use beyond the expiration date printed on the ADVATE label or carton.
- Do not freeze.

### 17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-Approved Patient Labeling and Instructions for Use.
- Advise patients to report any adverse reactions or problems following ADVATE administration to their physician or healthcare provider.
- Allergic-type hypersensitivity reactions have been reported with ADVATE. Warn patients of the early signs of hypersensitivity reactions, including hives, pruritus, generalized urticaria, angioedema, hypotension, shock, anaphylaxis and acute respiratory distress. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment.
- Inhibitor formation may occur with the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to consult with their physicians or healthcare provider prior to travel. While traveling, advise patients to bring an adequate supply of ADVATE based on their current response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to travel with their ADVATE patient insert.

To enroll in the confidential, industry-wide Patient Notification System, call 1-888-873-2838.

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Westlake Village, CA 91362 USA

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Printed in USA
S30199
AVATE (ad-vate)
[Antihemophilic Factor (Recombinant)]
This leaflet summarizes important information about AVATE. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about AVATE. If you have any questions after reading this, ask your healthcare provider.

What is the most important information I need to know about AVATE?
Do not attempt to do an infusion to yourself unless you have been taught how by your healthcare provider or hemophilia center.
You must carefully follow your healthcare provider’s instructions regarding the dose and schedule for infusing AVATE so that your treatment will work best for you.

What is AVATE?
AVATE is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called “classic” hemophilia). The product does not contain plasma or albumin. Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.
AVATE is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A.
Your healthcare provider may give you AVATE when you have surgery: AVATE can reduce the number of bleeding episodes in adults and children (0-16 years) when used regularly (prophylaxis).
AVATE is not used to treat von Willebrand disease.

Who should not use AVATE?
You should not use AVATE if you:
• Are allergic to mice or hamsters.
• Are allergic to any ingredients in AVATE.
Tell your healthcare provider if you are pregnant or breastfeeding because AVATE may not work for you.

How should I use AVATE?
AVATE is given directly into the bloodstream. You may infuse AVATE at a hemophilia treatment center, at your healthcare provider’s office or in your home. You should be trained on how to do infusions by your healthcare provider or hemophilia treatment center.
Many people with hemophilia A learn to infuse their AVATE by themselves or with the help of a family member.
Your healthcare provider will tell you how much AVATE to use based on your weight, the severity of your hemophilia A, and where you are bleeding.
You may have to have blood tests done after getting AVATE to be sure that your blood level of factor VIII is high enough to clot your blood.
Call your healthcare provider right away if your bleeding does not stop after taking AVATE.

What should I tell my healthcare provider before I use AVATE?
You should tell your healthcare provider if you:
• Have or have had any medical problems.
• Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
• Have any allergies, including allergies to mice or hamsters.
• Are breastfeeding. It is not known if AVATE passes into your milk and if it can harm your baby.
• Are pregnant or planning to become pregnant. It is not known if AVATE may harm your unborn baby.
• Have been told that you have inhibitors to factor VIII (because AVATE may not work for you).

What are the possible side effects of AVATE?
You can have an allergic reaction to AVATE.
Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea or fainting.
Side effects that have been reported with AVATE include:
cough  headache  joint swelling/aching
sore throat  fever  itching
unusual taste  dizziness  hematoma
abdominal pain  hot flashes  swelling of legs
diarrhea  chills  runny nose/congestion
nausea/vomiting  sweating  rash
Tell your healthcare provider about any side effects that bother you or do not go away.
These are not all the possible side effects with AVATE. You can ask your healthcare provider for information that is written for healthcare professionals.

What are the AVATE dosage strengths?
AVATE with 2 mL or 5 mL Sterile Water for Injection in a BAXJECT III system comes in six different dosage strengths: 250 International Units (IU), 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU and 4000 IU. The actual strength will be imprinted on the label of the housing and on the box.

- Light-blue: Dosage strength of approximately 250 International Units (200–400 IU) (with 2 mL sWFI)
- Pink: Dosage strength of approximately 500 International Units (401–800 IU) (with 2 mL sWFI)
- Green: Dosage strength of approximately 1000 International Units (801–1200 IU) (with 2 mL sWFI)
- Purple: Dosage strength of approximately 1500 International Units (1201–1800 IU) (with 2 mL sWFI)
- Orange: Dosage strength of approximately 2000 International Units (1801–2400 IU) (with 5 mL sWFI)
- Silver: Dosage strength of approximately 3000 International Units (2401–3600 IU) (with 5 mL sWFI)
- Dark Green: Dosage strength of approximately 4000 International Units (3601–4800 IU) (with 5 mL sWFI)

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider. Always check the expiration date printed on the box. Do not use the product after the expiration date printed on the box.

How do I store AVATE?
Do not freeze AVATE.
Store AVATE in a refrigerator (2° to 8°C [36° to 46°F]) or at room temperature (up to 30°C [86°F]) for up to 6 months.
If you choose to store AVATE at room temperature:
• Note the date that the product is removed from refrigeration on the box.
• Do not use after six months from this date or after the expiration date.
• Do not return the product back to the refrigerator.
Store AVATE in the original box and protect from extreme exposure to light. Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated. Discard any unused AVATE at the end of your infusion.

What else should I know about AVATE and Hemophilia A?
Your body may form inhibitors to factor VIII. An inhibitor is part of the body's normal defense system. If you form inhibitors, it may stop AVATE from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

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

Resources at Baxalta available to the patients:
For information on patient assistance programs that are available to you, including the Baxalta CARE Program, please contact the Baxalta Insurance Assistance Helpline at 1-888-229-8379.

Baxalta US Inc.
Westlake Village, CA 91362 USA
U.S. License No. 2020
Issued: 11/2016
ADVATE [Antihemophilic Factor (Recombinant)]
(For intravenous use only)

Do not attempt to do an infusion to yourself unless you have been taught how by your healthcare provider or hemophilia center.

See below for step-by-step instructions for reconstituting ADVATE in a BAXJECT III system.

- Always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using ADVATE. If you are unsure of the procedures, please call your healthcare provider before using.
- Call your healthcare provider right away if bleeding is not controlled after using ADVATE.
- Your healthcare provider will prescribe the dose that you should take.
- Your healthcare provider may need to take blood tests from time to time.
- Talk to your healthcare provider before traveling. Plan to bring enough ADVATE for your treatment during this time.
- Dispose of all materials, including any leftover reconstituted ADVATE product, in an appropriate container.

1. Prepare a clean flat surface and gather all the materials you will need for the infusion. Check the expiration date, and let the ADVATE warm up to room temperature. Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.

2. Open the ADVATE package by peeling away the lid. Remove the ADVATE from the package and visually inspect the contents of the product and diluent vial. The ADVATE powder should be white to off-white in color and the diluent should not contain particles. Do not use if discoloration or particles are seen.

3. Place on a flat surface with the diluent vial on top. The diluent vial has a blue stripe.

4. With one hand holding the ADVATE housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADVATE vial. Both vials will move into the housing when pressed. If you don’t see the diluent transfer to the product vial, press the vials again to assure they are completely inserted. Do not remove the blue cap until instructed in a later step.

5. Swirl the ADVATE gently and continuously until the ADVATE is completely dissolved. Do not shake. Do not refrigerate after reconstitution. Inspect the ADVATE solution for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance. If not, do not use the solution and notify your healthcare provider immediately.

6. Take off the blue cap from the housing and connect the syringe. Be careful to not inject air into the ADVATE.

7. Turn over the ADVATE so that the vial containing the ADVATE solution is on top. Draw the ADVATE solution into the syringe by pulling back the plunger slowly. If the solution does not draw into the syringe, be sure that both vials are pressed firmly together. The contents of more than one vial may be drawn into a single, appropriately sized syringe if you are using more than one vial of ADVATE.

8. Disconnect the syringe from the system. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.

9. Apply a tourniquet and get the injection site ready by wiping the skin well with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center).

10. Insert the needle into the vein and remove the tourniquet. Slowly infuse the ADVATE. Do not infuse any faster than 10 mL per minute.

11. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.

12. Do not recap the needle. Place the needle, syringe, and ADVATE in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.

13. Remove the peel-off label from the housing and place it in your logbook. Clean any spilled blood with a freshly prepared mixture of 1 part bleach and 9 parts water, soap and water, or any household disinfecting solution.

Important: Contact your healthcare provider or local hemophilia treatment center if you experience any problems.