**ADVATE WITH BAXJECT III SYSTEM**

**IT’S ALL CONNECTED**

**INSTRUCTIONS FOR USE**

1. **PRESS**
   - Place infusion materials on a clean flat surface. Check the expiration date, and let the ADVATE warm up to room temperature. Wash your hands. The use of exam gloves is optional if you are infusing yourself at home. Do not remove diluent or ADVATE vials from external housing.

2. **OPEN**
   - Open the ADVATE package by peeling away the lid. Remove the system from the package and place on a flat surface with the diluent vial on top. The diluent vial has a blue stripe. Visually inspect the contents of the product and diluent vials. Do not use if discoloration or particles are seen. Keep system vertical.

3. **SWIRL**
   - With one hand holding the housing, press down firmly and diluent vial with other hand until the system is fully collapsed and the diluent flows down into the ADVATE vial. Make sure the product and diluent vials are fully activated and pressed into the plastic housing. Do not remove the blue cap located on the side of the system until step 5.

4. **FLIP & WITHDRAW**
   - Swirl the system gently and continuously to dissolve ADVATE. Inspect ADVATE 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.

5. **INJECT AIR**
   - Remove the blue cap located on the side of the system. Remove the syringe from its packaging and connect to the system. Be careful to not inject air into the ADVATE with BAXJECT III system.

6. **DISCONNECT**
   - Turn over the system so that the vial with the ADVATE solution is on top (blue stripe at bottom). 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.

7. **DISCARD**
   - Disconnect the syringe from the system. It is acceptable for a small amount of liquid to remain in the vial. You are now ready to infuse (no faster than 10 mL per minute over a period of ≤5 minutes).

8. **DISPOSE**
   - Dispose of the used syringe and BAXJECT III system in a sharps container.

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**DETAILED IMPORTANT RISK 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.

**DETAILED IMPORTANT RISK INFORMATION continued**

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.

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.

**Visit www.advate.com | 888.4.ADVATE**

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ADVATE (Antihemophilic Factor [Recombinant])
Lyophilized Powder for Reconstitution for Intravenous Injection
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES
Dosage and Administration (2) 04/2014

INDICATIONS AND USAGE
ADVATE is a recombinant antihemophilic factor indicated for use in children and adults with hemophilia A 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. (1)

DOSAGE AND ADMINISTRATION
For intravenous injection after reconstitution only (2)
• Each vial of ADVATE contains the labeled amount of recombinant factor VIII in International Units (IU). (2)
• The required dosage is determined using the following formulas:
  Desired increment in factor VIII concentration (IU/dL or % of normal)= [(Total dose (IU)/body weight (kg)] x 2 [IU/dL]/[IU/kg];
  OR Required dose (IU) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL). (2)
• Frequency of ADVATE administration is determined by the type of bleeding episode and the recommendation of the treating physician. (2.1, 2.2)
• For prophylaxis regimen to prevent or reduce frequency of bleeding episodes, dose between 20 to 40 IU per kg every other day (3 to 4 times weekly). Alternatively, an every third day dosing regimen targeted to maintain FVIII trough levels ≥ 1% may be employed. (2.3)

ADVERSE REACTIONS
• Serious adverse drug reactions reported are hypersensitivity and factor VIII inhibitors. (6.1)
• The most common adverse drug reactions observed in ≥10% of patients are pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, and limb injury. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 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. Higher or more frequent dosing may be needed. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2014
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 or classic hemophilia) 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 Dosing Guidelines

- 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 on the external housing. 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:

- IU/dL (or % of normal) = [total dose (IU/body weight [kg]) x 2] / [IU/dL]/[IU/kg]

OR

- Required dose (International Units) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 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 x [2 IU/dL]/[IU/kg]/[IU/kg] = 50 IU/dL (50% of normal).

2. A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be 40 kg x 70 IU/dL/{[2 IU/dL]/[IU/kg]/[IU/kg]} = 1400 IU.

- Base the dose and frequency on the individual clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to ADVATE. Although you can estimate the dose by the calculations above, whenever possible, perform appropriate laboratory tests including serial factor VIII activity assays.

[see Warnings and Precautions (5.4) 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>
<thead>
<tr>
<th>Type of Bleeding Episodes</th>
<th>Factor VIII Level Required (% of normal or IU/dL)</th>
<th>Dose* (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>Every 12-24 hours (8 to 24 hours for patients under the age of 6)</td>
<td>Until the bleeding episode is resolved (as indicated by relief of pain) or healing is achieved (approximately 1 to 3 days).</td>
</tr>
<tr>
<td>Moderate</td>
<td>Muscle bleeding, bleeding into the oral cavity, definite hemarthroses, and known trauma.</td>
<td>30-60</td>
<td>Every 12-24 hours (8 to 24 hours for patients under the age of 6)</td>
<td>Until the bleeding episode is resolved (as indicated by relief of pain) or healing is achieved (approximately 2 to 3 days or more).</td>
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<td>Major</td>
<td>Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retroperitoneal or retroperitoneal spaces or iliohypogastric nerve, fractures, head trauma.</td>
<td>60-100</td>
<td>Every 8-24 hours (6 to 12 hours for patients under the age of 6)</td>
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* Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

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.

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Factor VIII Level Required (% of normal or IU/dL)</th>
<th>Dose* (IU/kg)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy (days)</th>
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<tbody>
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<td>60-100</td>
<td>30-50</td>
<td>Single dose within one hour of the operation.</td>
<td>Single dose or repeat as needed to control bleeding.</td>
</tr>
<tr>
<td>Major Intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery</td>
<td>40-60</td>
<td>10-120</td>
<td>Repeated after 12 to 24 hours for optional additional dosing as needed to control bleeding.</td>
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Dosing for Perioperative Management

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Dosing for Perioperative Management

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- Control and prevention of bleeding episodes.
- Perioperative management.
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2. DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only.

2.1 Dosing Guidelines

- 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.

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

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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.

Table 2

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Dosing for Perioperative Management

1. Use asceptic technique.

2. Remove the blue cap from the housing. Connect the syringe to the system (Figure D). Do not inject air into the ADVATE.

3. Turn the system upside down (factor concentrate vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly (Figure E).

4. Disconnect the syringe, attach a suitable needle, and inject intravenously as instructed. If a patient is to receive more than one ADVATE-BAXJECT II system or a combination of an ADVATE-BAXJECT II and an ADVATE-BAXJECT III system, the contents may be drawn into the same syringe.

5. Administer ADVATE over a period of ≤ 5 minutes (maximum infusion rate 10 mL/min). Determine the pulse rate before and during administration of ADVATE. Should a significant increase in pulse rate occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.
3. DOSAGE FORMS AND STRENGTHS
ADVATE is available as a lyophilized powder in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 3000, or 4000 IU. The 250-1500 IU strengths come with 2 mL Sterile Water for Injection (SWFI); the 2000-4000 IU strengths come with 5 mL of SWFI.

Each ADVATE is labeled on the housing with the recombinant anthemophilic factor (rAHF) activity expressed in International Units per system. This potency assignment employs a factor VIII concentrate standard that is referenced to a WHO (World Health Organization) international standard for factor VIII concentrates and is evaluated by appropriate methodology to ensure accuracy of the results.

4. CONTRAINDICATIONS
ADVATE is contraindicated 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, polyborate 80, and/or glutathione).

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE. Symptoms include dizziness, parathesias, rash, flushing, facial swelling, urticaria, dyspnea, and pruritus.

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG) ≤0.1 ng/IU ADVATE, and hamster proteins ≤1.5 ng/IU ADVATE. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins. Discontinue ADVATE if hypersensitivity symptoms occur and administer appropriate emergency treatment.

5.2 Neutralizing Antibodies
Neutralizing antibodies (inhibitors) have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs). Monitor all patients for the development of factor VIII inhibitors by appropriate clinical observation and laboratory testing. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled within an expected time frame, perform an assay that measures factor VIII inhibitor concentration. [see Warnings and Precautions (5.3)]

5.3 Monitoring Laboratory Tests
- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained when clinically indicated. [see Dosage and Administration (2.1)]
- Perform the Bethesda assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled within the expected dose of ADVATE, use Bethesda Units (BU) to titrate inhibitors.
  - If the inhibitor titer is less than 10 BU per mL, the administration of additional factor VIII activity concentrate may neutralize the inhibitor and may permit an appropriate hemostatic response.
  - If the inhibitor titer is above 10 BU per mL, adequate hemostasis may not be achieved. The inhibitor titer may rise following ADVATE infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6. ADVERSE REACTIONS
The serious adverse reactions seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to factor VIII. The most common adverse reactions observed in clinical trials (frequency ≥10% of subjects) were pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, and limb injury.

6.1 Clinical Trial 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 five completed clinical trials in previously treated patients (PTPs) and one ongoing trial in previously untreated patients (PUPs) with severe to moderately severe hemophilia A (factor VIII ≤2% of normal). A total of 234 subjects have been treated with ADVATE as of March 2006. Total exposure to ADVATE was 44,926 infusions. The median duration of participation per subject was 370.5 (range: 1 to 1,256) days and the median number of exposure days to ADVATE per subject was 128 (range: 1 to 598). The summary of adverse reactions with a frequency ≥5% (defined as adverse events occurring within 24 hours of infusion or any adverse event causally related occurring within the trial period) is shown in Table 3. No subject was withdrawn from a clinical trial due to an adverse reaction. There were no deaths in any of the clinical trials.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>MedDRA Preferred Term</th>
<th>Number of Adhs</th>
<th>Number of Subjects</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pynia</td>
<td>78</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>104</td>
<td>49</td>
<td>21</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Cough</td>
<td>75</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td>61</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>36</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthritis</td>
<td>44</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Injury, poising, and procedural complications</td>
<td>Limb injury</td>
<td>55</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>24</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Pharyngitis/arytenoid pain</td>
<td>23</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Nasal congestion</td>
<td>24</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>24</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>21</td>
<td>17</td>
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</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pain</td>
<td>19</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>16</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Urinary infection</td>
<td>16</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Injury, poising, and procedural complications</td>
<td>Procedural pain</td>
<td>16</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Rhinorrhea</td>
<td>15</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

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. Among patients treated with ADVATE, cases of serious allergic/hypersensitivity reactions including anaphylaxis have been reported and factor VIII inhibitor formation (observed predominantly in PUPs). Table 4 represents the most frequently reported post-marketing adverse reactions as MedDRA Preferred Terms.

Immunogenicity
The development of factor VIII inhibitors with the use of ADVATE was evaluated in clinical trials with pediatric PTPs (<8 years of age with >50 factor VIII exposures) and PTPs (>10 years of age with >150 factor VIII exposures). Of 198 subjects who were treated for at least 10 exposure days or on study for a minimum of 120 days, 1 adult developed a low-titer inhibitor (2 BU in the Bethesda assay) after 26 exposure days. Eight weeks later, the inhibitor was no longer detectable, and in vivo recovery was normal at 1 and 3 hours after infusion of another marketed recombinant factor VIII concentrate. This single event results in factor VIII inhibitor frequency in PTPs of 0.51% (95% CI of 0.03 and 2.91% for the risk of any factor VIII inhibitor development). 4 No factor VIII inhibitors were detected in the 53 treated pediatric PTPs. In clinical trials that enrolled previously untreated subjects (defined as having had up to 3 exposures to a factor VIII product at the time of enrollment), 5 (20%) of 25 subjects who received ADVATE developed inhibitors to factor VIII. 5 Four subjects developed high titer (>5 BU) and one patient developed low-titer inhibitors. Inhibitors were detected within a median of 11 exposure days (range 7 to 13 exposure days) to ADVATE. Inhibitor positivity was also evaluated by measuring the development of antibodies to heterologous proteins. 182 treated subjects were assessed for anti-Chinese hamster ovary (CHO) cell protein antibodies. Of these subjects, 3 showed an upward trend in antibody titer over time and 4 showed repeated but transient elevations of antibodies. 182 treated subjects were assessed for multig protein antibodies. Of these, 10 showed an upward trend in anti-multig antibody titer over time and 2 showed repeated but transient elevations of antibodies. Four subjects who demonstrated antibody elevations reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts. All of these subjects had numerous repeat exposures to the study product without recurrence of the events and a causal relationship between the antibody findings and these clinical events has not been established.

Of the 181 subjects who were treated and assessed for the presence of anti-human von Willebrand Factor (vWF) antibodies, none displayed laboratory evidence indicative of a positive serologic response. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADVATE with the incidence of antibodies to other products may be misleading.

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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. Among patients treated with ADVATE, cases of serious allergic/hypersensitivity reactions including anaphylaxis have been reported and factor VIII inhibitor formation (observed predominantly in PUPs). Table 4 represents the most frequently reported post-marketing adverse reactions as MedDRA Preferred Terms.
ADVATE (Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method)

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

In comparison to adults, children present with higher factor VIII clearance (based on per kg body weight) values and thus lower half-life and recovery of factor VIII. [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, larger 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. [see Clinical Studies (14)]

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 and the product 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 (Recombinant)]. 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 the same biological effects on clotting as human antihemophilic factor (rAHF). Structurally the recombinant protein has a similar combination of heterogeneous heavy and light chains as found in AWF (Human).

ADVATE is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. ADVATE in a single-use vial contains nominally 250, 500, 1000, 1500, 2000, 3000, or 4000 International Units (IU). The product contains the following stabilizers and excipients: mannitol, trehalose, sodium chloride, histidine, Tris, calcium chloride, polysorbate 80, and glutathione. Von Willebrand factor (VWF) is co-expressed with factor VIII and helps to stabilize it in culture. The final product contains no more than 2 ng VWF/IU rAHF, which will not have any clinically relevant effect in patients with von Willebrand disease.

The product contains no preservative. When reconstituted with the provided Sterile Water for Injection, USP, the final solution contains the following stabilizers and excipients in targeted amounts:

<table>
<thead>
<tr>
<th>Organ System [MedDRA Primary SOC]</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction*</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor VIII inhibition</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Fatigue/Malaise</td>
</tr>
<tr>
<td></td>
<td>Chest discomfort/pain</td>
</tr>
<tr>
<td></td>
<td>Less-than-expected therapeutic effect</td>
</tr>
</tbody>
</table>

* These reactions have been manifested by dizziness, paresthesia, rash, flushing, face swelling, urticaria, and/or pruritus.

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 RECOMBINATE [Antihemophilic Factor (Recombinant)] (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 preparation are presented in Table 6.

Table 4

<table>
<thead>
<tr>
<th>Organ System [MedDRA Primary SOC]</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction*</td>
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</tr>
<tr>
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<td>Injection site reaction</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Fatigue/Malaise</td>
</tr>
<tr>
<td></td>
<td>Chest discomfort/pain</td>
</tr>
<tr>
<td></td>
<td>Less-than-expected therapeutic effect</td>
</tr>
</tbody>
</table>

The approximate concentration of stabilizer and excipient after reconstitution is:

- Tris (hydroxymethyl) aminomethane: 25 mM
- Calcium Chloride: 4.2 mM
- Mannitol: 8% (w/v)
- Sodium Chloride: 225 mM
- α, α-Trehalose: 2% (w/v)
- Histidine: 25 mM
- Glutathione (Reduced): 0.2 mg/mL
- Polysorbate 80: 0.025% (w/v)

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.

The 90% confidence intervals for the ratios of the mean AUC_{0-48h} and 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. [see Clinical Studies (14.2)]

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 interim pharmacokinetic data for 51 subjects ≥16 years of age (intent-to-treat analysis) are available for 40 neonates, 3 infants, 21 children, and 27 adolescents as shown in Table 7. The clearance of ADVATE in infants, children, older children, and adolescents was 26%, 23%, 42%, and 23% higher than adults (0.031 dL/hr/kg). The half-life of ADVATE in infants, children, older children, and adolescents was 27%, 15%, 10%, and 3% lower than adults (12.08 hours). The extent to which these differences may be clinically significant is not known.
Table 7
Pharmacokinetic Parameters (Mean ± SD) of ADVATE by Age Group (N=51 Pediatric Subjects Age <16 years; Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Infants (N = 3)</th>
<th>Children (N = 8)</th>
<th>Older Children (N = 13)</th>
<th>Adolescents (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (hL/hr)</td>
<td>1,385 ± 476</td>
<td>1,545 ± 616</td>
<td>1,202 ± 549</td>
<td>1,474 ± 528</td>
</tr>
<tr>
<td>Cmax (IU/dL)</td>
<td>98.0 ± 16.5</td>
<td>106.4 ± 34.5</td>
<td>111.8 ± 25.7</td>
<td>113.3 ± 21.7</td>
</tr>
<tr>
<td>MRT (hrs)</td>
<td>11.6 ± 3.0</td>
<td>12.8 ± 2.3</td>
<td>13.1 ± 2.5</td>
<td>15.0 ± 6.6</td>
</tr>
<tr>
<td>t1/2beta (hrs)</td>
<td>0.039 ± 0.015</td>
<td>0.038 ± 0.016</td>
<td>0.044 ± 0.012</td>
<td>0.038 ± 0.012</td>
</tr>
<tr>
<td>Vss (dL/kg)</td>
<td>8.86 ± 1.7</td>
<td>10.27 ± 1.94</td>
<td>10.89 ± 1.60</td>
<td>11.70 ± 3.72</td>
</tr>
<tr>
<td>Vmax (IU/kg)</td>
<td>0.43 ± 0.08</td>
<td>0.46 ± 0.12</td>
<td>0.54 ± 0.07</td>
<td>0.53 ± 0.08</td>
</tr>
<tr>
<td>Recovery%</td>
<td>1.96 ± 0.21</td>
<td>2.05 ± 0.62</td>
<td>2.21 ± 0.44</td>
<td>2.24 ± 0.42</td>
</tr>
</tbody>
</table>

Table 8
Rate of New Bleeding Episodes During Prophylaxis

<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 ± 0.40</td>
</tr>
<tr>
<td>Post-traumatic</td>
<td>0.39 ± 0.40</td>
</tr>
<tr>
<td>Unknown/Indeterminate</td>
<td>0.33 ± 0.34</td>
</tr>
<tr>
<td>Overall</td>
<td>0.52 ± 0.71</td>
</tr>
</tbody>
</table>

Table 9
Surgical Procedures, Trial Duration, and Trial Medication Exposure

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Days of Study</th>
<th>ADVATE Exposure Days</th>
<th>Cumulative ADVATE Exposure (International Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement</td>
<td>16</td>
<td>16</td>
<td>91,698</td>
</tr>
<tr>
<td>Knee joint replacement</td>
<td>22</td>
<td>18</td>
<td>76,060</td>
</tr>
<tr>
<td>Knee arthrodesis</td>
<td>24</td>
<td>22</td>
<td>66,080</td>
</tr>
<tr>
<td>Transposition of the left ulnar nerve</td>
<td>5</td>
<td>5</td>
<td>14,560</td>
</tr>
<tr>
<td>Insertion of Medipore</td>
<td>28</td>
<td>28*</td>
<td>46,893</td>
</tr>
<tr>
<td>Dental extraction</td>
<td>18</td>
<td>6</td>
<td>16,599</td>
</tr>
<tr>
<td>Left elbow synovectomy</td>
<td>30</td>
<td>20</td>
<td>100,180</td>
</tr>
<tr>
<td>Teeth extraction</td>
<td>2</td>
<td>2</td>
<td>100,180</td>
</tr>
<tr>
<td>Right knee arthroscopy, Uncomplicated and synovectomy</td>
<td>13</td>
<td>10*</td>
<td>32,334</td>
</tr>
<tr>
<td>Wrist and thumb extraction</td>
<td>14</td>
<td>14</td>
<td>15,357</td>
</tr>
</tbody>
</table>

*ADVATE was administered by continuous infusion for the first 48 hours post-operatively, followed by bolus infusions for the remainder of the trial treatment.

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=13) who had completed at least 75 exposure days of treatment with ADVATE. Post-infusion levels and clearance of factor VIII during the perioperative period were examined in an interim analysis of subjects enrolled in a surgical trial. The pharmacokinetics of ADVATE was investigated in an interim analysis of a trial of pediatric previously treated subjects > 6 years of age. [See Use in Specific Population (8.4) and Clinical Pharmacology (12.3)].

From the continuation trial was conducted for 27 subjects who self-administered ADVATE on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE. Bleeding episodes were treated with ADVATE and the outcome of treatment was rated as excellent, good, fair, or none, based on the quality of hemostasis achieved. A total of 51 bleeding episodes occurred in 13 of the 27 subjects being treated with ADVATE. By etiology, 53% of these bleeding events resulted from trauma and 27% occurred spontaneously, the other 20% had an undetermined etiology. The response to treatment with ADVATE for 63% of all bleeding episodes was rated as excellent or good. In 86% of episodes, bleeding resolved with only 1 infusion and an additional 6% were resolved by a second infusion. In vivo recoveries at the onset of treatment and after 75 exposure days were compared for 62 subjects. There were no significant differences between the in vivo recoveries at the onset of treatment and the in vivo recoveries after ≥ 75 exposure days.

Perioperative Management Study

The safety and efficacy of ADVATE for perioperative management was investigated in 59 subjects who underwent 6 major surgeries and 2 procedures. Subjects received ADVATE (factor VIII < 7 to 13%) for up to 12 to 16 years of age. Five subjects underwent a combination of continuous and intermittent bolus infusion. Eight of the 10 subjects reported no adverse events to the infusion of ADVATE.

The rate of new bleeding episodes during the 75-exposure-day prophylactic regimen (≥ 25 IU/kg body weight 3-4 times per week) was calculated as a function of the etiology of hemorrhage from a surgical drain placed at the incision site in one subject. The quality of hemostasis achieved with ADVATE was rated as excellent or good for all assessments.

The pharmacokinetics of ADVATE were investigated at the beginning of the trial and at the end of treatment in a subset of subjects who had completed at least 75 exposure days of treatment with ADVATE. Post-infusion levels and clearance of factor VIII during the perioperative period were examined in an interim analysis of subjects enrolled in a surgical trial. The pharmacokinetics of ADVATE was investigated in an interim analysis of a trial of pediatric previously treated subjects > 6 years of age. [See Use in Specific Population (8.4) and Clinical Pharmacology (12.3)].

Continuation Study

Additional (open-label) safety and efficacy data were collected on 82 subjects who continued with treatment following participation in the pivotal clinical trial. An interim analysis of efficacy from the continuation trial was conducted for 27 subjects who self-administered ADVATE on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE. Bleeding episodes were treated with ADVATE and the outcome of treatment was rated as excellent, good, fair, or none, based on the quality of hemostasis achieved. A total of 51 bleeding episodes occurred in 13 of the 27 subjects being treated with ADVATE. By etiology, 53% of these bleeding events resulted from trauma and 27% occurred spontaneously, the other 20% had an undetermined etiology. The response to treatment with ADVATE for 63% of all bleeding episodes was rated as excellent or good. In 86% of episodes, bleeding resolved with only 1 infusion and an additional 6% were resolved by a second infusion. In vivo recoveries at the onset of treatment and after 75 exposure days were compared for 62 subjects. There were no significant differences between the in vivo recoveries at the onset of treatment and the in vivo recoveries after ≥ 75 exposure days.

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Routine Prophylaxis Study

In a multicenter, open-label, randomized, controlled postmarketing clinical trial of ADVATE in two prophylactic treatment regimens compared to that of on-demand treatment, 53 PTPs with severe to moderately severe hemophilia A (FVIII level < 2 IU/dL) were analyzed in the per-protocol group. Subjects were initially treated for 6 months of on-demand therapy and then randomized to 12 months of either ADVATE (20-40 IU/kg every 40-48 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 subject in the trial surpassed the upper boundary of 110% of the prescribed number of prophylactic infusions. 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.

The equation used to determine the weight-adjusted dose of the product used in the PK-driven prophylaxis arm, as calculated from the individual subject’s incremental recovery and half-life values to achieve a trough level of ≥ 1 IU/dL at the inter-dosing interval of 72 hours is defined as follows:
Table 10 Annual Bleed Rate of Prophylaxis Compared to On-Demand Treatment

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>On-Demand (n = 53)</th>
<th>Standard Prophylaxis (n=30)</th>
<th>PK-Driven Prophylaxis (n=23)</th>
<th>Either Standard or PK-Driven Prophylaxis (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) Actual Bleed Rate (ABR)</td>
<td>44.0 (20.8)</td>
<td>1.0 (2.1)</td>
<td>1.0 (4.1)</td>
<td>1.0 (4.1)</td>
</tr>
<tr>
<td>Median (IQR) Non-Joint BBR</td>
<td>38.7 (24.8)</td>
<td>0.5 (2.0)</td>
<td>1.0 (4.1)</td>
<td>1.0 (2.1)</td>
</tr>
<tr>
<td>Median (IQR) Non-Joint ABR</td>
<td>4.0 (1.9)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Median (IQR) Spontaneous ABR</td>
<td>32.0 (26.8)</td>
<td>0.0 (1.9)</td>
<td>0.0 (2.0)</td>
<td>0.0 (1.9)</td>
</tr>
<tr>
<td>Median (IQR) Traumatic ABR</td>
<td>11.5 (17.2)</td>
<td>0.0 (1.0)</td>
<td>1.0 (1.8)</td>
<td>0.0 (1.0)</td>
</tr>
</tbody>
</table>

* Inter-quartile range (IQR) is defined as the difference between the 75th percentile (third quartile) and the 25th percentile (first quartile).

The annualized bleed rates by age category during on-demand and either standard or PK-driven prophylaxis regimens are shown in Table 11.

Table 11 Annualized Bleed Rate by Age Category and Any Prophylaxis vs On-Demand (Per Protocol)

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Any Prophylaxis</th>
<th>On-Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Min Median Max</td>
<td>N Min Median Max</td>
<td>All subjects bled during On-Demand</td>
</tr>
<tr>
<td>Children (&lt;7 to &lt;12 years old)</td>
<td>3 0.0 5.2 8.7 33% 3 38.6 44.0 120.5</td>
<td></td>
</tr>
<tr>
<td>Adolescents (&lt;12 to &lt;16 years old)</td>
<td>4 0.0 5.0 10.0 25% 4 37.9 58.0 81.4</td>
<td></td>
</tr>
<tr>
<td>Adults (&lt;16 years old and older)</td>
<td>46 0.0 1.0 17.4 43% 46 22.7 44.7 117.8</td>
<td></td>
</tr>
<tr>
<td>All Subjects</td>
<td>53 0.0 1.0 17.4 42% 53 22.7 44.0 120.5</td>
<td></td>
</tr>
</tbody>
</table>

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 12).

Table 12 Mean Change in SF-36v1 Health Domain Scores Between End of On-Demand and End of Prophylaxis Treatment Regimens

<table>
<thead>
<tr>
<th>SF-36v1 Health Domain</th>
<th>Mean Change</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning (PF)</td>
<td>0.89</td>
<td>(-1.02, 2.81)</td>
</tr>
<tr>
<td>Role Physical (RP)</td>
<td>3.56</td>
<td>(0.32, 6.79)</td>
</tr>
<tr>
<td>Bodily Pain (BP)</td>
<td>4.13</td>
<td>(-0.63, 6.60)</td>
</tr>
<tr>
<td>General Health (GH)</td>
<td>1.36</td>
<td>(-0.72, 3.45)</td>
</tr>
<tr>
<td>Physical Component Score</td>
<td>3.56</td>
<td>(0.56, 5.56)</td>
</tr>
<tr>
<td>Vitality (VT)</td>
<td>0.21</td>
<td>(-12.23, 2.65)</td>
</tr>
<tr>
<td>Social Functioning (SF)</td>
<td>1.72</td>
<td>(-0.57, 4.00)</td>
</tr>
<tr>
<td>Role Emotional (RE)</td>
<td>-1.29</td>
<td>(-3.78, 1.19)</td>
</tr>
<tr>
<td>Mental Health (MH)</td>
<td>-0.20</td>
<td>(-2.89, 2.49)</td>
</tr>
<tr>
<td>Mental Component Score</td>
<td>-1.22</td>
<td>(-3.66, 1.22)</td>
</tr>
</tbody>
</table>

* Positive change values are in the favorable direction.

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 Microbone 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:

Nominal Strength
Factor VIII Potency Range
Carton NDC (Includes 2 mL SWFI Diluent) Carton NDC (Includes 5 mL SWFI Diluent)
250 IU 200-400 IU per vial 0844-3051-02
500 IU 401-800 IU per vial 0844-3052-02
1000 IU 801-1200 IU per vial 0844-3053-02
1500 IU 1201-1800 IU per vial 0844-3054-02
2000 IU 1801-2400 IU per vial 0944-3045-10
3000 IU 2401-3600 IU per vial 0944-3046-10
4000 IU 3601-4800 IU per vial 0944-3047-10

Actual factor VIII activity in International Units is stated on the label of each ADVATE housing or carton. The product is not made with natural rubber latex.

Storage and Handling
- Refrigerate ADVATE in powder form at 2° - 8°C (36° - 46°F).
- ADVATE may be stored 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 with resuscitative measures such as the administration of epinephrine and oxygen.
• Inhibitor formation may occur with the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center for further treatment and/ or assessment 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 regimen of treatment.

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

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Westlake Village, CA 91362 USA
U.S. License No. 140
Printed in USA

USBS/34/14-0101

Issued: 04/2014
What is ADVATE? 
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). The product does not contain plasma or albumin. Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

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.

Who should not use ADVATE? 
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 work for you.

How should I use ADVATE? 
ADVATE is given directly into the bloodstream. You may infuse ADVATE 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 ADVATE by themselves or with the help of a family member.

Your healthcare provider will tell you how much ADVATE 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 ADVATE 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 ADVATE.

What should I tell my healthcare provider before I use ADVATE? 
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 ADVATE passes into your milk and if it can harm your baby.
- Are pregnant or planning to become pregnant. It is not known if ADVATE may harm your unborn baby.
- Have been told that you have inhibitors to factor VIII (because ADVATE may not work for you).

What are the possible side effects of ADVATE? 
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 sore throat unusual taste abdominal pain diarrhea nausea/vomiting headache fever dizziness hot flashes chills sweating joint swelling/aching itching hematoma swelling of legs runny nose/congestion 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 ADVATE. You can ask your healthcare provider for information that is written for healthcare professionals.

What are the ADVATE dosage strengths? 
ADVATE 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 on the housing and on the box. The six different strengths are color coded, as follows:

- Dosage strength of approximately 250 International Units (200 – 400 IU) (with 2 mL SWFI)
- Dosage strength of approximately 500 International Units (401 – 800 IU) (with 2 mL SWFI)
- Dosage strength of approximately 1000 International Units (801 – 1200 IU) (with 2 mL SWFI)
- Dosage strength of approximately 1500 International Units (1201 – 1800 IU) (with 2 mL SWFI)
- Dosage strength of approximately 2000 International Units (1801 – 2400 IU) (with 5 mL SWFI)
- Dosage strength of approximately 3000 International Units (2401 – 3600 IU) (with 5 mL SWFI)
- 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 ADVATE? 
Do not freeze ADVATE.
Store ADVATE 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 ADVATE 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 ADVATE 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 ADVATE at the end of your infusion.

What else should I know about ADVATE 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 ADVATE from working properly. Consult with your healthcare provider to make sure you are...
Instructions For Use

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.

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 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. 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).

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

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

11. 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.

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.