HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADVATE safely and effectively. See full prescribing information for ADVATE.

ADVATE [*Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method*]
For Intravenous Use, Lyophilized Powder for Reconstitution
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage (1.3)	12/2011
Dosage and Administration (2.3)	12/2011

INDICATIONS AND USAGE

ADVATE is an Antihemophilic Factor (Recombinant) indicated for:

- Control and prevention of bleeding episodes in adults and children (0-16 years) with Hemophilia A. (1.1)
- Perioperative management in adults and children (0-16 years) with Hemophilia A. (1.2)
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children (0-16 years) with Hemophilia A. (1.3)

ADVATE is not indicated for the treatment of von Willebrand disease. (1)

DOSAGE AND ADMINISTRATION

For intravenous use 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 intravenous injection of the reconstituted product 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)

DOSAGE FORMS AND STRENGTHS

ADVATE with 5 mL of Sterile Water for Injection, USP, USP is available as a lyophilized powder in single-use vials containing nominally 250, 500, 1000, 1500, 2000 and 3000 IU.

ADVATE with 2 mL of Sterile Water for Injection, USP USP, USP is available as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 1500 IU. (3)

CONTRAINDICATIONS

Known anaphylaxis to mouse or hamster protein or other constituents of the product. (4)

WARNINGS and PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions 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 has been detected in patients receiving Factor VIII-containing products, including ADVATE. 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)

ADVERSE REACTIONS

The serious adverse drug reactions 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, 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: 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. (8.4).

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

Revised: XX/2011

FULL PRESCRIBING INFORMATION: CONTENTS

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] is an Antihemophilic Factor (Recombinant) indicated for control and prevention of bleeding episodes in adults and children (0-16 years) with Hemophilia A.

1.2 Perioperative Management

ADVATE is indicated in the perioperative management in adults and children (0-16 years) with Hemophilia A.

1.3 Routine Prophylaxis

ADVATE is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children (0-16 years) with Hemophilia A.

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

2. DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution Only

- Initiate treatment with ADVATE under the supervision of a physician experienced in the treatment of Hemophilia A.

- Each vial of ADVATE has the recombinant Factor VIII potency in International Units stated on the label. The expected *in vivo* peak increase in Factor VIII level expressed as IU/dL of plasma or percent normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by 2.

- The 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. [*See Dosage and Administration* (2.1) and (2.2)]

The expected *in vivo* peak increase in Factor VIII level expressed as IU/dL (or % 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

Dose (International Unit) = 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]}/[70 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]} = 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)*]

2.1 Control and Prevention of Bleeding Episodes

A guide for dosing in the treatment of bleeding episodes is provided in Table 1. The careful control of treatment dose is especially important in cases of life-threatening bleeding episodes.

Table 1
ADVATE Dosing for Treatment of Bleeding Episodes in Adults and Children

Type of Bleeding Episodes	Required Peak Post-infusion Factor VIII Activity in the Blood (as % of Normal or IU/dL)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding episode.	20-40	10-20 International Units per kg[a] Repeat infusions every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for one to three days until the bleeding episode is resolved (as indicated by relief of pain) or healing is achieved.
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	15-30 International Units per kg[a] Repeat infusions every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for three days or more until the bleeding episode is resolved (as indicated by relief of pain) or healing is achieved.

Major Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma.	60-100	Initial dose 30-50 International Units per kg[a] Repeat dose 30-50 International Units per kg every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until resolution of the bleeding episode has occurred.

[a] Dose (IU/kg) = Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

2.2 Perioperative Management

A guide for dosing in perioperative management is provided in Table 2. The careful control of dose and duration of treatment is especially important in cases of major surgery.

Table 2
ADVATE Dosing for Perioperative Management in Adults and Children

Type of Surgery	Required Peak Post-infusion Factor VIII Activity in the Blood (% of Normal or IU/dL)	Frequency of Infusion
Minor Including tooth extraction	60-100	A single bolus infusion (30-50 International Units/kg[a]) beginning within one hour of the operation. Optional additional dosing every 12 to 24 hours as needed to control bleeding. For dental procedures, adjunctive therapy may be considered.
Major Examples include intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery	80-120 (pre- and post-operative)	Preoperative bolus infusion: 40 – 60 International Units/kg[a]. Verify 100% activity has been achieved prior to surgery. Maintenance bolus infusion (40-60International Units/kg[a]) repeat infusions every 8 to 24 hours (6 to 24 hours for patients under the age of 6), depending on the desired level of Factor VIII and state of wound healing.

[a] Dose (IU/kg) = Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

2.3 Routine Prophylaxis

For prevention of bleeding episodes, doses between 20 to 40 International Units of Factor VIII per kg body weight every other day (3 to 4 times weekly) may be utilized. Alternatively, an every third day dosing regimen targeted to maintain FVIII trough levels ≥ 1% may be employed. Adjust dose based on the patient's clinical response.[1,2]

2.4 Instruction for Use

Administer ADVATE by intravenous (IV) injection after reconstitution. Ask patients to follow the specific preparation and administration procedures provided by their physicians.

For instructions, ask patients to follow the recommendations in the FDA-approved patient labeling. [*See FDA-approved patient labeling (17)*]

Perform reconstitution, product administration, and handling of the administration set and needles with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted ADVATE, in an appropriate container.

2.5 Preparation and Reconstitution

The procedures below are provided as general guidelines for the preparation and reconstitution of ADVATE. Always work on a clean surface and wash your hands before performing the following procedures:

1. Bring the ADVATE (dry factor concentrate) and Sterile Water for Injection, USP USP (diluent) to room temperature.

2. Remove caps from the factor concentrate and diluent vials.

3. Cleanse stoppers with germicidal solution and allow to dry prior to use. Place the vials on a flat surface.

4. Open the BAXJECT II device package by peeling away the lid, without touching the inside (Figure A). **Do not remove the device from the package.**

5. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper (Figure B).

6. Grip the BAXJECT II package at its edge and pull the package off the device (Figure C). **Do not remove the blue cap from the BAXJECT II device.** Do not touch the exposed white plastic spike.

7. Turn the system over so that the diluent vial is on top. Quickly insert the white plastic spike fully into the ADVATE vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the ADVATE vial.

8. Swirl gently until ADVATE is completely dissolved. **Do not refrigerate after reconstitution**.

2.6 Administration

ADVATE is for intravenous use after reconstitution only.

- Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless in appearance. If not, do not use the solution and notify Baxter immediately.

- Administer ADVATE at room temperature within 3 hours of reconstitution.

- Use plastic syringes with this product because proteins in the product tend to stick to the surface of glass syringes.

1. Use aseptic technique.

2. Remove the blue cap from the BAXJECT II device. Connect the syringe to the BAXJECT II device (Figure E). **Do not inject air**.

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 F).

4. Disconnect the syringe; attach a suitable needle and inject intravenously as instructed under **Administration by Bolus Infusion**. If a patient is to receive more than one vial of ADVATE, the contents of multiple vials may be drawn into the same syringe. **Please note that the BAXJECT II device is intended for use with a single vial of ADVATE and Sterile Water for Injection, USP only; therefore, reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II device.**

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.

Figure A

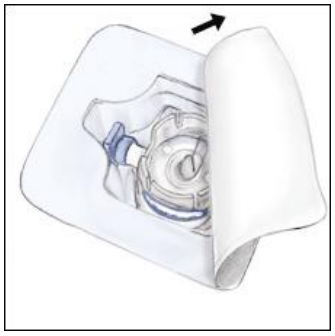


Figure B

Figure C

Figure D

Figure E

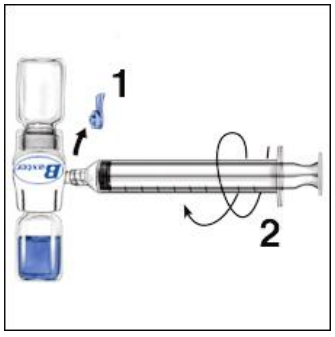
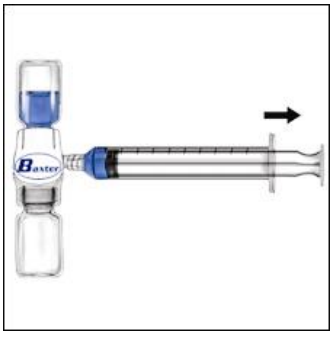


Figure F



3 DOSAGE FORMS AND STRENGTHS

ADVATE with 5 mL of Sterile Water for Injection, USP is available as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000, 1500, 2000 or 3000 International Units (IU). ADVATE with 2 mL of Sterile Water for Injection, USP is available as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 1500 IU.
Reconstitute using Sterile Water for Injection, USP (sWFI) provided in the kit.

Each vial of ADVATE is labeled with the recombinant antihemophilic factor (rAHF) activity expressed in International Units per vial. 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

Known anaphylaxis to mouse or hamster protein or other constituents of the product.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible and have been reported with ADVATE. Symptoms have manifested as dizziness, paresthesias,

rash, flushing, face swelling, urticaria, dypsnea, and pruritus. [*See Patient Counseling Information (17)*]

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG): maximum of 0.1 ng/IU ADVATE, and hamster proteins: maximum of 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

Carefully monitor patients treated with AHF products for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs). If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, perform an assay that measures Factor VIII inhibitor concentration. [*See Warnings and Precautions (5.3)*]

5.3 Monitoring Laboratory Tests

The clinical response to ADVATE may vary. If bleeding is not controlled with the recommended dose, determine the plasma level of Factor VIII and administer a sufficient dose of ADVATE to achieve a satisfactory clinical response. If the patient's plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, suspect the presence of an inhibitor (neutralizing antibodies) and perform appropriate tests as follows:

- 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)*]

- 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 with the expected dose of ADVATE, use Bethesda Units (BU) to titer inhibitors.

    - If the inhibitor titer is less than 10 BU per mL, the administration of additional Antihemophilic Factor 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.

ADVERSE REACTIONS

The serious adverse drug reactions (ADRs) seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to Factor VIII.

The most common ADRs observed in clinical trials (frequency ≥ 10% of subjects) were pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, 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 studies in previously treated patients (PTPs) and one ongoing study 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 128.0 (range: 1 to 598).[3]

The summary of adverse reactions (ADRs) with a frequency ≥5% (defined as adverse events occurring within 24 hours of infusion or any event causally related occurring within study period) is shown in Table 3.

No subject was withdrawn from a study due to an ADR. There were no deaths in any of the clinical studies.

Table 3
Summary of Adverse Reactions (ADRs)[a] with a Frequency ≥ 5% in 234 Treated Subjects[b]

MedDRA[c] System Organ Class	MedDRA Preferred Term	Number of ADRs	Number of Subjects	Percent of Subjects
General disorders and administration site conditions	Pyrexia	78	50	21
Nervous system disorders	Headache	104	49	21
Respiratory, thoracic and mediastinal disorders	Cough	75	44	19
Infections and infestations	Nasopharyngitis	61	40	17
Gastrointestinal disorders	Vomiting	35	27	12
Musculoskeletal and connective tissue disorders	Arthralgia	44	27	12
Injury, poisoning and procedural complications	Limb injury	55	24	10
Infections and infestations	Upper respiratory tract infection	24	20	9
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	23	20	9
Respiratory, thoracic and mediastinal disorders	Nasal congestion	24	19	8
Gastrointestinal disorders	Diarrhea	24	18	8
Gastrointestinal disorders	Nausea	21	17	8
General disorders and administration site conditions	Pain	19	17	8
Skin and subcutaneous tissue disorders	Rash	16	13	6
Infections and infestations	Ear infection	16	12	5
Injury, poisoning and procedural complications	Procedural pain	16	12	5
Respiratory, thoracic and mediastinal disorders	Rhinorrhea	15	12	5

[a] ADRs are defined as any Adverse Event that occurred within 24 hours after being infused with investigational product OR all Adverse Events assessed related or possibly related to investigational product OR Adverse Events for which the investigator's or sponsor's opinion of causality was missing or indeterminate.

[b] The ADVATE clinical program included 234 treated subjects from 5 completed studies in PTPs and 1 ongoing study in PUPs as of 27 March 2006.

[c] MedDRA version 8.1 was used.

Immunogenicity

The development of Factor VIII inhibitors with the use of ADVATE was evaluated in clinical studies with pediatric PTPs (<6 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 (2.0 [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 a 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).[3,4] No Factor VIII inhibitors were detected in the 53 treated pediatric PTPs.

In clinical studies 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.[3] Four patients developed high titer (> 5 BU) and one patient developed low-titer inhibitors. Inhibitors were detected at a median of 11 exposure days (range 7 to 13 exposure days) to investigational product.

Immunogenicity also was 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 patients, 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 muIgG protein antibodies. Of these, 10 showed an upward trend in anti-muIgG 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.

6.2 Post-Marketing 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.

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.

Table 4
Post-Marketing Experience

Organ System [MedDRA Primary SOC]	Preferred Term
Immune system disorders	Anaphylactic reaction [a] Hypersensitivity[a]
Blood and lymphatic system disorders	Factor VIII inhibition
General disorders and administration site conditions	Injection site reaction Chills Fatigue/Malaise Chest discomfort/pain Less-than-expected therapeutic effect

[a] These reactions have been manifested by dizziness, paresthesias, rash, flushing, face swelling, urticaria, and/or pruritus.

6. DRUG INTERACTIONS

There are no known drug interactions reported with ADVATE. Drug interaction studies have not been performed.

7. 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. Prescribe ADVATE only if clinically needed.

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of ADVATE during labor and delivery. Prescribe ADVATE only if clinically 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. Prescribe ADVATE only if clinically needed.

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. 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.[5] 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 Study, 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 (14.4)*]

8.5 Geriatric Use

Clinical studies 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.

10. OVERDOSAGE

No symptoms of overdose with ADVATE have been reported.

11. DESCRIPTION

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered CHO cell line. In culture, the CHO cell line expresses 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 [hAHF]. Structurally the recombinant protein has a similar combination of heterogeneous heavy and light chains as found in AHF (Human).

ADVATE is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. When reconstituted with the provided Sterile Water for Injection, USP, the product contains the following stabilizers and excipients in targeted amounts:

Table 5.
Approximate Concentration of Stabilizer and Excipient after Reconstitution

Stabilizer and Excipient	5 mL Reconstitution (for 250, 500, 1000, 1500, 2000, 3000 IU) Target	2 mL Reconstitution (for 250, 500, 1000, 1500 IU) Target
Tris (hydroxymethyl) aminomethane	10 mM	25 mM
Calcium Chloride	1.7 mM	4.2 mM
Mannitol	3.2% (w/v)	8 % (w/v)
Sodium Chloride	90mM	225 mM
α, α-Trehalose	0.8% (w/v)	2% (w/v)
Histidine	10 mM	25 mM
Glutathione (Reduced)	0.08 mg/mL	0.2 mg/mL
Polysorbate 80	0.01% (w/v)	0.025% (w/v)

ADVATE is available in single-dose vials that contain nominally 250, 500, 1000, 1500, 2000 and 3000 International Units (IU) per vial. The product contains the following stabilizers and excipients: mannitol, trehalose, sodium chloride, histidine, Tris, calcium chloride, polysorbate 80, and glutathione. 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.

Each vial of ADVATE is labeled with the rAHF activity expressed in International Units per vial. 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 study of ADVATE produced at Orth, Austria (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.[4] Pharmacokinetic parameters for adults for each study preparation in the per-protocol analysis are presented in Table 6.

Table 6
Pharmacokinetic Parameters for ADVATE and RECOMBINATE
(Per-Protocol Analysis, Adult Subjects Age > 16 years)

Parameter	RECOMBINATE (n=20)[a]	ADVATE (n=20)[a]
	Mean ± SD	Mean ± SD
$AUC_{0\text{-}48h}$ (IU·hrs/dL)[b]	1638 ± 357	1644 ± 338
In vivo recovery (IU/dL/IU/kg)[c]	2.74 ± 0.56	2.57 ± 0.53
Half-life (hrs)	11.16± 2.50	12.03 ± 4.15
C_{max} (IU/dL)	136 ± 29	128 ± 28
MRT (hrs)	14.68 ± 3.82	15.81 ± 5.91
V_{ss} (dL/kg)	0.43 ± 0.10	0.44 ± 0.10
CL (dL/hrs/kg)	0.03 ± 0.01	0.03 ± 0.01

[a] 56 subjects were enrolled in the clinical study. The per-protocol analysis included 30 patients (20 adults and 10 children). The PK parameters in the table are calculated for adult subjects only.

[b] Area under the plasma Factor VIII concentration x time curve from 0 to 48 hours post-infusion.

[c] Calculated as (C_{max} – baseline Factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion Factor VIII measurement.

The 90% confidence intervals for the ratios of the mean $AUC_{(0\text{-}48h)}$ 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 the description of the clinical study results for a discussion of the effect of long-term exposure on the pharmacokinetic properties of ADVATE. [*See Clinical Studies* (14.2)]

In an analysis of data from 58 unique subjects with 65 surgical procedures in the perioperative management study, 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 (per-protocol analysis) are available for 0 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;Intent to Treat Analysis)

Parameters	Infants (N = 3) (1 month to <2 yrs)	Children (N = 8) (2 to <5 yrs)	Older Children (N = 13) (5 to <12 yrs)	Adolescents (N = 27) (12 to <16 yrs)
AUC (IU hr/dL)	1385 ± 476	1545 ± 616	1282 ± 509	1447 ± 528
C_{max} (IU/dL)	98.0 ± 10.5	104.6 ± 34.5	111.8 ± 25.7	113.3 ± 21.7
MRT (hrs)	11.6 ± 3.0	12.8 ± 2.3	13.1 ± 3.5	15.0± 5.6
CL (dL/hr/kg)	0.039 ± 0.015	0.038 ± 0.016	0.044 ± 0.012	0.038 ± 0.012
Half-life (hrs)	8.86 ± 1.78	10.27 ± 1.94	10.89 ± 1.60	11.70 ± 3.72
V_{ss} (dL/kg)[a]	0.43 ± 0.08	0.46 ± 0.12	0.54 ± 0.07	0.53 ± 0.08
Recovery[b] IU/dL/IU/kg	1.96 ± 0.21	2.05 ± 0.62	2.21 ± 0.44	2.26 ± 0.42

[a] Volume of distribution at steady state
[b] Incremental recovery at C_{max} calculated as (C_{max} – baseline Factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion Factor VIII measurement

In a crossover pharmacokinetic study of rAHF-PFM reconstituted in 2 mL versus 5 mL Sterile Water for Injection, USP (sWFI) in previously treated severe Hemophilia A adult and adolescent patients, the AUCs of the two formulations were comparable and the 90% confidence interval ranged from 90.4 to 102.6, indicating that the two formulations are pharmacokinetically equivalent.

13. NONCLINICAL TOXICOLOGY

Single doses, severalfold higher than the recommended clinical dose (related to body weight), did not demonstrate any acute or toxic effect for ADVATE in laboratory animals (mouse, rat, rabbit, and dog). Multiple dose studies were not performed with ADVATE but were performed with the related product, RECOMBINATE, and with formulation buffers of ADVATE.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with the active ingredient in ADVATE to assess its mutagenic or carcinogenic potential. 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.

RECOMBINATE was tested for mutagenicity at doses considerably exceeding plasma concentrations *in vitro*, and at doses up to ten times the expected maximal clinical dose *in vivo*. At that concentration, it did not cause reverse mutations, chromosomal aberrations, or an increase in micronuclei formation in bone marrow polychromatic erythrocytes. Studies in animals have not been performed to evaluate carcinogenic potential.

14. CLINICAL STUDIES

14.1 Original Safety and Efficacy Study

The original safety and efficacy study evaluated the pharmacokinetics (double-blinded, randomized, cross-over), safety, immunogenicity, and hemostatic efficacy (open-label) of ADVATE in 111 subjects. The study was conducted with 103 Caucasian; 7 Black and 1 Asian US and European previously treated subjects (PTPs with ≥ 150 exposure days) diagnosed with moderate to severe hemophilia A (FVIII level ≤ 2% of normal), who were ≥ 10 years of age (20 were 10 to <13, 22 were 13 to <16, and 69 were 16 years and older). Subjects with a history of or a detectable FVIII inhibitor, portal vein hypertension (INR >1.4), presence of splenomegaly, spider angiomata, history of esophageal hemorrhage or documented esophageal varices, hypersensitivity to RECOMBINATE rAHF, or scheduled to receive immunomodulating drug were excluded. Subjects self-administered ADVATE for routine prophylaxis and for the treatment of bleeding episodes. A global assessment of efficacy was rendered by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using an ordinal scale of excellent, good, fair, or none, based on the quality of hemostasis achieved with ADVATE produced in the Orth facility for the treatment of each new bleeding episode. A total of 510 bleeding episodes were reported, with a mean (± SD) of 6.1 ± 8.2

bleeding episodes per subject. Of these 510 episodes, 439 (86%) were rated excellent or good in their response to treatment with ADVATE, 61 (12%) were rated fair, 1 (0.2%) was rated as having no response, and for 9 (2%), the response to treatment was unknown. A total of 411 (81%) bleeding episodes were managed with a single infusion, 62 (12%) required 2 infusions, 15 (3%) required 3 infusions, and 22 (4%) required 4 or more infusions of ADVATE for satisfactory resolution. A total of 162 (32%) bleeding episodes occurred spontaneously, 228 (45%) were the result of antecedent trauma, and for 120 (24%) bleeding episodes, the etiology was unknown.[4]

The rate of new bleeding episodes during the protocol-mandated 75 exposure day prophylactic regimen (≥ 25 IU/kg body weight 3-4 times per week) was calculated as a function of the etiology of bleeding episodes for 107 evaluable subjects (n = 274 new bleeding episodes).[4] These rates are presented in Table 8.

Table 8
Rate of New Bleeding Episodes During Prophylaxis

Bleeding Episode Etiology	Mean (± SD) New Bleeding Episodes/Subject/Month
Spontaneous	0.34 ± 0.49
Post-traumatic	0.39 ± 0.46
Unknown[a]	0.33 ± 0.34
Overall	0.52 ± 0.71

[a] Etiology was indeterminate

The pharmacokinetic properties of ADVATE were investigated at the beginning of treatment in a multicenter study 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 surgery study. The pharmacokinetics of ADVATE was investigated in an interim analysis of a study of pediatric previously treated subjects < 6 years of age. [*See Pediatric Use (8.4) and Clinical Pharmacology (12)*]

14.2 Continuation Study

Additional (open-label) safety and efficacy data were based on 82 subjects who continued with treatment following participation in the pivotal study. An interim analysis of efficacy from the continuation study was conducted for 27 subjects who self-administered ADVATE produced in Neuchâtel on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE. New 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 new 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 the majority (63%) of all new bleeding episodes was rated as excellent or good. 86% of the bleeding episodes 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.

14.3 Perioperative Management Study

The study design, key inclusion and exclusion criteria, treatment, number of subjects and age range for the original perioperative management study can be found in Table 9.

Table 9
Study Design, Key Inclusion and Exclusion Criteria, Treatment, Number of Subjects and Age Range for ADVATE Perioperative Management Study[6]

Treatment(s)	Number of Subjects	Age Range, Race
Perioperative Management **1. Preoperative** Dental loading dose: FVIII level 60-100% of normal; Major/Minor loading dose: FVIII level 80-120% of normal **2. Intra- and Post-Operative** *__BI__: as clinically indicated;*__CI__: initial rate for subjects >12y: 4 $IU \cdot kg^{-1} \cdot h^{-1}$; initial rate subjects 5-12y: 5 $IU \cdot kg^{-1} \cdot h^{-1}$ for; then investigator-determined **3. Home Replacement Therapy** Prescribed by investigator for up to 6 weeks for major orthopedic procedures and up to 2 weeks for all other procedures	**Interim**: 10 Procedures: Major: 6 Minor: 4 Orthopedic: 5 Dental: 0 **Final**: 59 Procedures: 65 Major: 22 Minor: 35 Orthopedic: 40 Dental: 8 7 to <13 years (n=3 subjects) 13 to <16 years (n=8 subjects) 16 or older (n=48 subjects)	**Interim**: 14-64 years Caucasian: 9 Black: 1 **Final**: 7-65 years Caucasian: 55 Black: 3 Asian: 1

*"BI"is intermittent bolus infusion and "CI" is continuous infusion

An interim analysis of the hemostatic efficacy of ADVATE during the perioperative management of subjects undergoing surgical procedures was conducted for 10 of 25 planned subjects. Ten subjects underwent 10 surgical procedures while receiving ADVATE. Eight subjects received ADVATE by intermittent bolus infusion and 2 subjects received a combination of continuous and intermittent bolus infusion. Nine of the 10 subjects completed the study. Six of the surgical procedures were classified as major, and 4 were minor. Of the 6 major surgeries, 5 were for orthopedic complications of hemophilia. A brief description of each surgical procedure, along with study duration and study medication exposure, is presented in Table 10.

Table 10
Surgical Procedures, Study Duration, and Study Medication Exposure

Surgery Type	Days of Study	ADVATE Exposure Days	Cumulative ADVATE Exposure (International Units)
Total hip replacement	16	15	61,600
Knee joint replacement	22	18	76,060
Knee arthrodesis	24	22	66,080
Transposition of the left ulnar nerve	5	3	14,560
Insertion of Mediport	28	8[a]	46,893
Dental extraction	18	6	16,599
Left elbow synovectomy	43	32	102,180
Teeth extraction	2	2	10,350
Right knee arthroscopy, chondroplasty and synovectomy	13	10[a]	32,334
Wisdom teeth extraction	14	5	15,357

[a]ADVATE was administered by continuous infusion for the first 48 hours post-operatively, followed by bolus infusions for the remainder of study treatment.

For each of the 10 subjects, intra- and post-operative quality of hemostasis achieved with ADVATE was assessed by the operating surgeon and study site investigator, respectively, using an ordinal scale of excellent, good, fair, or none. The same rating scale was used to evaluate control 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.

14.4 Routine Prophylaxis Study

In a multicenter, open-label, prospective, randomized, controlled postmarketing clinical study of the relative efficacy of ADVATE use in 2 prophylactic treatment regimens compared to that of on-demand treatment, 53 PTPs with severe to moderately severe Hemophilia A (FVIII level $\leq$ 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 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 hemorrhages per year upon entering the study. Each subject in the per protocol group was adherent to > 90% of the prescribed number of prophylactic infusions; no subject in the study 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 ($p<0.0001$). 22 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 study 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 $\geq$ 1 IU/dL at the inter-dosing interval of 72 hours is defined as follows:

$$D_i = (2)^{72/t_i} / r_i. \text{ (i is the subject)}$$

D = target FVIII dose (IU/kg) that ensures that a trough level of $\geq$1 IU/dL is achieved after 72 hours
r = FVIII incremental recovery (IU/dL / IU/kg) as determined by the subject's PK analysis
t = FVIII half-life (hrs) as determined by the subject's PK analysis

Table 11
Annual Bleed Rate of Prophylaxis Compared to On-Demand Treatment

Clinical Parameters	On -Demand (n=53)	Standard Prophylaxis (n=30)	PK-driven Prophylaxis (n=23)	Either Standard or PK-driven Prophylaxis (n=53)

Median (IQR) [1] Annual Bleed Rate(ABR)	44.0 (20.8)	1.0 (2.1)	1.0 (4.1)	1.0 (4.1)
Median (IQR) [1] Joint ABR	38.7 (24.8)	0.5 (2.0)	1.0 (4.1)	1.0 (2.1)
Median (IQR) [1] Non-Joint ABR[1]	4.0 (11.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median (IQR) [1]Spontaneous ABR	32.0 (26.8)	0.0 (1.9)	0.0 (2.0)	0.0 (1.9)
Median (IQR)[1]Traumatic ABR	11.5 (17.2)	0.0 (1.0)	1.0 (1.0)	0.0 (1.0)

1 Inter-quartile-range (IQR) is defined as the difference between the 75th percentile (3rd 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 12.

Table 12.
Annualized Bleed Rate by Age category and Any Prophylaxis vs On-Demand (Per Protocol)

Age category	Any Prophylaxis					On-Demand				
	N	Min	Median	Max	Percentage of Subjects With Zero Bleeds	N	Min	Median	Max	Percentage of Subjects With Zero Bleeds
Children (≥7 to <12 years old)	3	0.0	5.2	8.7	33%	3	38.6	44.0	120.5	All subjects bleed during On-Demand
Adolescents (≥12 to <16 years old)	4	0.0	5.0	10.0	25%	4	37.9	58.0	81.4	
Adults (≥16 years old and older)	46	0.0	1.0	17.4	43%	46	22.7	44.7	117.8	
All Subjects	53	0.0	1.0	17.4	42%	53	22.7	44.0	120.5	

As a secondary endpoint, the study 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 domain and 2 summary scores (Table 13).

Table 13
Mean Change in SF-36v1 Health Domain Scores Between end of On-demand and end of Prophylaxis Treatment Regimens[a]

SF-36v1 Health Domain	Mean Change	95% Confidence Interval
Physical Functioning (PF)	0.89	(-1.02, 2.81)

Role Physical (RP)	3.56	(0.32, 6.79)
Bodily Pain (BP)	4.13	(1.63, 6.62)
General Health (GH)	1.36	(-0.72, 3.45)
Vitality (VT)	0.21	(-2.22, 2.63)
Social Functioning (SF)	1.72	(-0.57, 4.00)
Role Emotional (RE)	-1.29	(-3.78, 1.19)
Mental Health (MH)	-0.20	(-2.89, 2.49)
Physical Component Score	3.56	(1.56, 5.56)
Mental Component Score	-1.22	(-3.66, 1.23)

[a] Positive change values are in the favorable direction.

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16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

Nominal Strength	Factor VIII Potency Range	NDC (Includes 5 mL sWFI Diluent)	NDC (Includes 2 mL sWFI Diluent)
250 IU	200-400 IU per vial	0944-2941-10	0944-2921-02
500 IU	401-800 IU per vial	0944-2942-10	0944-2922-02
1000 IU	801-1200 IU per vial	0944-2943-10	0944-2923-02
1500 IU	1201-1800 IU per vial	0944-2944-10	0944-2924-02
2000 IU	1801-2400 IU per vial	0944-2945-10	
3000 IU	2401-3600 IU per vial	0944-2946-10	

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

16.2 Storage and Handling

ADVATE is packaged with 5 mL or 2 mL of Sterile Water for Injection, USP, a BAXJECT II Needleless Transfer Device, one Terumo Microbore Infusion set (2 mL only), one full prescribing physician insert, and one patient insert.

ADVATE should be refrigerated (2° - 8°C [36° - 46°F]) in powder form.

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.

The date that ADVATE is removed from refrigeration should be noted on the carton.

Do not use beyond the expiration date printed on the vial or six months after date noted on the carton, whichever is earlier. After storage at room temperature, the product must not be returned to the refrigerator. Avoid freezing to prevent damage to the diluent vial.

17. PATIENT COUNSELING INFORMATION

See FDA approved patient labeling (Patient Information 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.

Patented under U.S. Patent Numbers: 5,733,873; 5,854,021; 5,919,766; 5,955,448; 6,313,102; 6,586,573; 6,649,386; 7,087,723 and 7,247,707. Made according to the method of U.S. Patent Numbers: 5,470,954; 6,100,061; 6,475,725; 6,555,391; 6,936,441; 7,094,574; 7,253,262 and 7,381,796.

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FDA-Approved Labeling – ADVATE (ad-vate)

[Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]

This leaflet summarizes important information about ADVATE. 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 ADVATE. If you have any questions after reading this, ask your healthcare provider.

ADVATE with 5 mL Diluent

ADVATE with 2 mL Diluent

What is the most important information I need to know about ADVATE?

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 ADVATE so that your treatment will work best for you.

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). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

ADVATE is used to prevent and control bleeding in people with Hemophilia A.

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

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 many not be right 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	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 ADVATE. You can ask your healthcare provider for information that is written for healthcare professionals.

What are the ADVATE dosage strengths?

ADVATE comes in six different dosage strengths50 International Units (IU), 500 IU, 1000 IU, 1500 IU, 2000 IU* and 3000 IU*.. The actual strength will be imprinted on the label and on the box. The six different strengths are color coded, as follows:

Light-blue	Dosage strength of approximately 250 International Units per vial (200 – 400 IU/vial)
Pink	Dosage strength of approximately 500 International Units per vial (401 – 800 IU/vial)
Green	Dosage strength of approximately 1000 International Units per vial (801 – 1200 IU/vial)
Purple	Dosage strength of approximately 1500 International Units per vial (1201 – 1800 IU/vial)
Orange	Dosage strength of approximately 2000 International Units per vial (1801 – 2400 IU/vial) (*available only with 5 mL sWFI)
Silver	Dosage strength of approximately 3000 International Units per vial (2401 – 3600 IU/vial) (*available only 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 vials containing powdered product (without sterile diluent added) 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 the expiration date listed on the vial, whichever is earlier.
- do not return the product back to the refrigerator.

Store vials in their original box and protect them 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 ADVATE left in the vial 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 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 ADVATE for a condition for which it is not prescribed. Do not share ADVATE with other people, even if they have the same symptoms that you have.

Resources at Baxter available to the patients:

For more product information on ADVATE, please visit www.advate.com or call 1-888-423-8283.

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

For information on additional Baxter patient resources, please visit www.advate.com.

Issued: December 2011

INSTRUCTIONS FOR USE

ADVATE

[Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]

(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 at the end of this leaflet.
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 vial with the ADVATE concentrate and the Sterile Water for Injection, USP (diluent) 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. If you are using more than one vial of ADVATE, **make sure you mix each vial of ADVATE with the Sterile Water for Injection, USP that is provided in the box**.

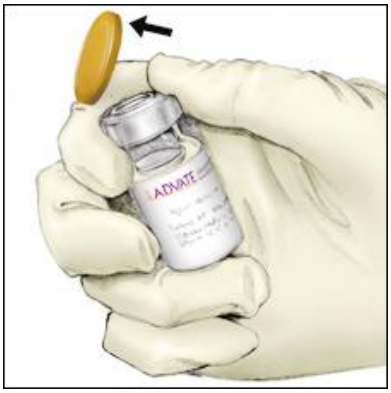
    a. When ADVATE is provided with 5 mL of Sterile Water for Injection, USP, the drug product and its diluent are provided in an **orange box;** the 5 mL diluent vial has a **grey cap**.

    b. When ADVATE is provided with 2 mL of Sterile Water for Injection, USP, the drug product and its diluent are provided in a **purple box**; the 2 mL diluent vial has a **transparent cap**.

ADVATE with 5 mL Diluent

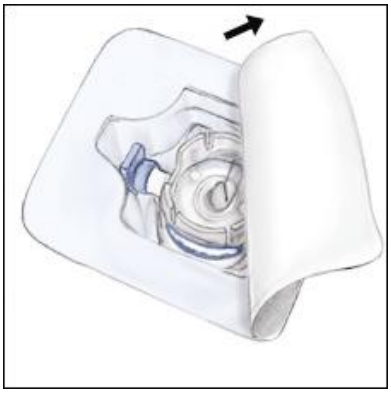
ADVATE with 2 mL Diluent

2. Remove caps from the ADVATE concentrate and diluent vials to expose the centers of the rubber stoppers.



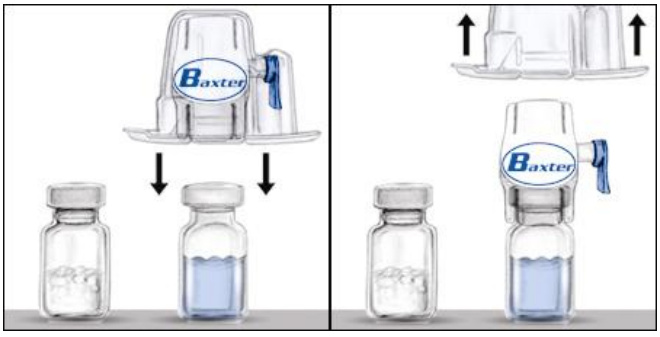
3. Disinfect the stoppers with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center) by rubbing the stoppers firmly for several seconds and allow them to dry prior to use. Place the vials on a flat surface.

4. Open the BAXJECT II device package by peeling away the lid, without touching the inside of the package. **Do not remove the BAXJECT II device from the package**.



5. Turn the package with the BAXJECT II device upside down and place it over the top of the diluent vial. Fully insert the clear plastic spike of the device into the center of the diluent vial's stopper by pushing straight down. Grip the package at its edge and lift it off the device. Be careful not to touch the white plastic spike. **Do not remove the blue cap from the BAXJECT II device.**

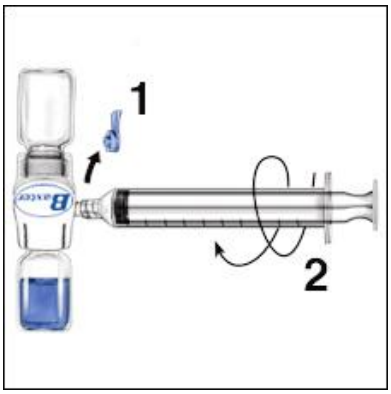
The diluent vial now has the BAXJECT II device connected to it and is ready to be connected to the ADVATE vial.



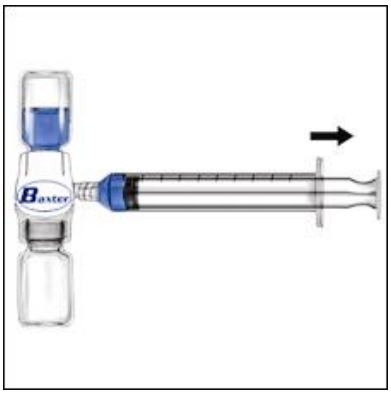
6. To connect the diluent vial to the ADVATE vial, turn the diluent vial over and place it on top of the vial containing ADVATE concentrate. Fully insert the white plastic spike into the ADVATE vial's stopper by pushing straight down. Diluent will flow into the ADVATE vial. This should be done right away to keep the liquid free of germs.

7. Swirl the connected vials gently and continuously until the ADVATE is completely dissolved. **Do not shake**. The ADVATE solution should look clear and colorless. If not, do not use it and notify Baxter immediately.

8. Take off the blue cap from the BAXJECT II device and connect the syringe. **Be careful to not inject air**.

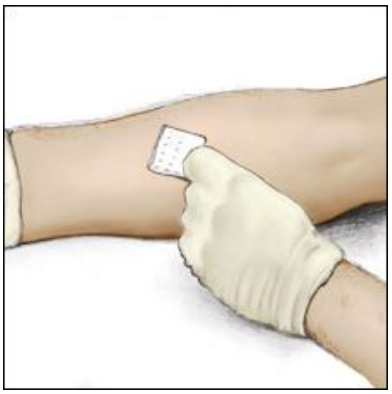


9. Turn over the connected vials so that the ADVATE vial is on top. Draw the ADVATE solution into the syringe by pulling back the plunger slowly. Disconnect the syringe from the vials. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up 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.

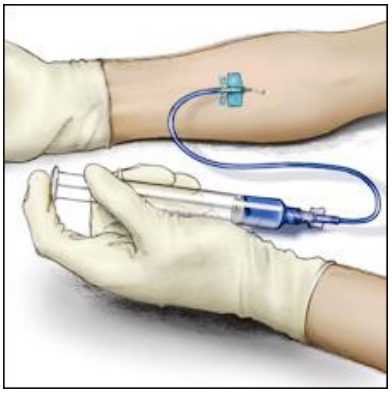


10. If you are using more than one vial of ADVATE, the contents of more than one vial may be drawn into the same syringe. **Make sure you mix each vial of ADVATE with the Sterile Water for Injection, USP that is provided in the box** (Following Steps 1-9). You will need a separate BAXJECT II device to mix each additional vial of ADVATE.

    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).



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



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

    Do not recap the needle. Place it with the used syringe in a hard-walled Sharps container for proper disposal.

    Remove the peel-off label from the ADVATE vial 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.

13. Dispose of the used vials and BAXJECT II system in your hard-walled Sharps container without taking them apart. Do not dispose of these supplies in ordinary household trash.

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

Patented under U.S. Patent Numbers: 5,733,873; 5,854,021; 5,919,766; 5,955,448; 6,313,102; 6,586,573; 6,649,386; 7,087,723 and 7,247,707. Made according to the method of U.S. Patent Numbers: 5,470,954; 6,100,061; 6,475,725; 6,555,391; 6,936,441; 7,094,574; 7,253,262 and 7,381,796.

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