March 18, 2025

Global Discontinuation of HEMOFIL® M [Antihemophilic Factor (Human), Method M, Monoclonal Purified] and RECOMBINATE® [Antihemophilic Factor (Recombinant)]

Dear Valued Patient,

The purpose of this letter is to inform you that Takeda has decided to globally discontinue HEMOFIL® M [Antihemophilic Factor (Human), Method M, Monoclonal Purified] and RECOMBINATE® [Antihemophilic Factor (Recombinant)].

This was not a decision we made lightly. As the treatment landscape evolves, we decided to discontinue these medicines as hemophilia patients continue to transition to alternate treatment options in the space, including those within our own hematology portfolio. It is important to note there is no quality issue with either HEMOFIL M or RECOMBINATE and that their safety and efficacy remains consistent with the product Prescribing Information.

We understand that this directly impacts you and are here to support the hemophilia community during this transition. **We intend to supply HEMOFIL M and RECOMBINATE to patients already receiving these medicines until inventory is depleted or expired in mid-2026.** Exact timing will vary based on potency and demand.

Transitioning to Alternative Treatment
We recommend beginning to have discussions with your healthcare team to ensure ample time for creating a longer-term, alternative treatment plan.

For more than 70 years, we've pioneered innovations and worked tirelessly to improve the standard of care for hemophilia patients. We are proud to offer alternative treatment options within the Takeda factor VIII portfolio, namely ADVATE® [Antihemophilic Factor (Recombinant)] and ADYNOVATE® [Antihemophilic Factor (Recombinant), PEGylated], that may meet your individual needs and are similar to HEMOFIL M and RECOMBINATE. Please visit ADVATE.com and ADYNOVATE.com for more information.

What is ADYNOVATE [Antihemophilic Factor (Recombinant), PEGylated], ADVATE [Antihemophilic Factor (Recombinant)], RECOMBINATE [Antihemophilic Factor (Recombinant)] and HEMOFIL M [Antihemophilic Factor (Human), Method M, Monoclonal Purified]?

- ADYNOVATE and ADVATE are prescription, injectable medicines that are used to replace clotting factor, to help treat and control bleeding in children and adults with hemophilia A (congenital factor VIII deficiency, also called "classic" hemophilia).
- RECOMBINATE and HEMOFIL M are used to prevent and control bleeding in people with hemophilia A.
- Your healthcare provider (HCP) may give you ADYNOVATE, ADVATE or RECOMBINATE when you have surgery.
- ADYNOVATE and ADVATE can each reduce the number of bleeding episodes when used regularly (prophylaxis).

ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M are not used to treat von Willebrand disease.

Please see Detailed Important Risk Information below and discuss with your healthcare provider.

Takeda Support
Our commitment to supporting you throughout this transition remains strong and unwavering. For more information, visit HemophiliaJourney.com.

Please contact your healthcare provider directly to discuss alternative treatment plans.

For patients prescribed a Takeda treatment, our dedicated Takeda Patient Support team is available to direct you to financial assistance options and insurance support, help you get your medication delivered and help you understand your condition and prescribed Takeda treatment. To learn more about Takeda Patient Support, visit TakedaPatientSupport.com or call 1-888-229-8379, Monday through Friday, 8 AM to 8 PM ET.

Reporting Adverse Events
Healthcare providers and patients are encouraged to report adverse reactions and/or quality problems related to HEMOFIL M or RECOMBINATE to Takeda at 1-877-TAKEDA-7 (1-877-825-3327). 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.

This letter is not intended as a complete description of the benefits and risks related to the use of HEMOFIL M, RECOMBINATE, ADVATE and/or ADYNOVATE. Please visit ADVATE.com and ADYNOVATE.com to learn more about our safety and efficacy profiles.

DETAILED IMPORTANT RISK INFORMATION: ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M

Who should not use ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M?
Do not use ADYNOVATE or ADVATE if you:
- Are allergic to mouse or hamster proteins.
- Are allergic to any ingredients in ADYNOVATE or ADVATE.

Do not use RECOMBINATE if you:
- Are allergic to mouse, hamster or bovine proteins.
- Are allergic to any ingredients in RECOMBINATE.

Do not use HEMOFIL M if you:
- Are allergic to mice.
- Are allergic to any ingredients in HEMOFIL M.

Tell your HCP if you are pregnant or breastfeeding because ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M may not be right for you.

What should I tell my HCP before using ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M?
Tell your HCP 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 mouse, hamster or bovine proteins.
- Are breastfeeding. It is not known if ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M pass into your milk or if they can harm your baby.

- Are or become pregnant. It is not known if ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M may harm your unborn baby.
- Have been told that you have inhibitors to factor VIII (because ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M may not work for you).

What important information do I need to know about ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M?

- You can have an allergic reaction to ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M. Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, flushing, facial swelling, tightness of the throat, chest pain or tightness, wheezing, difficulty breathing, lightheadedness, dizziness, nausea or fainting.
- Do not attempt to infuse yourself with ADYNOVATE, ADVATE, RECOMBINATE or HEMOFIL M unless you have been taught by your HCP or hemophilia center.
- Because HEMOFIL M is made from human blood, it may carry a risk of transmitting infectious agents, such as parvovirus B19, hepatitis A and Creutzfeldt-Jakob disease agent. Symptoms of parvovirus B19 infection include fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain. Symptoms of hepatitis A may include several days to weeks of poor appetite, tiredness and low-grade fever followed by nausea, vomiting, stomach pain, dark urine and a yellowed complexion. Discontinue use of HEMOFIL M and contact your healthcare provider right away if such symptoms occur. Any infections your doctor thinks may have been transmitted by this product should be reported to Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

What else should I know about ADYNOVATE, ADVATE, RECOMBINATE, HEMOFIL M 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 ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M from working properly. Talk with your HCP to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

What are possible side effects of ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M?

- **Adynovate**: The common side effects of ADYNOVATE are headache, diarrhea, rash, nausea, dizziness and hives. These are not all the possible side effects with ADYNOVATE.
- **Advate**: 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 and rash.
- **Recombinate**: The most common side effects reported during clinical studies with RECOMBINATE include: chills, flushing, rash and nose bleeds.
- **Hemofil M:** The most common side effects reported during clinical studies with HEMOFIL M include: factor VIII inhibitors, dizziness, headache, unusual taste, fever and infusion site inflammation.

Tell your HCP about any side effects that bother you or do not go away or if your bleeding does not stop after taking ADYNOVATE, ADVATE, RECOMBINATE or HEMOFIL M. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088**.**

Please click for Full Prescribing Information for ADYNOVATE, ADVATE, RECOMBINATE and HEMOFIL M and discuss with your HCP.

Sincerely,
Anthea Cherednichenko
Vice President, Franchise Head, U.S. Hematology

Enclosure: HEMOFIL M, RECOMBINATE, ADVATE and ADYNOVATE Full Prescribing Information.

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)] lyophilized

powder for reconstitution, for intravenous injection
Initial U.S. Approval: 2003

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). (2.1)

Control and Prevention of Bleeding Episodes and Perioperative Management (2.1)

- Dose (IU) = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Determine treatment frequency based on type of bleeding episode.

Routine Prophylaxis (2.1)

- 20 to 40 IU per kg every other day (3 to 4 times weekly).
- Alternatively, use every third day dosing regimen targeted to maintain FVIII trough levels ≥1%.

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. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, may occur. Patients may develop hypersensitivity to mouse or hamster protein, which is present in trace amounts in the product. Should symptoms occur, discontinue treatment with ADVATE and administer appropriate treatment. (5.1)
- Development of activity-neutralizing antibodies may occur. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration. (5.2, 5.3)

ADVERSE REACTIONS

- Serious adverse drug reactions reported are hypersensitivity and factor VIII inhibitors. (6.1)
- The most common adverse drug reactions observed in greater than 5% of patients are pyrexia, headache, cough, nasopharyngitis, arthralgia, vomiting, upper respiratory tract infection, limb injury, nasal congestion, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pediatric Use: Clearance (based on per kg body weight) is higher in the pediatric population. Dose adjustment may be needed. (8.4)

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

Revised: 3/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

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

2 DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only.

2.1 Dose

- Dosage and duration of treatment depend on the severity of factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- Each vial of ADVATE has the recombinant factor VIII potency in International Units (IU) stated on the label. The expected *in vivo* peak increase in factor VIII level expressed as IU/dL of plasma or percent of normal can be estimated using the following formulas:

  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 postinfusion 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 the dose can be estimated by the calculations above, whenever possible, perform appropriate laboratory tests including serial factor VIII activity assays *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]*.

<u>Control and Prevention of Bleeding Episodes</u>

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

Table 1: Dosing for Control and Prevention of Bleeding Episodes

Type of Bleeding Episodes	Factor VIII Level Required (% of normal or IU/dL)	Dose[a] (IU/kg)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding episode.	20 to 40	10 to 20	12 to 24 (Every 8 to 24 hours for patients under the age of 6)	Until the bleeding is resolved (approximately 1 to 3 days).
Moderate Muscle bleeding, bleeding into the oral cavity, definite hemarthroses, and known trauma.	30 to 60	15 to 30	12 to 24 (Every 8 to 24 hours for patients under the age of 6)	Until the bleeding is resolved (approximately 3 days or more).
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 to 100	30 to 50	8 to 24 (Every 6 to 12 hours for patients under the age of 6)	Until bleeding is resolved.

a) 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 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (% of normal or IU/dL)	Dose[a] (IU/kg)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Including tooth extraction	60 to 100	30 to 50	Single dose within 1 hour of the operation. 12 to 24 (as needed to control bleeding)	Single dose or repeat until bleeding is resolved. For dental procedures, adjunctive therapy may be considered.
Major Intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery	80 to 120 (pre- and postoperative)	40 to 60	One dose preoperative to achieve 100% activity. Every 8 to 24 to keep factor VIII activity in desired range. (Every 6 to 24 hours for patients under the age of 6)	Until healing is complete.

a) Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Routine Prophylaxis

- Use dose of 20 to 40 International Units of factor VIII per kg body weight every other day (3 to 4 times weekly).
- Alternatively, use every third day dosing regimen targeted to maintain FVIII trough levels ≥1%.
- Adjust dose based on the patient's clinical response.[1,2]

2.2 Preparation and Reconstitution

Preparation

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

Reconstitution

1. Allow the ADVATE package to reach room temperature.
2. Open the package by peeling away the lid. Remove ADVATE from the package and verify that the expiration date on the label has not passed and the potency unit number is same as expected. Inspect parenteral drug products for discoloration and particulate matter. The ADVATE powder should be white to off-white in color and the diluent free from foreign particles. Do not use if the criteria are not met.
3. Place the ADVATE on a flat surface with the diluent vial on top (Figure A). The diluent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
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 (Figure B). Do not tilt the system until the transfer is complete.
5. Verify that diluent transfer is complete. Swirl gently until the powder is completely dissolved (Figure C). Do not shake. Do not refrigerate after reconstitution.

Figure A

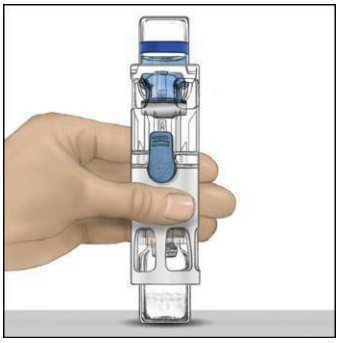


Figure B

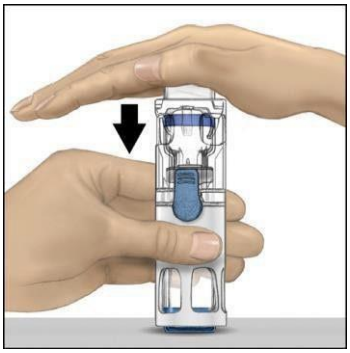
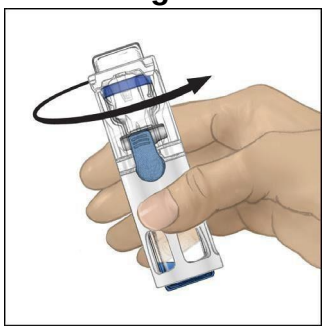


Figure C



2.3 Administration

For intravenous injection after reconstitution only.

- Inspect parenteral drug products 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 Takeda Pharmaceuticals U.S.A., Inc. 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 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 III 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.

Figure D

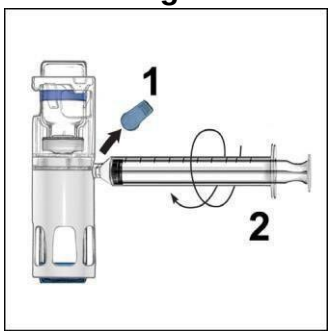
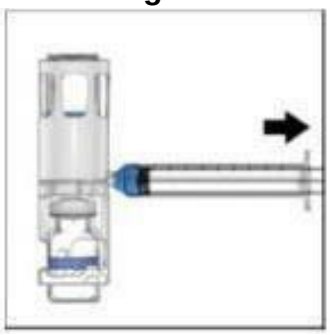


Figure E



3 DOSAGE FORMS AND STRENGTHS

ADVATE is available as a lyophilized white to off-white powder in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 3000, or 4000 International Units (IU, unit). The 250 to 1500 IU strengths come with 2 mL Sterile Water for Injection (sWFI); the 2000 to 4000 IU strengths come with 5 mL of sWFI.

Each ADVATE is labeled on the housing with the recombinant antihemophilic factor (rAHF) activity expressed in IU 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, polysorbate 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, paresthesia, rash, flushing, facial swelling, urticaria, dyspnea, pruritus, and vomiting.

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 nonhuman 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 with an expected dose, 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)]*.
- Monitor for development of factor VIII inhibitors. 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.

6 ADVERSE REACTIONS

Serious adverse reactions seen with ADVATE are hypersensitivity reactions, including anaphylaxis, and the development of high-titer inhibitors necessitating alternative treatments to factor VIII.
The most common adverse reactions observed in clinical trials (frequency greater than 5% of subjects) were pyrexia, headache, cough, nasopharyngitis, arthralgia, vomiting, upper respiratory tract infection, limb injury, nasal congestion, and diarrhea.

6.1 Clinical Trials Experience

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

ADVATE has been evaluated in 11 clinical trials in previously treated patients (PTPs) and one trial in previously untreated patients (PUPs) with severe to moderately severe hemophilia A (factor VIII ≤2% of normal). A total of 418 subjects have been treated with ADVATE as of January 2012. Total exposure to ADVATE was 63,188 infusions. The median duration of participation per subject was 397 (min-max: 2−1620) days and the median number of exposure days to ADVATE per subject was 97 (min-max: 1−709).

The summary of adverse reactions with a frequency >5% are shown in *Table 3* below.

No subject was withdrawn from a clinical trial due to an adverse reaction.

Table 3: Summary of Adverse Reactions (ARs)[a] with a Frequency Greater than 5% in 418[b] Subjects

MedDRA[c] System Organ Class	MedDRA Preferred Term	Number of Adverse Reactions	Number of Subjects	Percent of Subjects
General Disorders and Administration Site Conditions	Pyrexia	110	66	16
Nervous System Disorders	Headache	114	56	13
Respiratory, Thoracic and Mediastinal Disorders	Cough	86	54	13
Infections and Infestations	Nasopharyngitis	72	49	12
Musculoskeletal and Connective Tissue Disorders	Arthralgia	49	32	8
Gastrointestinal Disorders	Vomiting	41	31	7
Infections and Infestations	Upper Respiratory Tract Infection	35	29	7
Injury, Poisoning and Procedural Complications	Limb Injury	56	25	6
Respiratory, Thoracic and Mediastinal Disorders	Nasal Congestion	32	25	6
Gastrointestinal Disorders	Diarrhea	29	24	6
Injury, Poisoning and Procedural Complications	Procedural Pain	26	22	5
Respiratory, Thoracic and Mediastinal Disorders	Oropharyngeal Pain	25	22	5
Infections and Infestations	Ear Infection	30	21	5

a) Adverse reactions are defined as all adverse events that occurred (a) within 24 hours after being infused with investigational product, or (b) all adverse events assessed related or possibly related to investigational product, or (c) adverse events for which the investigator's or sponsor's opinion of causality was missing or indeterminate.

b) The ADVATE clinical program included 418 treated subjects from 11 completed studies in PTPs and 1 completed trial in PUPs.

c) MedDRA version 8.1 was used.

Immunogenicity

The development of factor VIII inhibitors with the use of ADVATE was evaluated in clinical trials with pediatric PTPs (<6 years of age with ≥50 factor VIII exposures) and PTPs (≥10 years of age with ≥150 factor VIII exposures). Of 276 subjects who were treated with ADVATE 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 event results in a factor VIII inhibitor frequency in PTPs of 0.4% (95% CI of 0.01 and 2% for the risk of any factor VIII inhibitor development).[3] 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), 16 (29.1%) of 55 subjects who received ADVATE developed inhibitors to factor VIII. Seven subjects developed high-titer (>5 BU) and nine subjects developed low-titer inhibitors. Inhibitors were detected at a median of 13 exposure days (min-max: 6 to 26 exposure days) to the product.

Immunogenicity also was evaluated by measuring the development of antibodies to heterologous proteins. When assessed for anti-Chinese hamster ovary (CHO) cell protein antibodies, of 229 treated subjects, 3 showed an upward trend in antibody titer over time and 10 showed repeated but transient elevations of antibodies. When assessed for muIgG protein antibodies, of the 229 treated subjects, 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 to CHO cell or muIgG proteins, reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts. All of these subjects had numerous repeat exposures to the product without recurrence of the events and a causal relationship between the antibody findings and these clinical events has not been established.

When assessed for the presence of anti-human von Willebrand Factor (VWF) antibodies, of the 228 treated subjects, 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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.
Table 4 represents the most frequently reported postmarketing adverse reactions as MedDRA Preferred Terms.

Table 4: Postmarketing Experience

Organ System [MedDRA Primary SOC]	Preferred Term
Immune System Disorders	Anaphylactic reaction Hypersensitivity
General Disorders and Administration Site Conditions	Injection site reaction Chills Fatigue/Malaise Chest discomfort/pain Decreased therapeutic effect

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with ADVATE use in pregnant women to inform a drug-associated risk. 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.
In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

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

8.4 Pediatric Use
Pharmacokinetic studies in children have demonstrated higher clearance, a shorter half-life and lower recovery of factor VIII compared to adults *[see Clinical Pharmacology (12.3)]*. This may be explained by differences in body composition and should be taken into account when dosing or following factor VIII levels in the pediatric population.[4] Because clearance (based on per kg body weight) has been demonstrated to be higher in the pediatric population, dose adjustment or more frequent dosing based on per kg body weight may be needed in this population *[see Clinical Pharmacology (12.3)]*. In the ADVATE routine prophylaxis clinical trial, 3 children aged 7 to <12 and 4 adolescents aged 12 to <16 were included in the per-protocol analysis. The reductions in annualized bleeding rate per subject per year during any prophylaxis regimen as compared to during on-demand therapy were similar among children, adolescents, and adults *[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 from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and other drug therapy.

11 DESCRIPTION
ADVATE [Antihemophilic Factor (Recombinant)] is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line but does not contain plasma or albumin. The CHO cell line employed in the production of ADVATE is derived from that used in the biosynthesis of RECOMBINATE [Antihemophilic Factor (Recombinant)]. ADVATE has been shown to be comparable to RECOMBINATE with respect to its biochemical and physicochemical properties, as well as its nonclinical *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 (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, nonpyrogenic, 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 5: Approximate Concentration of Stabilizer and Excipient after Reconstitution

Stabilizer and Excipient	2 mL Reconstitution (for 250, 500, 1000, 1500 IU) Target	5 mL Reconstitution (for 2000, 3000, 4000 IU) Target
Tris (hydroxymethyl) aminomethane	25 mM	10 mM
Calcium Chloride	4.2 mM	1.7 mM
Mannitol	8% (w/v)	3.2% (w/v)
Sodium Chloride	225 mM	90 mM
α, α-Trehalose	2% (w/v)	0.8% (w/v)
Histidine	25 mM	10 mM
Glutathione (Reduced)	0.2 mg/mL	0.08 mg/mL
Polysorbate 80	0.025% (w/v)	0.01% (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.

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 nonbleeding 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.[3] The per-protocol analysis included 30 patients (20 adults and 10 children). Pharmacokinetic parameters for the 20 adults for each trial are presented in *Table 6*.

Table 6: Pharmacokinetic Parameters (Mean ± SD) for ADVATE and RECOMBINATE (N=20 Adult Subjects Age >16 Years)

Parameter	RECOMBINATE (N=20)	ADVATE (N=20)
$AUC_{0\text{-}48h}$ (IU·hrs/dL) [a]	1638 ± 357	1644 ± 338
In vivo recovery (IU/dL/IU/kg)[b]	2.7 ± 0.6	2.6 ± 0.5
Half-life (hrs)	11.2 ± 2.5	12.0 ± 4.2
C_{max} (IU/dL)	136 ± 29	128 ± 28
MRT (hrs)	14.7 ± 3.8	15.8 ± 5.9
V_{ss} (dL/kg)	0.4 ± 0.1	0.4 ± 0.1
CL (mL/kg*hr)	3 ± 1	3 ± 1

a) Area under the plasma factor VIII concentration x time curve from 0 to 48 hours postinfusion.
b) Calculated as (C_{max} – baseline factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal postinfusion 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.

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

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

Table 7: Pharmacokinetic Parameters (Mean ± SD) of ADVATE by Age Group <16 Years (N=98; Intent-to-Treat PK Analysis Set)

PK Parameter	Infants (N=7) (1 month to <2 yrs)	Children (N=32) (2 to <5 yrs)	Older Children (N=24) (5 to <12 yrs)	Adolescents (N=35) (12 to <16 yrs)
$AUC_{0\text{-}inf}$ (IU*hr/dL)	1240 ± 330	1164 ± 424	1396 ± 506	1300 ± 469
Incremental Recovery at C_{max}[a] (IU/dL per IU/kg)	2.1 ± 0.5	1.8 ± 0.4	2.1 ± 0.6	2.1 ± 0.5
Half-Life (hr)	8.7 ± 1.4	9.5 ± 1.8	11.2 ± 3.5	12.0 ± 2.9
Maximum Plasma Concentration Postinfusion (IU/dL)	104 ± 27	91 ± 19	105 ± 34	103 ± 25
Mean Residence Time (hr)	10.4 ± 2.5	11.8 ± 2.8	14.3 ± 4.3	14.9 ± 4.6
Volume of Distribution at Steady State (dL/kg)	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	0.6 ± 0.1
Clearance (mL/kg*hr)	4.3 ± 1.0	4.8 ± 1.5	4.1 ± 1.5	4.2 ± 1.2

a) 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 postinfusion factor VIII measurement.

In a crossover pharmacokinetic trial of recombinant antihemophilic factor, plasma/albumin free method (rAHF-PFM) reconstituted in 2 mL vs 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

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.

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.

13.2 Animal Toxicology and/or Pharmacology

Single doses up to 4,750 IU/kg did not demonstrate any acute or toxic effect for ADVATE in laboratory animals (rat and rabbit).

14 CLINICAL STUDIES

Original Safety and Efficacy Study

A safety and efficacy trial evaluated the pharmacokinetics (double-blinded, randomized, crossover), safety, immunogenicity, and hemostatic efficacy (open-label) of ADVATE in 111 subjects. The trial was conducted in the US and Europe with 103 Caucasian, 7 Black, and 1 Asian 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 were excluded.

Subjects self-administered ADVATE for routine prophylaxis (≥25 IU/kg body weight 3 to 4 times per week) and for the on-demand 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 a scale of excellent, good, fair, or none, based on the quality of hemostasis achieved with ADVATE 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.[3]

The rate of new bleeding episodes during the 75-exposure-day prophylactic regimen was calculated as a function of the etiology of bleeding episodes for 107 evaluable subjects (n = 274 bleeding episodes).[3] These rates are presented in *Table 8*. The overall rate of new bleeding episodes in the prophylaxis study was 0.52 ± 0.71.

Table 8: Rate of New Bleeding Episodes During Prophylaxis

Types of Bleeding Episode	Mean (± SD) New Bleeding Episodes/Subject/Month
Spontaneous	0.34 ± 0.49
Post-traumatic	0.39 ± 0.46
Unknown/Indeterminate	0.33 ± 0.34

The pharmacokinetic properties of ADVATE were investigated at the beginning of treatment in a multicenter trial of previously treated subjects and at the end of treatment in a subset of subjects (N=34) who had completed at least 75 exposure days of treatment with ADVATE *[see 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 original safety and efficacy study. 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. Final analysis of efficacy was conducted for 81 subjects who self-administered ADVATE on a routine prophylactic regimen for a minimum period of 75 exposure days.

A total of 837 bleeding episodes occurred in 70 of the 81 subjects. The other 11 subjects experienced no bleeding episodes. The response to treatment with ADVATE was rated as excellent or good for 80.4% of all bleeding episodes. Most (88%) bleeding episodes required only 1 or 2 infusions to obtain hemostasis. Among the 837 bleeding episodes, 2 (0.3%) did not require treatment (0 infusions), 521 (62.2%) required 1 infusion, 216 (25.8%) required 2 infusions, 23 (2.7%) required 3 infusions, and 75 (9.0%) required 4 or more infusions. By etiology, 45.3% of these bleeding events were secondary to trauma and 27.7% occurred spontaneously; the other 27% had an undetermined etiology.

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

Perioperative Management Study

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

Prior to surgery, subjects received a pre-operative loading dose aimed at increasing the plasma factor VIII level to 60 to 100% of normal for dental procedures or 80 to 120% of normal for all other surgical procedures. During the surgery, subjects received replacement therapy by either bolus (47 procedures) or continuous infusion (18 procedures). For continuous infusion, the initial rate was 4 IU/kg/hr for subjects >12 years of age and 5 IU/kg/hr for subjects 5 to 12 years of age. After discharge, subjects continued to receive ADVATE for control of hemostasis as prescribed by the investigator for up to 6 weeks for major orthopedic procedures and up to 2 weeks for all other procedures.

Intraoperative efficacy was rated as excellent or good (Excellent intraoperative blood loss was less than expected for the type of procedure performed; Good intraoperative blood loss was as expected for the type of procedure performed) for 61 (93.9%) of the 65 procedures; the rating was not done for 3 procedures and unknown for 1 procedure. Postoperative efficacy was rated as excellent or good for 62 (95.4%) of the 65 procedures; the rating was unknown for 2 procedures and not done for 1 procedure. Of the 24 procedures requiring surgical drains, efficacy assessments at the time of drain removal were rated as excellent or good for 20 (83.3%) procedures and fair (Fair intraoperative blood loss was more than expected for the type of procedure performed) for 2 (8.3%) procedures; the rating was unknown for 1 procedure and not done for 1 procedure. Both procedures requiring surgical drains with fair ratings were major orthopedic surgeries.

Routine Prophylaxis Study

In a multicenter, open-label, prospective, randomized, controlled postmarketing clinical trial of ADVATE use in two prophylactic treatment regimens compared to that of on-demand 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 a standard prophylaxis regimen (20 to 40 IU/kg every 48 hours) or PK-driven prophylaxis regimen (20 to 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 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:

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

D = target FVIII dose (IU/kg) that ensures that a trough level of ≥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

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 ($p<0.0001$). Twenty-two of 53 (42%) subjects experienced no

bleeding episodes while on prophylaxis for one year. While there was no statistically significant difference in bleeding frequency observed between the two prophylaxis regimens studied, the trial was not powered to demonstrate equivalence in bleeding rate between the two prophylaxis arms.

Table 9: 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)[a] Annual Bleed Rate(ABR)	44.0 (20.8)	1.0 (2.1)	1.0 (4.1)	1.0 (4.1)
Median (IQR)[a] Joint ABR	38.7 (24.8)	0.5 (2.0)	1.0 (4.1)	1.0 (2.1)
Median (IQR)[a] Non-Joint ABR[1]	4.0 (11.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median (IQR)[a] Spontaneous ABR	32.0 (26.8)	0.0 (1.9)	0.0 (2.0)	0.0 (1.9)
Median (IQR)[a] Traumatic ABR	11.5 (17.2)	0.0 (1.0)	1.0 (1.0)	0.0 (1.0)

[a)] 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 10*.

Table 10: Annualized Bleed Rate by Age Category and Any Prophylaxis vs On-Demand (Per Protocol)

		Any Prophylaxis		On-Demand	
Age Category	**Number of Subjects**	**Median**	**Percentage of Subjects with Zero Bleeds**	**Median**	**Percentage of Subjects with Zero Bleeds**
Children (≥7 to <12 years old)	3	5.2	33%	44.0	All subjects bleed during On-Demand
Adolescents (≥12 to <16 years old)	4	5.0	25%	58.0	
Adults (≥16 years old and older)	46	1.0	43%	44.7	
All Subjects	53	1.0	42%	44.0	

As a secondary endpoint, the trial assessed all Short Form Health Survey (SF-36v1) domains. The SF-36v1 is a valid and reliable measure of health-related quality of life that is comprised of 8 domains categorized into 2 summary scores *(Table 11)*.

Table 11: 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)
Physical Component Score	3.56	(1.56, 5.56)
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)
Mental Component Score	-1.22	(-3.66, 1.23)

a) Positive change values are in the favorable direction.

Human Factors Usability Study

A human factors study was performed with 44 participants to evaluate the usability of the ADVATE in the BAXJECT III reconstitution system. Participants in the study included 15 patients, 16 caregivers, and 13 healthcare providers.

During the study, participants viewed an instructional video then performed the reconstitution steps utilizing the Instructions For Use (IFU). Objective performance data were collected and evaluated. Participants' comments from a postevaluation interview were reviewed for their appropriateness and applicability. As a result, the content of the package insert was revised to clarify the instructions for use.

15 REFERENCES

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5. Negrier C, Shapiro A, Berntorp E *et al*. Surgical evaluation of a recombinant factor VIII prepared using a plasma/albumin-free method: efficacy and safety of ADVATE in previously treated patients. *Thromb.Haemost* 2008 100:217-223.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

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

Nominal Strength	Factor VIII Potency Range	Potency Color Code	Carton NDC (Includes 2 mL sWFI Diluent)	Carton NDC (Includes 5 mL sWFI Diluent)
250 IU	200 to 400 IU per vial	Light blue	0944-3051-02	
500 IU	401 to 800 IU per vial	Pink	0944-3052-02	
1000 IU	801 to 1200 IU per vial	Green	0944-3053-02	
1500 IU	1201 to 1800 IU per vial	Purple	0944-3054-02	
2000 IU	1801 to 2400 IU per vial	Orange		0944-3045-10
3000 IU	2401 to 3600 IU per vial	Silver		0944-3046-10
4000 IU	3601 to 4800 IU per vial	Dark Green		0944-3047-10

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

Not made with natural rubber latex.

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (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.
- Inhibitor formation may occur with the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.

- Advise patients to consult with their physicians or healthcare provider prior to travel. While traveling, advise patients to bring an adequate supply of ADVATE based on their current regimen of treatment.

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

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ADV372

Patient Information
ADVATE (ad-vate)
[Antihemophilic Factor (Recombinant)]

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.

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). 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 to16 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 to 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 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.

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.

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 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:

Light-blue	Dosage strength of approximately 250 International Units (200 to 400 IU) (with 2 mL sWFI)
Pink	Dosage strength of approximately 500 International Units (401 to 800 IU) (with 2 mL sWFI)
Green	Dosage strength of approximately 1000 International Units (801 to 1200 IU) (with 2 mL sWFI)
Purple	Dosage strength of approximately 1500 International Units (1201 to 1800 IU) (with 2 mL sWFI)
Orange	Dosage strength of approximately 2000 International Units (1801 to 2400 IU) (with 5 mL sWFI)
Silver	Dosage strength of approximately 3000 International Units (2401 to 3600 IU) (with 5 mL sWFI)
Dark Green	Dosage strength of approximately 4000 International Units (3601 to 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?
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 Takeda available to the patients:
For more product information on ADVATE, please visit www.ADVATE.com or call 1-877-TAKEDA-7 (1-877-825-3327).

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Patented: see www.takeda.com/en-us/patents

Revised: 3/2023 ADV372

Instructions For Use
ADVATE
[Antihemophilic Factor (Recombinant)]
(For intravenous use only)

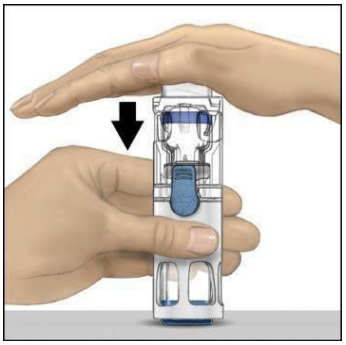
Do not attempt to do an infusion to yourself unless you have been taught how by your healthcare provider or hemophilia center.

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

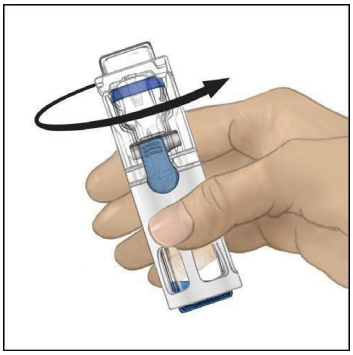
- Always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using ADVATE. If you are unsure of the procedures, please call your healthcare provider before using.
- Call your healthcare provider right away if bleeding is not controlled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

1. Prepare a clean flat surface and gather all the materials you will need for the infusion. Check the expiration date, and let the ADVATE warm up to room temperature. Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.
2. Open the ADVATE package by peeling away the lid. Remove the ADVATE from the package and visually inspect the contents of the product and diluent vial. The ADVATE powder should be white to off-white in color and the diluent should not contain particles. Do not use if discoloration or particles are seen.
3. Place on a flat surface with the diluent vial on top. The diluent vial has a blue stripe.

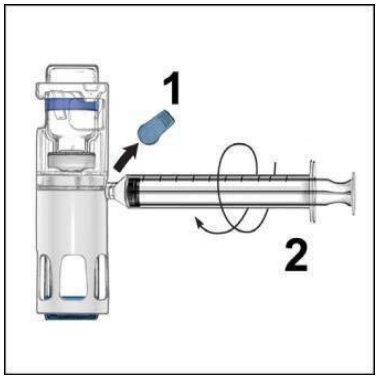
4. With one hand holding the ADVATE housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADVATE vial. Both vials will move into the housing when pressed. If you don’t see the diluent transfer to the product vial, press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



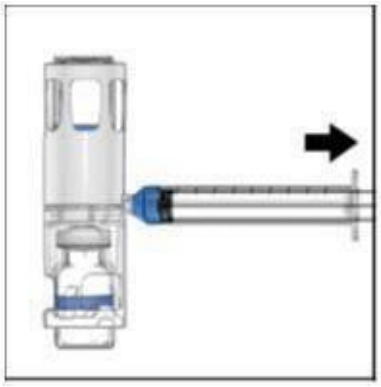
5. Swirl the ADVATE gently and continuously until the ADVATE is completely dissolved. Do not shake. Do not refrigerate after reconstitution. Inspect the ADVATE solution for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance. If not,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



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



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



8. Disconnect the syringe from the system. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
9. Apply a tourniquet and get the injection site ready by wiping the skin well with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center).

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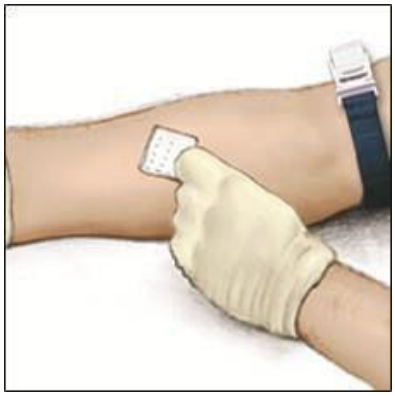
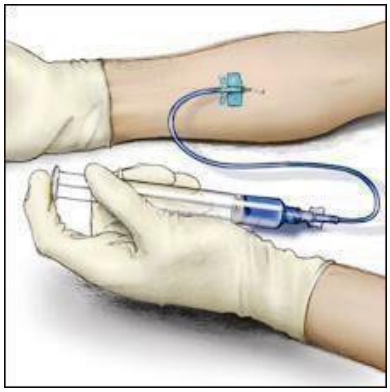


10. Insert the needle into the vein and remove the tourniquet. Slowly infuse the ADVATE. Do not infuse any faster than 10 mL per minute.



11. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.
12. **Do not recap the needle.** Place the needle, syringe, and ADVATE in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.

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

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

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Revised: 3/2023 ADV372

FPI-0282

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

ADYNOVATE, (Antihemophilic Factor, Recombinant, PEGylated) Lyophilized Powder for Solution For Intravenous Injection.
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.1) 8/2023

----------INDICATIONS AND USAGE----------
ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, is a human antihemophilic factor indicated in children and adults with hemophilia A (congenital factor VIII deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

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

----------DOSAGE AND ADMINISTRATION----------
For intravenous use after reconstitution only.
- One unit per kilogram body weight will raise the factor VIII level by 2% international units per deciliter (IU per dL). Each vial of ADYNOVATE is labeled with the actual amount of recombinant factor VIII present in IU. (2.1)
- On-demand treatment and control of bleeding episodes and perioperative management:
  - Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)
  - Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)

Routine prophylaxis:
  - Administer 40-50 IU/kg body weight twice weekly in adults and adolescents (12 years and older).
  - Administer 55 IU/kg twice weekly in children (<12 years) with a maximum of 70 IU/kg
  - Adjust the dose and dosing intervals based on the patient's clinical response.
- Inject intravenously over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min). (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
ADYNOVATE is available as a lyophilized powder in single-dose vials containing nominally (approximately) 250, 500, 750, 1000, 1500, 2000, or 3000 international units. (3)

----------CONTRAINDICATIONS----------
Do not use in patients who have had prior anaphylactic reaction to ADYNOVATE, the parent molecule (ADVATE), mouse or hamster protein, or excipients of ADYNOVATE. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity reactions, including anaphylaxis, have been reported. Should symptoms occur, discontinue treatment with ADYNOVATE and administer appropriate treatment. (5.1)
- Development of factor VIII neutralizing antibodies (inhibitors) may occur. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration. (5.2, 5.3)
-

----------ADVERSE REACTIONS----------
The most common adverse reactions reported in ≥1% of subjects in the clinical studies were headache, diarrhea, rash, nausea dizziness and urticaria. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Pediatric Use: Higher clearance, a shorter half-life and lower incremental recovery of factor VIII has been observed in children (<12 years). Dose adjustment 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: 8/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, is a human antihemophilic factor indicated in children and adults with hemophilia A (congenital factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- Each vial label of ADYNOVATE states the actual factor VIII potency in international units. This may be more or less than the nominal vial potency/content. One international unit corresponds to the activity of factor VIII contained in one milliliter of normal human plasma.
- 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 monitoring of replacement therapy is necessary in cases of serious or life-threatening bleeding episodes.
- Potency assignment is determined using a one-stage clotting assay. Plasma factor VIII levels can be monitored clinically using a one-stage clotting assay.
- Calculate the dose of ADYNOVATE based on the empirical finding that one international unit of ADYNOVATE per kg body weight increases the plasma factor VIII level by 2 IU per dL of plasma. Use the following formula to estimate the expected *in vivo* peak increase in factor VIII level expressed as IU per dL (or % of normal) and the dose to achieve a desired *in vivo* peak increase in factor VIII level:

Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)

- Patients vary in their pharmacokinetic (e.g., clearance, half-life, *in vivo* recovery) and clinical response.
  Base the dose and frequency of ADYNOVATE on the individual clinical response.

On-demand Treatment and Control of Bleeding Episodes

A guide for dosing of ADYNOVATE for the on-demand treatment and control of bleeding episodes is provided in Table 1. Maintain plasma factor VIII activity level at or above the described plasma levels (in IU per dL or % of normal).

Table 1: Dosing for On-demand Treatment and Control of Bleeding Episodes

Type of Bleeding	Target Factor VIII Level (IU/dL or % of normal)	Dose[a] (IU/kg)	Frequency of Dosing (hours)	Duration of Therapy
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding episode.	20-40	10-20	12-24	Until the bleeding is resolved
Moderate Muscle bleeding, moderate bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	15-30	12-24	Until the bleeding is resolved
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	30-50	8-24	Until bleeding is resolved.

[a] 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 ADYNOVATE during surgery (perioperative management) is provided in Table 2. Consideration should be given to maintain a factor VIII activity at or above the target range.

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (% of normal or IU/dL)	Dose (IU/kg)	Frequency of Doses (hours)	Duration of Treatment
Minor Including tooth extraction	60-100	30-50	Within one hour before surgery. Repeat after 24 hours if necessary	Single dose or repeat as needed until bleeding is resolved.
Major Intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery	80-120 (pre- and post-operative)	40-60	Within one hour before the operation to achieve 100% activity. Repeat every 8 to 24 hours (6 to 24 hours for patients <12 years of age) to maintain FVIII activity within the target range	Until adequate wound healing

Routine Prophylaxis

Administer 40-50 IU/ kg body weight twice weekly in adults and adolescents (12 years and older). Administer 55 IU per kg body weight two times per week in children (< 12 years) with a maximum of 70 IU/kg. Adjust the

dose and dosing intervals based on the patient's clinical response.

2.2 Preparation and Reconstitution

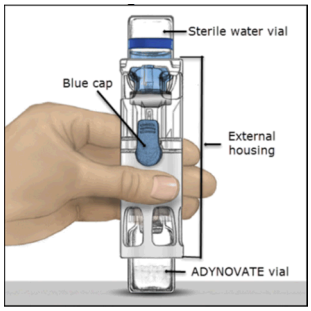
Preparation

- Do not remove ADYNOVATE or diluent vials from the external housing.
- Examine the packaging containing ADYNOVATE to ensure no damage or peeling of the lid is evident. Do not use if the lid is not completely sealed on the blister.
- Use aseptic technique (clean and germ free) and a flat work surface during the reconstitution procedure.

Reconstitution

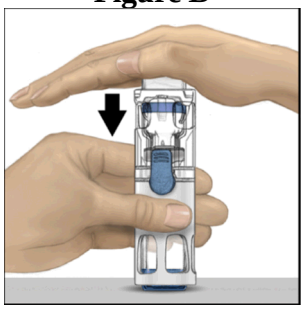
1. Allow the ADYNOVATE package to reach room temperature before use.
2. Open the package by peeling away the lid. Remove ADYNOVATE from the package and verify that the expiration date on the label has not passed and the potency unit number is same as expected. Inspect parenteral drug products for discoloration and particulate matter. The ADYNOVATE powder should be white to off-white in color and the diluent free from foreign particles. Do not use if the criteria are not met.
3. Place the ADYNOVATE on a flat surface with the diluent vial on top (Figure A). The diluent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.

Figure A



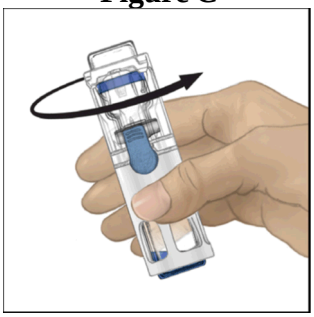
4. With one hand holding the ADYNOVATE housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADYNOVATE vial (Figure B). Do not tilt the system until the transfer is complete.

Figure B



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

Figure C



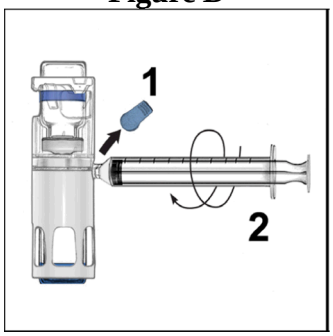
2.3 Administration

- Visually inspect the reconstituted ADYNOVATE solution for particulate matter and discoloration prior to administration, whenever solution and container permit. The final ADYNOVATE solution should be clear and colorless. Do not use if particulate matter or discoloration is observed.
- Administer ADYNOVATE as soon as possible, but no later than 3 hours after reconstitution.

Administration Steps:

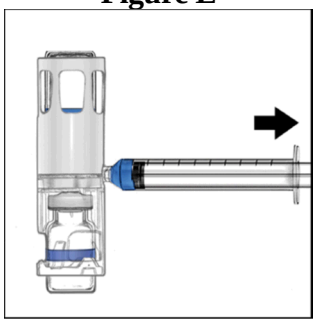
1. Remove the blue cap from the housing. Connect the syringe to the system (Figure D). Do not inject air into the ADYNOVATE.

Figure D



2. Turn the system upside down (ADYNOVATE vial now on top). Draw the ADYNOVATE solution into the syringe by pulling the plunger back slowly (Figure E).

Figure E



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

4. Administer ADYNOVATE intravenously over a period of less than or equal to 5 minutes (maximum infusion rate 10 mL per min).

3 DOSAGE FORMS AND STRENGTHS

ADYNOVATE is a lyophilized powder in single-dose vials containing nominally (approximately) 250, 500, 750, 1000, 1500, 2000, and 3000 International Units (IU, units). The 250-1500 IU strengths come with 2 mL Sterile Water for Injection (sWFI); the 2000 and 3000 IU strengths come with 5 mL of sWFI. The actual factor VIII potency/content is labeled on each ADYNOVATE vial.

The 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

ADYNOVATE is contraindicated in patients who have had prior anaphylactic reaction to ADYNOVATE, to the parent molecule (ADVATE), mouse or hamster protein, or excipients of ADYNOVATE (e.g. Tris, mannitol, trehalose, glutathione, and/or polysorbate 80).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions including anaphylaxis, have been reported with ADYNOVATE. Hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, pruritus, and nausea and vomiting. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to factor VIII can occur following administration of ADYNOVATE. Monitor patients regularly for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Perform an assay that measures factor VIII inhibitor concentration if the plasma factor VIII level fails to increase as expected, or if bleeding is not controlled with expected dose.

5.3 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity by performing a validated one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained *[see Dosage and Administration (2)]*.
- Monitor for the development of factor VIII inhibitors. Perform the Bethesda inhibitor 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 ADYNOVATE, use Bethesda Units (BU) to determine inhibitor levels.

6 ADVERSE REACTIONS

The most common adverse reactions (≥1% of subjects) reported in the clinical studies were headache, diarrhea, rash, nausea, dizziness and urticaria.

6.1 Clinical Trials Experience

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

The safety of ADYNOVATE was evaluated in 365 previously treated patients (PTPs) and previously untreated patients (PUPs) with severe hemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVATE in 6 completed multi-center, prospective, open label clinical studies and 1 ongoing clinical studies. The total number of infusions within the safety database is 74487. Table 3 lists the adverse reactions reported during clinical studies.

Table 3: Adverse Reactions Reported for ADYNOVATE

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%) (N=365)
Gastrointestinal Disorders	Diarrhea	25 (6.8%)
	Nausea	8 (2.2%)
Eye Disorders	Ocular Hyperaemia	3 (0.8%)
Immune System Disorder	Hypersensitivity[a]	2 (0.5%)
Nervous System Disorders	Headache	41 (11.2%)
	Dizziness	7 (1.9%)
Skin and Subcutaneous Tissue Disorders	Rash	10 (2.7%)
	Urticaria	7 (1.9%)
	Rash Pruritic	1 (0.3%)
Vascular Disorders	Flushing	1 (0.27%)
Investigations	Eosinophil Count Increased	2 (0.5%)
Injury, Poisoning and Procedural Complications	Infusion Related Reaction	2 (0.5%)

[a] The event of hypersensitivity was a mild transient non-serious rash, occurring in one 2-year old patient who had developed a previous rash while on ADYNOVATE.

Two cases of acute pancreatitis, with no precipitating cause identified in one case, were reported in adults during an extension study of the clinical trial which evaluated 216 subjects. Administration of ADYNOVATE continued and both cases resolved.

6.2 Immunogenicity

Clinical trial subjects were monitored for neutralizing (inhibitory) antibodies to FVIII. Of the 6 completed clinical trials in previously treated patients (PTPs), in the randomized controlled trial comparing different dosing regimens of Adynovate, one previously treated patient developed a transient low titer FVIII inhibitor at 0.6 BU while receiving more frequent dosing with Adynovate. In a continuation study with Adynovate, one patient developed a transient low titer (0.6BU) FVIII inhibitor. Repeat testing did not confirm the presence of inhibitor. Both of these subjects continued treatment without change in the dose of Adynovate.

Immunogenicity also was evaluated by measuring the development of binding IgG and IgM antibodies against factor VIII, PEGylated (PEG)-factor VIII, PEG and Chinese hamster ovary (CHO) protein using validated ELISA assays. Persistent treatment-emergent binding antibodies against FVIII, PEG-FVIII or PEG were not detected. Out of 365 subjects, thirty six subjects in total showed pre-existing antibodies to factor VIII (n=5), PEG-factor VIII (n=31) and/or PEG (n=6) prior to the first exposure to ADYNOVATE. Twenty four subjects

who tested negative at screening developed transient antibodies against factor VIII (n= 10), PEG-FVIII (n= 16) and/or PEG (n=3) at one or two consecutive study visits. Antibodies were transient and not detectable at subsequent visits. Two subjects showed positive results for binding antibodies at study completion or at the time of data cutoff. Binding antibodies that were detected prior to exposure to ADYNOVATE, that transiently developed during the trial or were still detectable at study completion or data cutoff could not be correlated to any impaired treatment efficacy or altered PK parameters. There was no causal relationship between observed adverse events and binding antibodies except in one subject where a causal relationship cannot be ruled out based on available data. No subject had pre-existing or treatment-emergent antibodies to CHO protein.

From an ongoing study in previously untreated patients <6 years with severe hemophilia A, 9 cases of FVIII inhibitor development associated with treatment with Adynovate were reported.

The detection of antibodies that are reactive to factor VIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ADYNOVATE with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience
Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Immune System Disorders: Anaphylactic Reaction

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

There are no data with ADYNOVATE use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with ADYNOVATE. It is unknown whether ADYNOVATE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary

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

8.4 Pediatric Use
Safety and efficacy studies have been performed in 91 previously treated, pediatric patients age 1 year to <18 years who received at least one dose of ADYNOVATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects age 12 to <18 (n=25) were enrolled in the

adult and adolescent safety and efficacy trial, and subjects <12 years of age (n=66) were enrolled in a pediatric trial. The safety and efficacy of ADYNOVATE in routine prophylaxis and the treatment of bleeding episodes were comparable between children and adults. *[see Clinical Studies (14)]*

Pharmacokinetic studies in children (<12 years) have demonstrated higher clearance, a shorter half-life and lower incremental recovery of factor VIII compared to adults. Because clearance (based on per kg body weight) has been demonstrated to be higher in children (<12 years), dose adjustment or more frequent dosing based on per kg body weight may be needed in this population. *[see Clinical Pharmacology (12.3)]*

8.5 Geriatric Use
Clinical studies of ADYNOVATE did not include subjects aged 65 and over.

11 DESCRIPTION
ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, is formulated as a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-dose vials containing nominal (approximate) potencies of 250, 500, 750, 1000, 1500, 2000, or 3000 international units (IU). Each vial of ADYNOVATE is labeled with the actual factor VIII activity in IU determined using one-stage clotting assay, using a reference material calibrated against a World Health Organization (WHO) International Standard for factor VIII concentrates. One IU, 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.

When reconstituted with 2 mL or 5 mL sterile water for injection, the final solution contains the following excipients and stabilizers in targeted amounts per mL of reconstituted product:

Stabilizer and Excipient	2 mL Reconstitution (for 250, 500, 750, 1000, 1500 IU) Target (per mL)	5 mL Reconstitution (for 2000, 3000 IU) Target (per mL)
Tris (hydroxymethyl) aminomethane	3.05 mg	1.22 mg
Calcium Chloride	0.60 mg	0.24 mg
Mannitol	80 mg	32 mg
Sodium Chloride	13.15 mg	5.26 mg
Trehalose Dihydrate	20 mg	8 mg
Glutathione	0.2 mg	0.08 mg
Histidine	3.90 mg	1.56 mg
Polysorbate 80	0.25 mg	0.10 mg

ADYNOVATE contains no preservative. The specific activity of ADYNOVATE is 2700 - 8000 IU/mg protein.

ADYNOVATE is a recombinant full-length human coagulation factor VIII (2,332 amino acids with a molecular weight (MW) of 280 kDa) covalently conjugated with one or more molecules of polyethylene glycol (MW 20 kDa) *[see Clinical Pharmacology (12.1)]*. The therapeutic activity of ADYNOVATE is derived from its parent drug substance, ADVATE [Antihemophilic Factor (Recombinant)], which is produced by recombinant DNA technology from the CHO cell line. ADVATE 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 factor VIII from the medium. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. The ADVATE molecule is then covalently conjugated with the polyethylene glycol, which mainly targets lysine residues.

The cell culture, pegylation, purification process and formulation used in the manufacture of ADYNOVATE do not use additives of human or animal origins.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADYNOVATE, a PEGylated form of recombinant antihemophilic factor (ADVATE), *[see Description (11)]*, temporarily replaces the missing coagulation factor VIII needed for effective hemostasis in congenital hemophilia A patients. ADYNOVATE exhibits an extended terminal half-life through pegylation of the parent molecule, ADVATE, which reduces binding to the physiological factor VIII clearance receptor (LRP1).

12.2 Pharmacodynamics

Hemophilia A is a disorder characterized by a deficiency of functional coagulation factor VIII, resulting in a prolonged, patient plasma clotting time as measured by the activated partial thromboplastin time (aPTT). Treatment with ADYNOVATE normalizes the aPTT over the effective dosing period. The administration of ADYNOVATE increases plasma levels of factor VIII and can temporarily correct the coagulation defect in hemophilia A patients.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ADYNOVATE were evaluated in a multi-center, prospective, open label clinical trial and compared with ADVATE in 26 subjects prior to initiation of prophylactic treatment with ADYNOVATE and in 22 subjects after 6 months of treatment with ADYNOVATE. A single dose of 45 IU/kg was utilized for both products. The PK parameters, as shown in Table 4, were based on plasma coagulation factor VIII activity measured by the one-stage clotting assay and are presented by age groups.

Incremental recovery was comparable between both products. The PK parameters determined after 6 months of prophylactic treatment with ADYNOVATE were consistent with the initial parameter estimates.

Pediatric Pharmacokinetics

Pharmacokinetic parameters calculated from 39 subjects <18 years of age (intent-to-treat analysis) are available for 14 children (2 to <6 years), 17 older children (6 to <12 years) and 8 adolescent subjects (12 to <18 years of age), as shown in Table 4. The mean clearance (based on body weight) of ADYNOVATE was higher and the mean half-life was lower in children <12 years of age than adults. A dose adjustment may be required in children <12 years of age.

Table 4: Pharmacokinetic Parameters (Arithmetic Mean ± SD)

PK Parameters	Pediatric Population PK with Sparse Sampling[a]		Adult and Adolescent Individual PK with Full Sampling[b]	
	<6 years N=14	6 to <12 years N=17	12 to <18 years N = 8	≥18 years N = 18
Terminal half-life [h]	11.8 ± 2.43	12.4 ± 1.67	13.43 ± 4.05	14.69 ± 3.79
MRT [h]	17.0 ± 3.50	17.8 ± 2.42	17.96 ± 5.49	20.27 ± 5.23
CL [mL/(kg·h)]	3.53 ± 1.29	3.11 ± 0.76	3.87 ± 3.31 (2.73 ± 0.93)[d]	2.27 ± 0.84
Incremental Recovery [(IU/dL)/(IU/kg)]	1.89 ± 0.49	1.95 ± 0.47	2.12 ± 0.60	2.66 ± 0.68
$AUC_{0\text{-}Inf}$ [IU·h/dL]	1947 ± 757	2012 ± 495	1642 ± 752	2264 ± 729
Vss [dL/kg]	0.56 ± 0.12	0.54 ± 0.09	0.56 ± 0.18	0.43 ± 0.11
C_{max} [IU/dL]	115 ± 30	115 ± 33	95 ± 25	122 ± 29
T_{max} [h]	[c]	[c]	0.26 ± 0.10	0.46 ± 0.29

Abbreviations: MRT: mean residence time; CL: clearance; CI: confidence interval; AUC: area under the curve; V_{ss}: body weight adjusted volume of distribution at steady-state; C_{max}: maximum observed activity; T_{max}: time to reach the maximum concentration.

[a] Population PK model with 3 post-infusion samples based on randomized drawing schedule.

[b] Individual PK with 12 post-infusion samples.

[c] Tmax could not be calculated for subjects in the pediatric study as only one sample was drawn (15-30 minutes post-infusion) within the first 3 hours of the infusion.

[d] Estimated mean and SD calculated not including one subject whose clearance estimate was 11.8 mL/(kg.h). Median including all subjects is 2.78 mL/(kg.h).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of ADYNOVATE or studies to determine the effects of ADYNOVATE on genotoxicity or fertility have not been performed.

14 CLINICAL STUDIES

Original Safety and Efficacy Clinical Trial

The safety, efficacy, and PK of ADYNOVATE were evaluated in a multicenter, open-label, prospective, non-randomized, two-arm clinical trial that compared the efficacy of a twice weekly prophylactic treatment regimen to on-demand treatment and determined hemostatic efficacy in the treatment of bleeding episodes. A total of 137 male PTPs (12 to 65 years of age) with severe hemophilia A received at least one infusion with ADYNOVATE. Twenty-five of the 137 subjects were adolescents (12 to less than 18 years of age).

Subjects received either prophylactic treatment (n = 120) with ADYNOVATE at a dose of 40-50 IU per kg twice weekly or on-demand treatment (n = 17) with ADYNOVATE at a dose of 10-60 IU per kg for a 6-month period. The mean (SD) dose per prophylaxis infusion was 44.4 (3.9) IU per kg with a median dosing interval of 3.6 days. There were 91 out of 98 (93%) subjects previously treated prophylactically prior to enrollment, who experienced a reduction in dosing frequency during routine prophylaxis in the trial, with a median reduction of 33.7% (approximately one more day between doses). One hundred eighteen of 120 (98%) prophylaxis subjects remained on the starting recommended regimen without dose adjustment, and 2 subjects increased their dose to 60 IU/kg during prophylaxis due to bleeding in target joints.

On-demand Treatment and Control of Bleeding Episodes

A total of 518 bleeding episodes were treated with ADYNOVATE in the per-protocol population, i.e. dosed according to the protocol specific dosing requirements. Of these, 361 bleeding episodes (n=17 subjects) occurred in the on-demand arm and 157 (n=61 subjects) occurred in the prophylaxis arm. The median dose per infusion to treat all bleeding episodes in the per-protocol population was 29 (Q1: 20.0; Q3: 39.2) IU per kg. The median dose per infusion to treat a minor, moderate, or severe/major bleeding episode in the per-protocol population was 25.5 (Q1: 16.9; Q3: 37.6) IU/kg, 30.9
(Q1: 23.0; Q3: 43.1) IU/kg, or 36.4 (Q1: 29.0; Q3: 44.5) IU/kg, respectively.

A total of 591 bleeding episodes were treated with ADYNOVATE in the treated population, which was identical to the safety analysis set of subjects assigned to routine prophylaxis or on-demand treatment with ADYNOVATE and who received at least one dose of the product. Of these, 361 bleeding episodes (n=17 subjects) occurred in the on-demand arm and 230 bleeding episodes (n=75 subjects) occurred in the routine prophylaxis arm. Efficacy in control of bleeding episodes is summarized in Table 5.

Table 5: Summary of Efficacy in Control of Bleeding (Treated Population)

Bleeding Episode Etiology		**All**	**Joint**	**Non-joint**
Number of bleeds treated		591	455	136
Number of infusions to treat bleeding episodes	1 infusions:	85.4%	85.9%	83.8%
	2 infusions:	10.8%	10.8%	11.0%
	Total (1 or 2 infusions):	96.2%	96.7%	94.8%
Rate of success to treat bleeding episodes*	Excellent or good	95.3%	95.8%	93.4%

* Excellent defined as full relief of pain and objective signs of bleeding cessation; Good defined as definite pain relief and/or improvement in signs of bleeding; Fair defined as probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution; None defined as no improvement or condition worsened.

Routine Prophylaxis

A total of 120 subjects (treated population) received a twice a week regimen in the prophylaxis arm, and an additional 17 subjects were treated episodically in the on-demand arm. In the treated population, the median [mean] annualized bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [4.7] while on a twice a week prophylaxis regimen (Table 6). In the per-protocol population, the median [mean] annualized bleed rate (ABR) in the on-demand treatment arm was 41.5 [40.8] compared to 1.9 [3.7] while on a twice a week prophylaxis regimen. Using a negative binomial model to estimate the ABR, there was a significant reduction in the ABR ($p < 0.0001$) for subjects in the prophylaxis arm compared to the on-demand arm.

Table 6: Annualized Bleed Rate by Treatment for ≥ 12 years of age (Treated Population)

Bleeding Episode Etiology	**On-Demand Treatment**		**Routine Prophylaxis Treatment**	
	Median	Mean (SD)	Median	Mean (SD)
Overall	41.5	40.8 (16.3)	1.9	4.7 (8.6)
Joint	38.1	34.7 (15.1)	0.0	2.9 (8.0)
Non-Joint	3.7	6.1 (6.7)	0.0	1.8 (3.0)
Spontaneous	21.6	26.0 (19.6)	0.0	2.9 (7.1)
Traumatic	9.3	14.9 (15.3)	0.0	1.8 (3.1)

In the treated population, the median [mean] ABR for the 23 adolescent subjects age 12 to <18 years of age on routine prophylaxis was 2.1 [5.2] compared to a median [mean] ABR of 1.9 [4.6] for the 97 subjects 18 years and older. Reduction in ABR between the treatment arms was observed regardless of baseline subgroups examined, including age, presence or absence of target joints, and pre-trial treatment regimen. The majority of the bleeding episodes during prophylaxis (95%) were of minor/moderate severity. Forty-five out of 120 subjects (38%) experienced no bleeding episodes and 68 out of 120 subjects (57%) experienced no joint bleeding episodes in the prophylaxis arm. Of those subjects who were compliant to regimen (per-protocol population), 40 out of 101 subjects (40%) experienced no bleeding episodes. All subjects in the on-demand arm experienced a bleeding episode, including a joint bleeding episode.

Routine Prophylaxis Clinical Trial in Pediatric Subjects (<12 years of age)

The safety and efficacy of ADYNOVATE was evaluated in a total of 73 pediatric PTPs with severe hemophilia A, of which 66 subjects were dosed (32 subjects aged <6 years and 34 subjects aged 6 to <12 years) in a separate pediatric clinical trial. The prophylactic regimen was 40 to 60 IU/kg of ADYNOVATE twice a week, with a mean (SD) dose of 51.1 IU/kg (5.5). The median [mean] overall ABR was 2.0 [3.61] for the 66 subjects in the treated population and the median [mean] ABRs for spontaneous and joint bleeding episodes were both 0 [1.18 and 1.12, respectively]. Of the 66 subjects treated prophylactically, 25 (38%) experienced no bleeding episodes, 44 (67%) experienced no spontaneous bleeding episodes, and 48 (73%) experienced no joint bleeding episodes.

Of the 70 bleeding episodes observed during the pediatric trial, 82.9% were controlled with 1 infusion and 91.4% were controlled with 1 or 2 infusions. Control of bleeding was rated excellent or good in 63 out of 70 (90%) bleeding episodes. The definitions of excellent or good in the pediatric clinical trial were unchanged as compared to the previously conducted prophylaxis clinical trial in adolescent and adult subjects.
An extension study in adult and pediatric patients evaluated the safety and efficacy of prophylactic treatment regimen in 216 previously treated patients with severe hemophilia A. Majority had completed the adult and adolescent study or the pediatric study. Similar efficacy was noted in this extension study.

Perioperative Management Clinical Trial

Twenty-one major surgical procedures comprised of 14 orthopedic, and 7 non-orthopedic procedures, and 5 additional minor surgeries were performed in 21 subjects. The preoperative loading dose ranged from 36 IU/kg to 99 IU/kg (median: 60 IU/kg) and the total postoperative dose ranged from 23 IU/kg to 769 IU/kg (median: 183 IU/kg). The median total dose (including all administrations from pre-surgical PK and loading doses to post-hospital follow up) was 629 IU/kg (range: 464 – 1,457 IU/kg) for major orthopedic surgeries, 489 IU/kg (range: 296 – 738 IU/kg) for major non-orthopedic surgeries.

Overall hemostatic efficacy was rated as excellent (blood loss less than or equal to that expected for the same type of procedure performed in a non-hemophilic patient, for all 24 (21 major, 3 minor) procedures with available assessments.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ADYNOVATE in a BAXJECT III system is packaged with 2 mL or 5 mL of Sterile Water for Injection, one Terumo Microbore Infusion set (2 mL only), one full prescribing physician insert and one patient insert. Components not made with natural rubber latex.

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

Nominal Strength	Potency Color Code	Carton NDC (Includes 2 mL sWFI Diluent)	Carton NDC (Includes 5 mL sWFI Diluent)
250 IU	Light Blue	0944-4622-01	
500 IU	Pink	0944-4623-01	
750 IU	Red	0944-4626-01	
1000 IU	Light Green	0944-4624-01	
1500 IU	Purple	0944-4627-01	
2000 IU	Orange		0944-4625-01
3000 IU	Silver		0944-4628-01

Actual factor VIII activity in IU is stated on the label of each ADYNOVATE carton and housing.

Storage and Handling

- Store ADYNOVATE in powder form at 2°C to 8°C (36°F to 46°F).
- Do not freeze.
- ADYNOVATE may be stored at room temperature not to exceed 30°C (86°F) for a period of up to 3 months not to exceed the expiration date. If stored at room temperature, write the date on the carton when ADYNOVATE is removed from refrigeration.
- After storage at room temperature, do not return the product to the refrigerator.
- Do not use beyond expiration date printed on the carton or housing.
- Store ADYNOVATE in the original box and protect from extreme exposure to light.

17 PATIENT COUNSELING INFORMATION

Advise the patients to:

- Read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to factor VIII therapy because this may be a sign of inhibitor development.
- Consult with their physicians or healthcare provider prior to travel. While traveling, advise patients to bring an adequate supply of ADYNOVATE 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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FDA-Approved Patient Labeling
Patient Information

ADYNOVATE
[Antihemophilic Factor (Recombinant), PEGylated]

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

What is the most important information I need to know about ADYNOVATE?
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 ADYNOVATE so that your treatment will work best for you.

What is ADYNOVATE?
ADYNOVATE is an injectable medicine that is used to help treat and control bleeding in children and adults with hemophilia A (congenital Factor VIII deficiency). Your healthcare provider may give you ADYNOVATE when you have surgery. ADYNOVATE can reduce the number of bleeding episodes when used regularly (prophylaxis).

ADYNOVATE is not used to treat von Willebrand disease.

Who should not use ADYNOVATE?
You should not use ADYNOVATE if you:

- Are allergic to mice or hamster protein
- Are allergic to any ingredients in ADYNOVATE or ADVATE

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

How should I use ADYNOVATE?
ADYNOVATE is given directly into the bloodstream.

You may infuse ADYNOVATE 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 ADYNOVATE by themselves or with the help of a family member.

Your healthcare provider will tell you how much ADYNOVATE to use based on your individual weight, level of physical activity, the severity of your hemophilia A, and where you are bleeding.

Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated. Discard any ADYNOVATE left in the vial at the end of your infusion as directed by your healthcare professional.

You may have to have blood tests done after getting ADYNOVATE 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 ADYNOVATE.

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

What are the possible side effects of ADYNOVATE?
You can have an allergic reaction to ADYNOVATE.

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.

The common side effects of ADYNOVATE are headache, diarrhea, rash, nausea dizziness and hives. 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 ADYNOVATE. You can ask your healthcare provider for information that is written for healthcare professionals.

What are the ADYNOVATE dosage strengths?

ADYNOVATE with 2 mL or 5 mL Sterile Water for Injection in a BAXJECT III system comes in seven different dosage strengths: 250 International Units (IU), 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU. The actual strength will be imprinted on the label and on the box. The seven different strengths are color coded, as follows:

Light Blue	Dosage strength of approximately 250 International Units per vial (with 2 mL sWFI)
Pink	Dosage strength of approximately 500 International Units per vial (with 2 mL sWFI)
Red	Dosage strength of approximately 750 International Units per vial (with 2 mL sWFI)
Light Green	Dosage strength of approximately 1000 International Units per vial (with 2 mL sWFI)
Purple	Dosage strength of approximately 1500 International Units per vial (with 2 mL sWFI)
Orange	Dosage strength of approximately 2000 International Units per vial (with 5 mL sterile Water For Injection)
Silver	Dosage strength of approximately 3000 International Units per vial (with 5 mL sterile Water For Injection)

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 ADYNOVATE?

- Do not freeze.
- Store at refrigerated temperature 2°C to 8°C (36°F to 46°F).
- May store at room temperature not to exceed 30°C (86°F) for up to 3 months.
  - Write the date on the carton when ADYNOVATE is removed from refrigeration.
  - After storage at room temperature, do not return product back to the refrigerator.
- Do not use beyond the expiration date printed on the carton or vial.
- Store ADYNOVATE in the original box and protect from extreme exposure to light.

What else should I know about ADYNOVATE 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 ADYNOVATE 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 ADYNOVATE for a condition for which it is not prescribed. Do not share ADYNOVATE with other people, even if they have the same symptoms that you have.

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Revised: 3/2023

FDA-Approved Patient Labeling
Instructions for Use

ADYNOVATE
[Antihemophilic Factor (Recombinant), PEGylated]
(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.

Step-by-step instructions for reconstituting ADYNOVATE are found 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 ADYNOVATE. 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 ADYNOVATE.

Your healthcare provider will prescribe the dose that you should take.

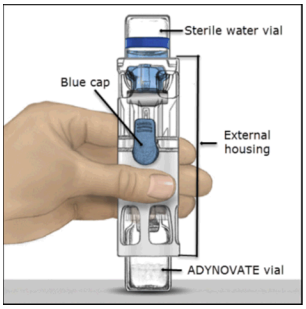
Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated.

Your healthcare provider may need to take blood tests from time to time.

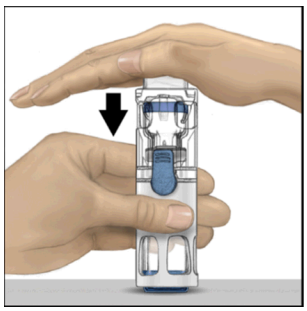
Talk to your healthcare provider before traveling. Plan to bring enough ADYNOVATE for your treatment during this time.

Dispose of all materials, including any leftover reconstituted ADYNOVATE product, in an appropriate container.

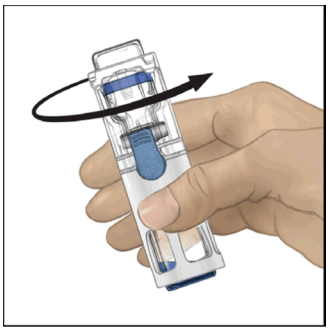
1. Prepare a clean flat surface and gather all the materials you will need for the infusion.
   - Check the expiration date, and let the ADYNOVATE warm up to room temperature.
   - Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.
2. Open the ADYNOVATE package by peeling away the lid. Remove the ADYNOVATE from the package and visually inspect the contents of the product and diluent vial. The ADYNOVATE 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.



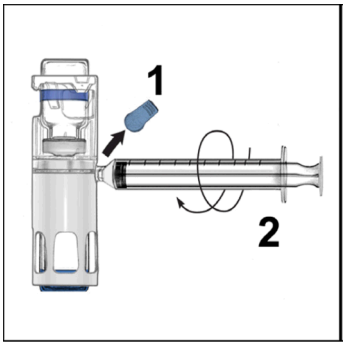
4. With one hand holding the ADYNOVATE housing, press down firmly on the diluent vial with the other hand until the system is fully collapsed and the diluent flows down into the ADYNOVATE vial. Both vials will move into the housing when pressed. If you don't see the diluent transfer to the product vial,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



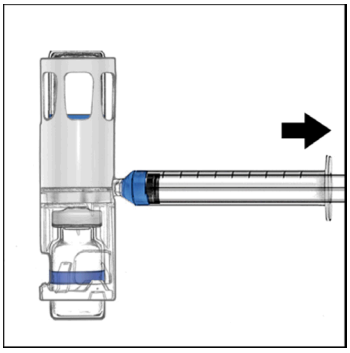
5. Swirl the ADYNOVATE gently and continuously until the ADYNOVATE is completely dissolved. Do not shake. Do not refrigerate after reconstitution. Inspect the ADYNOVATE solution for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance.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



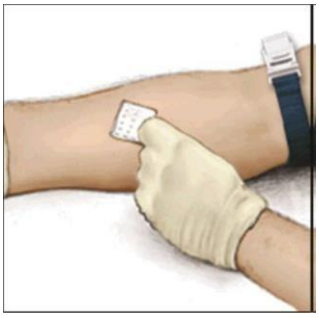
6. Take off the blue cap from the housing and connect the syringe. Be careful to not inject air into the ADYNOVATE.



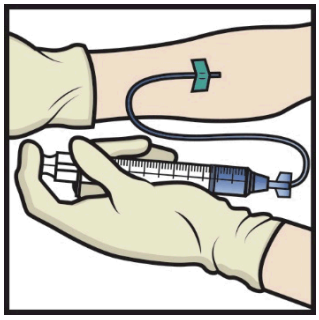
7. Turn over the ADYNOVATE so that the vial containing the ADYNOVATE solution is on top. Draw the ADYNOVATE solution into the syringe by pulling back the plunger slowly. If the solution does not draw into the syringe, be sure that both vials are pressed firmly together. The contents of more than one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



8. Disconnect the syringe from the system. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
9. Apply a tourniquet and get the injection site ready by wiping the skin well with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center).



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



11. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.
12. Remove the peel-off label from blister lid 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. Do not recap the needle. Place needle, syringe and ADYNOVATE system in a hard-walled Sharps container for proper disposal. 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.

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HEMOFIL M
Antihemophilic Factor (Human), Method M, Monoclonal Purified
Nanofiltered

DESCRIPTION
HEMOFIL M, Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, is a sterile, nonpyrogenic, dried preparation of antihemophilic factor (Factor VIII, Factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 22 AHF International Units/mg of total protein. HEMOFIL M contains a maximum of 12.5 mg/mL Albumin, and per AHF International Unit, 0.07 mg polyethylene glycol (3350), 0.39 mg histidine as stabilizing agents, not more than 0.1 mg glycine, 0.1 ng mouse protein, 18 ng organic solvent (tri-n-butyl phosphate) and 50 ng detergent (octoxynol 9). In the absence of the added Albumin (Human), the specific activity is approximately 2,000 AHF International Units/mg of protein *[see Clinical Pharmacology]*.

HEMOFIL M is prepared by the Method M process from pooled human plasma by immunoaffinity chromatography utilizing a murine monoclonal antibody to Factor VIII:C, followed by an ion exchange chromatography step for further purification. Source material may be provided by other US licensed manufacturers. HEMOFIL M also includes an organic solvent (tri-n-butyl phosphate) and detergent (octoxynol 9) virus inactivation step designed to reduce the risk of transmission of hepatitis and other viral diseases. The process further includes a nanofiltration step between immunoaffinity chromatography and ion-exchange chromatography as an additional viral clearance step to further improve the viral safety margin of the final product.

Use of an organic solvent (tri-n-butyl phosphate; TNBP) in the manufacture of Antihemophilic Factor (Human) has little or no effect on AHF activity, while lipid enveloped viruses, such as hepatitis B and human immunodeficiency virus (HIV) would be inactivated.[1] The nanofiltration step integrated into the manufacture of AHF-M further enhances the safety margin with respect to adventitious viruses.
Each bottle of HEMOFIL M is labeled with the AHF activity expressed in International Units (IU) per bottle. This potency assignment is referenced to the World Health Organization International Standard. The purity of HEMOFIL M has been thought to influence the difficulty of producing an accurate potency measurement. Experiments have shown that to achieve accurate activity levels, such a potency assay should be conducted using plastic test tubes and pipets as well as substrate containing normal levels of von Willebrand's Factor.

In vitro studies demonstrate that the HEMOFIL M manufacturing process provides for viral reduction. These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during solvent/detergent treatment, and immunoaffinity chromatography. Introduction of a nanofiltration step with the 0.1µm prefilter and the ASAHI Planova 20N nanofilter provides a virus removal capacity for human immunodeficiency virus, Type 1 (HIV-1), hepatitis A virus (HAV), bovine viral diarrhea virus (BVDV), pseudorabies virus (PRV), mice minute virus (MMV), and human parvovirus B19 (B19V) in the order of four (4) logs or higher. B19V removal data were obtained with a Polymerase Chain Reaction (PCR) assay not correlated to an infectivity assay.

Studies for nanofiltration and other process steps, summarized in Table 1, demonstrate virus clearance during the HEMOFIL M manufacturing process using HIV-1; BVDV, a generic model for lipid enveloped RNA viruses, such as hepatitis C virus (HCV); PRV, a model for lipid enveloped DNA

viruses, such as hepatitis B virus (HBV); canine parvovirus (CPV), a model for non-lipid enveloped DNA viruses, such as B19V, HAV, and MMV.

Table 1
***In Vitro* Virus Clearance During the Manufacture of HEMOFIL M**

Process Step Evaluated	Virus Clearance, log $_{10}$					
	Lipid-enveloped			Non-Lipid enveloped		
	HIV-1	BVDV	PRV	HAV	CPV	MMV
Solvent/Detergent Treatment	>4.8	>6.8	>6.9	NT*	NT*	NT*
Immunoaffinity Chromatography	N.A.**	N.A.**	N.A.**	≥4.5	≥3.9	NT
Nanofiltration	>5.5	>4.6	>4.4	>5.4	NT	>5.0
Cumulative Total, $\log_{10}$	**>10.3**	**>11.4**	**>11.3**	**>9.9**	**≥3.9**	**>5.0**

NT not tested
* As Solvent/Detergent treatment does not inactivate non-lipid enveloped viruses.
** Not Applicable for lipid enveloped viruses due to the presence of (virucidal) solvent/detergent reagents in the starting material.

CLINICAL PHARMACOLOGY

Antihemophilic factor (AHF) is a protein found in normal plasma which is necessary for clot formation. The administration of HEMOFIL M provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with hemophilia A (classical hemophilia). The half-life of HEMOFIL M administered to Factor VIII deficient patients has been shown to be 14.8 ± 3.0 hours.

INDICATIONS AND USAGE

HEMOFIL M is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.

HEMOFIL M is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

HEMOFIL M is contraindicated in patients with a known hypersensitivity to the active substance, to excipients, or to mouse proteins.

WARNINGS

Hypersensitivity

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with HEMOFIL M and have been manifested by bronchospasm, dyspnea, hypotension, chest pain, facial edema, urticaria, rash, flushing, pruritus, and nausea.

Neutralizing Antibodies

The development of neutralizing antibodies (inhibitors) to Factor VIII is a known complication of the treatment of patients with Hemophilia A. Inhibitors have predominantly been reported in previously untreated patients. The risk of developing inhibitors is correlated to the extent of exposure to Factor VIII, the risk being highest within the first 20 exposure days, and to other genetic and environmental factors. The risk for inhibitor development depends on a number of factors relating to the characteristics of the patient (e.g., type of the Factor VIII gene mutation, family history, ethnicity), which are believed to represent the most significant risk factors for inhibitor formation.

Transmission of Infectious Agents
Because HEMOFIL M is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. The physician should discuss the risks and benefits of this product with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly non-A, non-B hepatitis. As indicated under *Clinical Pharmacology*, however, a group of such patients treated with HEMOFIL M did not demonstrate signs or symptoms of non-A, non-B hepatitis over observation periods ranging from three to nine months.

PRECAUTIONS
Identification of the clotting defect as a Factor VIII deficiency is essential before the administration of HEMOFIL M is initiated.

Factor VIII Inhibitors
Evaluate patients for the development of Factor VIII inhibitors if the expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled with an appropriate dose.

No benefit may be expected from this product in treating other deficiencies.

Formation of Antibodies to Mouse Protein
HEMOFIL M contains trace amounts of mouse protein (less than 0.1 ng/AHF activity units). The possibility exists that patients treated with HEMOFIL M may develop hypersensitivity to the mouse proteins. There have been no cases of hypersensitivity to the mouse proteins reported.

Increase in Pulse Rate
Determine the pulse rate before and during administration of HEMOFIL M. Should a significant increase occur, reduce the rate of administration or temporarily halt the injection to allow the symptoms to disappear promptly.

Laboratory Tests
Perform appropriate laboratory tests on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained.

If the AHF content of the patient's plasma fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralized by each mL of plasma or by the total estimated plasma volume.

If the inhibitor is at low levels (i.e., <10 Bethesda units per mL), after administration of sufficient AHF units to neutralize the inhibitor, additional AHF units will elicit the predicted response.

Pregnancy
Animal reproduction studies have not been conducted with HEMOFIL M. The safety of HEMOFIL M for use in pregnant women has not been established. It is not known whether HEMOFIL M can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HEMOFIL M should be given to a pregnant woman only if clearly needed.

Nursing Mothers
The safety of HEMOFIL M for use in nursing mothers has not been established. It is not known whether this drug is excreted into human milk. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing HEMOFIL M. HEMOFIL M should be given to nursing mothers only if clinically indicated.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials
The adverse reactions presented in this section have been identified based on clinical trial experience with HEMOFIL M in patients previously treated with other Factor VIII concentrates or blood products (N = 74), and previously untreated patients (PUPs; N = 50).

Clinical Trial Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Number of Cases (Frequency Percentage)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Factor VIII inhibition	3 (5.7%)[a]
NERVOUS SYSTEM DISORDERS	Dizziness	1 (0.8%)
	Headache	1 (0.8%)
	Dysgeusia	1 (0.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia	1 (0.8%)
	Infusion site inflammation	2 (1.6%)

[a] In a study that included 43 evaluable PUPs and 10 minimally treated patients (MTPs), i.e., patients with a single exposure to other Factor VIII concentrates or blood products, 3 of the total of 53 patients (5.7%) developed an inhibitor while on study.

HEMOFIL M was administered to 11 patients previously untreated with Antihemophilic Factor (Human). They have shown no signs of hepatitis or HIV infection following three to nine months of evaluation.

A study of 25 patients treated with HEMOFIL M and monitored for three to six months has demonstrated no evidence of antibody response to mouse protein. More than 1,000 infusions of HEMOFIL M have been administered during the clinical trials. Reported events included a single episode each of chest tightness, fuzziness and dizziness, and one patient reported an unusual taste after each infusion.

Post-marketing Adverse Reactions

In addition to clinical trials, the following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term.

Immune System Disorders: anaphylactic reaction, hypersensitivity

Eye Disorders: visual impairment, ocular hyperemia
Cardiac Disorders: cyanosis, bradycardia, tachycardia
Vascular Disorders: hypotension, flushing
Respiratory, Thoracic, and Mediastinal Disorders: bronchospasm, dyspnea, cough, hyperventilation
Gastrointestinal Disorders: diarrhea, vomiting, nausea, abdominal pain
Skin and Subcutaneous Tissue Disorders: urticaria, rash, pruritus, hyperhidrosis
Musculoskeletal and Connective Tissue Disorders: musculoskeletal pain
General Disorders and Administration Site Conditions: facial edema, edema, chills, fatigue, chest pain, irritability

DOSAGE AND ADMINISTRATION

For intravenous use only.

The expected *in vivo* peak AHF level, expressed as IU/dL of plasma or % (percent) of normal, can be calculated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical finding by Abildgaard, *et al*,[2] which is supported by data from the collaborative study of *in vivo* recovery and survival with 15 different lots of HEMOFIL M on 56 hemophiliacs that demonstrated a mean peak recovery point above the mean pre-infusion baseline of about 2.0 IU/dL per infused IU/kg body weight.[3]

Examples:
(1) A dose of 1750 IU AHF administered to a 70 kg patient, i.e., 25 IU/kg (1750/70), should be expected to cause a peak post-infusion AHF increase of 25 x 2 = 50 IU/dL (50% of normal).
(2) A peak level of 70% is required in a 40 kg child. In this situation the dose would be 70/2 x 40 = 1400 IU.

Recommended Dosage Schedule

Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

HEMORRHAGE		
Degree of hemorrhage	**Required peak post-infusion AHF activity in the blood (as % of normal or IU/dL plasma)**	**Frequency of infusion**
Early hemarthrosis or muscle bleed or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for usually three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.
SURGERY		
Type of operation		
Minor surgery, including tooth	60-80	A single infusion plus oral

extraction		antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

If bleeding is not controlled with the prescribed dose, determine the plasma level of Factor VIII and administer a sufficient dose of HEMOFIL M to achieve a satisfactory clinical response.

Under certain circumstances (e.g., presence of a low titer inhibitor) doses larger than those recommended may be necessary as per standard care. In patients with high titer Factor VIII inhibitors, HEMOFIL M therapy may not be effective and other therapeutic options should be considered.
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 hemorrhages.

Reconstitution: Use Aseptic Technique

1. Bring HEMOFIL M (dry concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from concentrate and diluent bottles to expose central portion of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective covering from one end of double-ended needle and insert exposed needle through diluent stopper.
5. Remove protective covering from other end of double-ended needle. Invert diluent bottle over upright HEMOFIL M bottle, then rapidly insert free end of the needle through the HEMOFIL M bottle stopper at its center. The vacuum in the HEMOFIL M bottle will draw in the diluent.
6. Disconnect the two bottles by removing needle from diluent bottle stopper, then remove needle from HEMOFIL M bottle. Swirl gently until all material is dissolved. Be sure that HEMOFIL M is completely dissolved; otherwise active material will be removed by the filter.

Note: Do not refrigerate after reconstitution.

Administration: Use Aseptic Technique

- Intravenous administration only.
- Administer at room temperature not more than 3 hours after reconstitution.
- Record the name and batch number of the product in order to maintain a link between the patient and the batch of the product.

Intravenous Syringe Injection

- Visually inspect parenteral product for particulate matter and discoloration prior to administration. The solution should be colorless in appearance. Do not administer if particulate matter or discoloration is found.
- Plastic syringes are recommended for use with this product. The ground glass surface of all-glass syringes tend to stick with solutions of this type.

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into syringe.
2. Insert needle into reconstituted HEMOFIL M.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.

4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under *Rate of Administration*.
5. If a patient is to receive more than one bottle of HEMOFIL M, the contents of two bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. This practice lessens the loss of HEMOFIL M. Filter needles are intended to filter the contents of a single bottle of HEMOFIL M only.

Rate of Administration
Administer HEMOFIL M at a rate of up to 10 mL per minute. Infuse HEMOFIL M at a rate of administration that ensures the comfort of the patient *[see Precautions: Increase of Pulse Rate]*.

HOW SUPPLIED

HEMOFIL M is available as single-dose bottles that contain the following nominal potencies:

Nominal Potency	Kit NDC Number
250 IU	0944-3940-02
500 IU	0944-3942-02
1000 IU	0944-3944-02
1700 IU	0944-3946-02

Each bottle is labeled with the potency in International Units, and is packaged together with 10 mL of Sterile Water for Injection, USP, a double-ended needle, and a filter needle.

Not made with natural rubber latex.

Storage

HEMOFIL M can be stored at 2°C to 8°C (36°F to 46°F) or at room temperature, not to exceed 30°C (86°F), until expiration date noted on the package.

Do not freeze.

Information for Patients
- Advise patients to report any adverse reactions or problems following HEMOFIL M administration to their physician or healthcare provider.
- Advise pregnant women or immune compromised individuals of the effects of Parvovirus B19. Symptoms include fever, drowsiness, chills, runny nose followed about two weeks later by a rash, and joint pain.
- Inform patients of the signs and symptoms of hepatitis A, which include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and pain in the belly. Dark urine and a yellowed complexion are also common symptoms. Encourage patients to consult their physician if such symptoms appear.
- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, facial edema, flushing, nausea, tightness of the chest, wheezing, dyspnea, hypotension, and anaphylaxis. Advise patients to discontinue use of the product and contact their physician if these symptoms occur.

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3. Addiego, Jr. JE, Gomperts E, Liu S. *et al*: Treatment of hemophilia A with a highly purified Factor VIII concentrate prepared by Anti-FVIIIc immunoaffinity chromatography. **Thrombosis and Haemostasis 67**:19-27, 1992.

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FPI-0283

RECOMBINATE

[Antihemophilic Factor (Recombinant)]

Lyophilized Powder for Reconstitution for injection

Reconstitute with 5 mL of Sterile Water for Injection using BAXJECT II

DESCRIPTION

RECOMBINATE [Antihemophilic Factor (Recombinant)] is a glycoprotein synthesized by a genetically engineered Chinese Hamster Ovary (CHO) cell line. In culture, the CHO cell line secretes recombinant Factor VIII (rFVIII) into the cell culture medium. The rFVIII is purified from the culture medium utilizing a series of chromatography columns. A key step in the purification process is an immunoaffinity chromatography methodology in which a purification matrix, prepared by immobilization of a monoclonal antibody directed to Factor VIII, is utilized to selectively isolate the rFVIII in the medium. The synthesized rFVIII produced by the CHO cells has the same biological effects as human Factor VIII. Structurally the protein has a similar combination of heterogenous heavy and light chains as found in human Factor VIII.

RECOMBINATE is formulated as a sterile, nonpyrogenic, off-white to faint yellow, lyophilized powder preparation of concentrated recombinant Factor VIII for intravenous injection. RECOMBINATE is available in single-dose vials, which contain nominally 250, 500, 1000, 1500, and 2000 International Units per vial. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: For 5 mL reconstitution volume: 25 mg/mL Albumin (Human), 0.40 mg/mL calcium, 3 mg/mL polyethylene glycol (3350), 360 mEq/L sodium, 110 mM histidine, 1.5 µg/Factor VIII International Unit (IU) polysorbate-80. Recombinant Von Willebrand Factor (rVWF) is coexpressed with the rFVIII and helps to stabilize it. The final product contains not more than 2 ng rVWF/IU rFVIII, which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative.

Each vial of RECOMBINATE is labeled with the Factor VIII activity expressed in IU per vial. Biological potency is determined by an *in vitro* assay which is referenced to the World Health Organization (WHO) International Standard for Factor VIII:C Concentrate.

CLINICAL PHARMACOLOGY

Factor VIII is the specific clotting factor deficient in patients with hemophilia A (classical hemophilia). Hemophilia A is a genetic bleeding disorder characterized by hemorrhages, which may occur spontaneously or after minor trauma. The administration of RECOMBINATE provides an increase in plasma levels of Factor VIII and can temporarily correct the coagulation defect in these patients.

Pharmacokinetic studies on sixty-nine (69) patients revealed the circulating mean half-life for RECOMBINATE to be 14.6 ± 4.9 hours (n=67), which was not statistically significantly different from plasma-derived HEMOFIL M, [Antihemophilic Factor (Human), Method M, Monoclonal Purified]. The mean half-life of HEMOFIL M was 14.7 ± 5.1 hours (n=61). The actual baseline recovery observed with RECOMBINATE was 123.9 ± 47.7 IU/dL (n=23), which is significantly higher than the actual HEMOFIL M baseline recovery of 101.7 ± 31.6 IU/dL (n=61). However, the calculated ratio of actual to expected recovery with RECOMBINATE (121.2 ± 48.9%) is not different on average from HEMOFIL M (123.4 ± 16.4%).

The clinical study of RECOMBINATE in previously treated patients (individuals with hemophilia A who had been treated with plasma derived Factor VIII) was based on observations made on a study group of 69 patients. These individuals received cumulative amounts of Factor VIII ranging from 20,914 to 1,383,063 IU over the 48 month study. Patients were given a total of 17,700 infusions totaling 28,090,769 IU RECOMBINATE.

These patients were successfully treated for bleeding episodes on a demand basis and also for the prevention of bleeds (prophylaxis). Spontaneous bleeding episodes successfully managed include hemarthroses, soft tissue and muscle bleeds. Management of hemostasis was also evaluated in surgeries. A total of 24 procedures on 13 patients were performed during this study. These included minor (e.g. tooth extraction) and major (e.g. bilateral osteotomies, thoracotomy and liver transplant) procedures. Hemostasis was maintained perioperatively and postoperatively with individualized Factor VIII replacement.

A study of RECOMBINATE in previously untreated patients was also performed as part of an ongoing study. The study group was comprised of seventy-nine (79)[1] patients, of whom seventy-six (76) had received at least one infusion of RECOMBINATE. To date, this cohort has been given 12,209 infusions totaling over 11,277,043 IU of RECOMBINATE. Hemostasis was appropriately managed in spontaneous bleeding episodes, intracranial hemorrhage and surgical procedures.

INDICATIONS AND USAGE

The use of RECOMBINATE [Antihemophilic Factor (Recombinant)] is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.[2] RECOMBINATE is also indicated in the perioperative management of patients with hemophilia A (classical hemophilia).

RECOMBINATE can be of therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per mL.[3] In clinical studies with RECOMBINATE, patients with inhibitors who were entered into the previously treated patient trial and those previously untreated children who have developed inhibitor activity on study, showed clinical hemostatic response when the titer of

inhibitor was less than 10 Bethesda Units per mL. However, in such uses, the dosage of RECOMBINATE should be controlled by frequent laboratory determinations of circulating Factor VIII levels as well as the clinical status of the patient.

RECOMBINATE is not indicated in von Willebrand's disease.

CONTRAINDICATIONS

RECOMBINATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including bovine, mouse or hamster proteins.

WARNINGS

General

The clinical response to RECOMBINATE may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of RECOMBINATE should be administered 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, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed. (see ***PRECAUTIONS*** - *Monitoring Laboratory Tests*).

Anaphylaxis and Severe Hypersensitivity Reactions

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with RECOMBINATE and have been manifested as dizziness, pruritus, rash, urticaria, flushing, angioedema/face swelling, laryngeal edema, dyspnea, pallor, pyrexia, nausea, paresthesia, hypotension, and loss of consciousness. Discontinue RECOMBINATE if symptoms occur and seek immediate emergency treatment. RECOMBINATE contains trace amounts of bovine proteins, mouse immunoglobulin G (MuIgG), and hamster (CHO) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Neutralizing Antibodies

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of RECOMBINATE predominantly in previously untreated and minimally treated patients. The risk of developing inhibitors is highest during the first 20 exposure days. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed (*see* ***PRECAUTIONS*** - *Monitoring Laboratory Tests*).

PRECAUTIONS

General

Certain components used in the packaging of this product contain natural rubber latex.

Identification of the clotting defect as a Factor VIII deficiency is essential before the administration of RECOMBINATE [Antihemophilic Factor (Recombinant)] is initiated. No benefit may be expected from this product in treating other deficiencies.

Formation of Antibodies to Mouse, Hamster or Bovine Protein

As RECOMBINATE contains trace amounts of mouse protein (maximum of 0.1 ng/IU RECOMBINATE), hamster protein (maximum of 1.5 ng CHO protein/IU RECOMBINATE), and bovine protein (maximum of 1 ng BSA/IU RECOMBINATE), the remote possibility exists that patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Information for Patients

The patient and physician should discuss the risks and benefits of this product.

Allergic type hypersensitivity reactions have been observed with RECOMBINATE. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, symptoms of laryngeal edema, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician if these symptoms occur. Additionally, patients should be informed that local tissue irritation may occur when infusing RECOMBINATE reconstituted with 5 mL sWFI.

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***).
- Monitor for development of factor VIII inhibitors. Perform 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 RECOMBINATE. Use Bethesda Units (BU) to titer inhibitors.
    - If the inhibitor is less than 10 BU per mL, the administration of additional RECOMBINATE concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.
    - Adequate hemostasis may not be achieved if inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following RECOMBINATE 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

RECOMBINATE was tested for mutagenicity at doses considerably exceeding plasma concentrations of Factor VIII *in vitro* and at doses up to ten times the expected maximum clinical dose *in vivo*, and did not cause reverse mutations, chromosomal aberrations, or an increase in micronuclei in bone marrow polychromatic erythrocytes. Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Pediatric Use

RECOMBINATE is appropriate for use in children of all ages, including the newborn. Safety and efficacy studies have been performed in both previously treated (n=23) and previously untreated (n=75) children. (See ***CLINICAL PHARMACOLOGY*** and ***PRECAUTIONS***).

Pregnancy

Animal reproduction studies have not been conducted with RECOMBINATE. The safety of RECOMBINATE for use in pregnant women has not been established. It is not known whether RECOMBINATE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing RECOMBINATE. RECOMBINATE should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if RECOMBINATE is administered to nursing mothers. RECOMBINATE should be given to nursing mothers only if clinically needed.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

During controlled clinical studies with RECOMBINATE enrolling 210 subjects, the most commonly reported adverse drug reactions were chills, flushing, rash and epistaxis.

System Organ Class (SOC)	Preferred MedDRA Term	Number of Subjects	Percent of Evaluable Subjects*
GASTROINTESTINAL DISORDERS	Nausea	1	0.48
GENERAL DISORDERS AND	Chills Fatigue	3 1	1.43 0.48

System Organ Class (SOC)	Preferred MedDRA Term	Number of Subjects	Percent of Evaluable Subjects*
ADMINISTRATION SITE CONDITIONS	Pyrexia	1	0.48
INFECTIONS AND INFESTATIONS	Ear infections	1	0.48
INVESTIGATIONS	Acoustic stimulation tests abnormal	1	0.48
MUSCULOSKELETAL AND CONNECTIVE TISSUES DISORDERS	Pain in extremity	1	0.48
NERVOUS SYSTEM DISORDERS	Dizziness Tremors	1 1	0.48 0.48
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Pharyngolaryngeal pain	1	0.48
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis Pruritus Rash Rash maculopapular	1 1 2 1	0.48 0.48 0.95 0.48
VASCULAR DISORDERS	Epistaxis Flushing Hematoma Hypotension Pallor Peripheral coldness	1† 2 1 1 1 1	0.48 0.95 0.48 0.48 0.48 0.48

* Number of evaluable subjects experiencing the event/total number of evaluable subjects [% relative to 210, the total number of unique subjects who received at least 1 infusion of RECOMBINATE].

† One subject experienced 11 events of epistaxis.

During the Previously Treated Patients (PTP) study, none of the 71 subjects developed *de novo* evidence of Factor VIII inhibitor. However, during the phase II/III portion of the study, 1 subject with a history of inhibitors exhibited inhibitor activity at 6 months (0.8 Bethesda Units [BU]), which resolved by 9 months. One other subject in this study had detectable Factor VIII inhibitor at baseline (1.26 BU) and exhibited an anamnestic response at 6 months (10.3 BU). During a prospective pharmaco-surveillance study of subjects who received batches of RECOMBINATE containing modestly increased Chinese Hamster Ovary (CHO) cell protein levels, none of the 34 treated subjects developed a Factor VIII inhibitor.

During the Previously Untreated Patients (PUP) study, 22 of the 73 evaluable subjects developed inhibitors to Factor VIII. Of these, 13 subjects displayed no detectable Factor VIII inhibitors at study exit.

Post-Marketing Adverse Reactions
In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These adverse reactions are listed by MedDRA (version 12.1) System Organ Class (SOC), then by MedDRA coding system Preferred Term in order of severity.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Factor VIII inhibition
CARDIAC DISORDERS: Tachycardia, Cyanosis
GASTROINTESTINAL DISORDERS: Vomiting, Abdominal pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Malaise, Injection site reactions, Chest pain, Chest discomfort
IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity
NERVOUS SYSTEM DISORDERS: Loss of consciousness, Headache, Paresthesia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Dyspnea, Cough, Laryngeal edema
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema, Urticaria, Erythema

DOSAGE AND ADMINISTRATION

Each vial of RECOMBINATE is labeled with the Factor VIII activity expressed in IU per vial. This potency assignment is referenced to the World Health Organization International Standard for Factor VIII:C Concentrate and is evaluated by appropriate methodology to ensure accuracy of the results.

The expected *in vivo* peak increase in Factor VIII level expressed as IU/dL of plasma or % (percent) of normal can be estimated by multiplying the dose administered per kg body weight (IU/kg) by two. This calculation is based on the clinical findings of Abildgaard *et al* [4] and is supported by the data generated by 419 clinical pharmacokinetic studies with RECOMBINATE in 67 patients over time. This pharmacokinetic data demonstrated a peak recovery point above the pre-infusion baseline of approximately 2.0 IU/dL per IU/kg body weight.

Examples (Assuming patient's baseline Factor VIII level is at <1%):
(1) A dose of 1750 IU RECOMBINATE administered to a 70 kg patient, *i.e.* 25 IU/kg (1750 IU/70 kg), should be expected to cause a peak post-infusion Factor VIII increase of 25 IU/kg x 2 (IU/dL)/(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 dose would be 70 IU/dL/[2(IU/dL)/(IU/kg)] x 40 kg = 1400 IU.

Recommended Dosage Schedule
Physician supervision of the dosage is required. The following dosage schedule may be used as a guide.

Hemorrhage		
Degree of hemorrhage	**Required peak post-infusion Factor VIII activity in the blood (as % of normal or IU/dL plasma)**	**Frequency of Infusion**
Early hemarthrosis or muscle bleed or oral bleed	20-40	Begin infusion every 12 to 24 hours for one-three days until the bleeding episode is resolved (as indicated by pain), or healing is achieved.
More extensive hemarthrosis, muscle bleed, or hematoma	30-60	Repeat infusion every 12 to 24 hours for (usually) three days or more until pain and disability are resolved.
Life threatening bleeds such as head injury, throat bleed, severe abdominal pain	60-100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Type of operation		
Minor surgery, including tooth extraction	60-80	A single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases.
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours depending on state of healing.

If bleeding is not controlled with the recommended dose, the plasma level of Factor VIII should be determined and a sufficient dose of RECOMBINATE should be administered to achieve a satisfactory clinical response.

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening hemorrhages. In presence of a low titer inhibitor, doses larger than those recommended may be necessary as per standard care.
Although dosage can be estimated by the calculations above, it is strongly recommended that whenever possible, appropriate laboratory tests including serial Factor VIII assays be performed on the patient's plasma at suitable intervals to assure that adequate Factor VIII levels have been reached and are maintained.

Patients should be evaluated for the development of Factor VIII inhibitors, if the expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose.

Reconstitution: Use Aseptic Technique

1. Bring RECOMBINATE (dry factor concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from concentrate and diluent vials.
3. Cleanse stoppers with germicidal solution and allow to dry prior to use. Place vials on a flat surface.

4. Open the BAXJECT II device package by peeling away the lid, without touching the inside. **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.
6. Grip the BAXJECT II package at its edge and pull the package off the device. **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 RECOMBINATE vial stopper by pushing straight down. The vacuum will draw the diluent into the RECOMBINATE vial.
8. Swirl gently until RECOMBINATE is completely dissolved. After reconstitution, the solution should be colorless to faint yellow, and substantially free from foreign particles.

NOTE: Do not refrigerate after reconstitution. (see ***Administration***)

Administration: Use Aseptic Technique

RECOMBINATE is administered by intravenous (IV) injection after reconstitution.
Administer at room temperature.
RECOMBINATE should be administered not more than 3 hours after reconstitution.

Intravenous Syringe Injection

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be colorless to faint yellow in appearance. If not, do not use the solution and notify Takeda Pharmaceuticals U.S.A., Inc. immediately.
Plastic syringes are recommended for use with this product since proteins such as RECOMBINATE tend to stick to the surface of glass syringes.

1. Remove the blue cap from the BAXJECT II device. Connect the syringe to the BAXJECT II device. DO NOT INJECT AIR.
2. Turn over the connected vials so that the RECOMBINATE vial is on top. Draw the factor concentrate into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe; attach a suitable needle and inject intravenously as instructed (see *Rate of Administration*)
4. If a patient is to receive more than one vial of RECOMBINATE, 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 RECOMBINATE and Sterile Water for Injection only, therefore reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II device.**

Rate of Administration
The rate of administration should be a rate that ensures the comfort of the patient. Preparations of RECOMBINATE can be administered at a rate of up to 5 mL per minute when reconstituted with 5 mL of sWFI.

The pulse rate should be determined before and during administration of RECOMBINATE. 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.

HOW SUPPLIED

RECOMBINATE is available in five different strengths in single-dose vials. The strength is designated on the outer box and on the vial label using the following color codes:

Color Code	Dosage Strength	RECOMBINATE Supplied with 5 mL sWFI
Light blue bar	220 – 400 IU per vial	NDC 0944-2841-10
Pink bar	401-800 IU per vial	NDC 0944-2842-10
Green bar	801-1240 IU per vial	NDC 0944-2843-10
Purple bar	1241-1800 IU per vial	NDC 0944-2844-10
Orange bar	1801-2400 IU per vial	NDC 0944-2845-10

RECOMBINATE is packaged with 5 mL of Sterile Water for Injection, USP, a BAXJECT II Needleless Transfer Device, one physician insert and one patient insert.

Storage
RECOMBINATE can be refrigerated [2° - 8°C (36° - 46°F)] or stored at room temperature, not to exceed 30°C (86°F). Avoid freezing to prevent damage to the diluent vial. Do not use beyond the expiration date printed on the box.

CLINICAL STUDIES

Over the investigational period of the original safety and efficacy study of RECOMBINATE, none of the 69 subjects without an inhibitor at entry into the study, developed an inhibitor. In the previously untreated patient group there were 73 eligible subjects with Factor VIII levels less than or equal to 2% who received at least one RECOMBINATE treatment (median days 100, range 3-821) and who were tested for an inhibitor after treatment with RECOMBINATE. Of this group, 23 individuals (32%) developed a detectable inhibitor (median days on treatment at time of detection 10, range 3-69) and of these, 8 subjects (11%) showed a titer greater than 10 B.U.

REFERENCES

1. Bray GL, Gomperts ED, Courter S, Gruppo R, *et al*: A Multicenter Study of Recombinant Factor VIII (Recombinate): Safety, Efficacy, and Inhibitor Risk in Previously Untreated Patients with Hemophilia A **Blood 83:**2428-2435, 1994
2. White GC, McMillan CW, Kingdon HS, *et al*: Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. **New Eng J Med 320**:166-170, 1989
3. Kessler CM: An Introduction to Factor VIII Inhibitors: The Detection and Quantitation. **Am J Med 91 (Suppl 5A):** 1S-5S, 1991
4. Abildgaard CF, Simone JV, Corrigan JJ, *et al*: Treatment of hemophilia with glycine-precipitated Factor VIII. **New Eng J Med 275**:471-475, 1966

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

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Revised: 3/2023

Patient Information
RECOMBINATE
[Antihemophilic Factor (Recombinant)]

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

Do not attempt to self-infuse unless you have been taught how by your doctor or hemophilia center.

What is RECOMBINATE [Antihemophilic Factor (Recombinant)]?

RECOMBINATE is a medicine used to replace a 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.

RECOMBINATE is used to prevent and control bleeding in people with hemophilia A.

RECOMBINATE is not used to treat von Willebrand's Disease.

Who should not use RECOMBINATE [Antihemophilic Factor (Recombinant)]?

You should not use RECOMBINATE if you

- are allergic to mouse, hamster or bovine proteins.
- are allergic to any ingredients in RECOMBINATE (such as calcium, histidine, human albumin, polyethylene glycol, polysorbate-80 and sodium).

Tell your healthcare provider if you are pregnant or breast-feeding because RECOMBINATE may not be right for you.

How should I use RECOMBINATE [Antihemophilic Factor (Recombinant)]?

RECOMBINATE is given directly into the blood stream.

You may infuse RECOMBINATE 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 hemophilia treatment center or healthcare provider. Many people

with hemophilia A learn to infuse their RECOMBINATE by themselves or with the help of a family member.
You must carefully follow your doctor's or other healthcare provider's instructions regarding the dose and schedule for infusing RECOMBINATE so that your treatment will work best for you.
Your healthcare provider will tell you how much RECOMBINATE 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 RECOMBINATE 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 RECOMBINATE.

What should I tell my healthcare provider before I use RECOMBINATE [Antihemophilic Factor (Recombinant)]?
You should tell your healthcare provider if you

- have or have had any medical problems.
- take any medicines, including non-prescription medicines, dietary supplements and herbal remedies.
- have any allergies, including allergies to mouse, hamster or bovine proteins.
- are nursing.
- are pregnant or planning to become pregnant.
- have been told that you have inhibitors to Factor VIII (because Factor VIII may not work for you).

What are the possible side effects of RECOMBINATE [Antihemophilic Factor (Recombinant)]?
You could have an allergic reaction to RECOMBINATE.
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
- light-headed, dizziness
- fainting

The most common side effects are chills, flushing, rash and nose bleeds. These are not all possible side effects with RECOMBINATE. You can ask your healthcare provider for information that is written for healthcare professionals. Tell your doctor about any side effect that bothers you or that does not go away.

What are the RECOMBINATE [Antihemophilic Factor (Recombinant)] dosage strengths?
RECOMBINATE comes in five different dosage strengths. The actual strength will be imprinted on the label and on the box. The five different strengths are coded, as follows:

Light-blue	Nominal dosage strength of approximately 250 IU per vial (220 – 400 IU/vial).
Pink	Nominal dosage strength of approximately 500 IU per vial (401 – 800 IU/vial).
Green	Nominal dosage strength of approximately 1000 IU per vial (801 – 1240 IU/vial).
Purple	Nominal dosage strength of approximately 1500 IU per vial (1241-1800 IU/vial)
Orange	Nominal dosage strength of approximately 2000 IU per vial (1801-2400 IU/vial)

Always check the potency printed on the label to make sure you are using the strength prescribed by your doctor. Always check the expiration date printed on the box. You should not use the product after the expiration date printed on the box.

How do I store RECOMBINATE [Antihemophilic Factor (Recombinant)]?
RECOMBINATE vials containing powdered product (without sterile diluent added) should be stored in a refrigerator (2° to 8°C [36° to 46°F]) or at room temperature (up to 30°C [86°F]).
If you choose to store RECOMBINATE at room temperature:

- it should remain at room temperature until infused.
- do not put room temperature product back in the refrigerator.

Store vials in their original box and protect them from extreme exposure to light. Do not freeze.
Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated. Any RECOMBINATE left in the vial at the end of your infusion should be discarded.

What else should I know about RECOMBINATE [Antihemophilic Factor (Recombinant)] 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 RECOMBINATE from working properly. Call your healthcare provider right away if your bleeding does not stop after taking RECOMBINATE. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to Factor VIII.

Resources at Takeda available to the patients:
Contact Takeda for more product information: 1-877-TAKEDA-7 (1-877-825-3327).

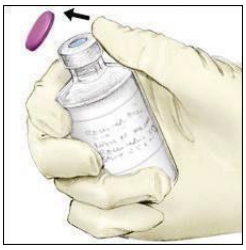
INSTRUCTIONS FOR USE

RECOMBINATE
[Antihemophilic Factor (Recombinant)]
(For intravenous use only)

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

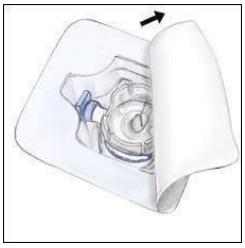
1. In a quiet place, prepare a clean flat surface and gather all the materials you will need for the infusion. Check the expiration date, and let the vial with the RECOMBINATE concentrate and the Sterile Water for Injection, USP (diluent) warm up to room temperature. Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.

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

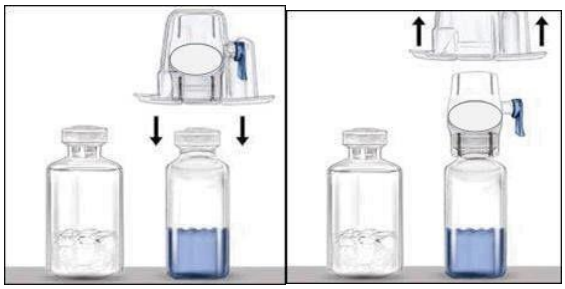


3. Disinfect the stoppers with an alcohol swab (or other suitable solution suggested by your doctor or hemophilia center) by rubbing the stoppers firmly for several seconds, and allow to dry prior to use. Place the vials on a flat surface.

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



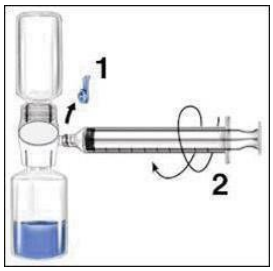
5. Turn the package with the BAXJECT II device upside down, and place it over the top of the diluent vial. Fully insert the clear plastic spike of the device into the center of the diluent vial's stopper by pushing straight down. Grip the package at its edge and lift it off the device. Be careful not 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 RECOMBINATE vial.



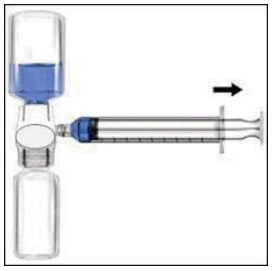
6. To connect the diluent vial to the RECOMBINATE vial, turn the diluent vial over and place it on top of the vial containing RECOMBINATE concentrate. Fully insert the white plastic spike into the RECOMBINATE vial's stopper by pushing straight down. Diluent will flow into the RECOMBINATE vial. This should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

7. Swirl the connected vials gently and continuously until the RECOMBINATE is completely dissolved. **Do not shake**. The RECOMBINATE solution should be colorless to light-yellow in appearance. If not, do not use it and notify Takeda Pharmaceuticals U.S.A., Inc. immediately.

8. Take off the blue cap from the BAXJECT II device and connect the syringe. **BE CAREFUL TO NOT INJECT AIR**.

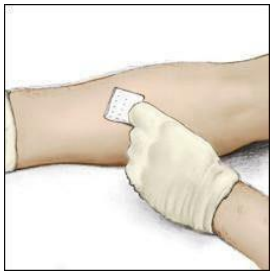


9. Turn over the connected vials so that the RECOMBINATE vial is on top. Draw the RECOMBINATE solution into the syringe by pulling back the plunger slowly. Disconnect the syringe from the vials. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the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

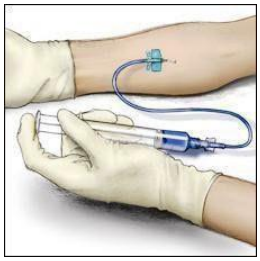


If you are using more than one vial of RECOMBINATE, the contents of more than one vial may be drawn into the same syringe. However, you will need a separate diluent and BAXJECT II device to mix each additional vial of RECOMBINATE.

10. 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 doctor or hemophilia center).



11. Insert the needle into the vein, and remove the tourniquet. Slowly infuse the RECOMBINATE. **Do not infuse any faster than 5 mL per minute for RECOMBINATE dissolved with 5 mL of sWFI**. Redness of the skin or irritation may be seen when infusing RECOMBINATE dissolved with 5 mL diluent.



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.

13. Remove the peel-off label from the RECOMBINATE 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.

14. 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 doctor or local Hemophilia Treatment Center if you experience any problems.

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