

RECOMBINATE

Antihemophilic Factor

(Recombinant)

Baxter

Description

RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) is a glycoprotein synthesized by a genetically engineered Chinese Hamster Ovary (CHO) cell line. In culture, the CHO cell line secretes recombinant antihemophilic factor (rAHF) into the cell culture medium. The rAHF 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 rAHF in the medium. The synthesized rAHF produced by the CHO cells has the same biological effects as Antihemophilic Factor (Human) [AHF (Human)]. Structurally the protein has a similar combination of heterogenous heavy and light chains as found in AHF (Human).

RECOMBINATE rAHF is formulated as a sterile, nonpyrogenic, off-white to faint yellow, lyophilized powder preparation of concentrated recombinant AHF for intravenous injection. RECOMBINATE rAHF is available in single-dose bottles which contain nominally 250, 500 and 1000 International Units per bottle. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 12.5 mg/mL Albumin (Human), 0.20 mg/mL calcium, 1.5 mg/mL polyethylene glycol (3350), 180 mEq/L sodium, 55 mM histidine, 1.5 µg/AHF international Unit (IU) polysorbate-80. Von Willebrand Factor (vWF) is coexpressed with the Antihemophilic Factor (Recombinant) and helps to stabilize it. The final product contains not more than 2 ng vWF/IU rAHF which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative.

Manufacturing of RECOMBINATE rAHF is shared by Baxter Healthcare Corporation and Wyeth BioPharma. The recombinant Antihemophilic Factor Concentrate (For Further Manufacturing Use), is produced by Baxter Healthcare Corporation and Wyeth BioPharma (For Further Manufacturing Use) and subsequently formulated and packaged at Baxter Healthcare Corporation.

Each bottle of RECOMBINATE rAHF is labeled with the AHF activity expressed in IU per bottle. 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

AHF 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 rAHF provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect in these patients. Pharmacokinetic studies on sixty-nine (69) patients revealed the circulating mean half-life for rAHF to be 14.6 ± 4.9 hours (n=67), which was not statistically significantly different from plasma-derived **HEMOFIL M**, Antihemophilic Factor (Human) (AHF) (pdAHF). The mean half-life of **HEMOFIL M** AHF was 14.7 ± 5.1 hours (n=61). The actual baseline recovery observed with rAHF was 123.9 ± 47.7 IU/dl (n=23) which is significantly higher than the actual **HEMOFIL M** AHF baseline recovery of 101.7 ± 31.6 IU/dl (n=61). However, the calculated ratio of actual to expected recovery with rAHF ($121.2 \pm 48.9\%$) is not different on average from **HEMOFIL M** AHF ($123.4 \pm 16.4\%$).

The clinical study of rAHF in previously treated patients (individuals with hemophilia A who had been treated with plasma derived AHF) 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 rAHF.

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 AHF replacement.

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

Indications and Usage

The use of RECOMBINATE rAHF is indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.¹ RECOMBINATE rAHF is also indicated in the perioperative management of patients with hemophilia A (classical hemophilia).

RECOMBINATE rAHF can be of therapeutic value in patients with acquired AHF inhibitors not exceeding 10 Bethesda Units per mL². In clinical studies with RECOMBINATE rAHF, 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 rAHF should be controlled by frequent laboratory determinations of circulating AHF levels.

RECOMBINATE rAHF is not indicated in von Willebrand's disease.

Contraindications

Known hypersensitivity to mouse, hamster or bovine protein may be a contraindication to the use of Antihemophilic Factor (Recombinant) (see **Precautions**).

Warnings

None.

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) (rAHF) is initiated. No benefit may be expected from this product in treating other deficiencies.

The formation of neutralizing antibodies, inhibitors to factor VIII, is a known complication in the management of individuals with hemophilia A. The reported prevalence of these antibodies in patients receiving plasma derived AHF is 10-20%^{3-7, 10-12}. These inhibitors are invariably IgG immunoglobulins, the factor VIII procoagulant inhibitory activity of which is expressed as Bethesda Units (B.U.) per mL of plasma or serum³⁻⁷. Over the investigational period, none of the 69 previously treated individuals, without an inhibitor at entry into the study, developed an inhibitor. In the previously untreated patient group there were 73 eligible patients with factor VIII levels less than or equal to 2% who received at least one rAHF treatment (median days 100, range 3-821) and who were tested for inhibitor after treatment with RECOMBINATE rAHF. Of this group, 23 individuals developed detectable inhibitor (median days 10, range 3-69) and of these, 8 patients showed a titer greater than 10 B.U. Patients treated with rAHF should be carefully monitored for the development of antibodies to rAHF by appropriate clinical observations and laboratory tests.

Formation of Antibodies to Mouse, Hamster or Bovine Protein

As RECOMBINATE rAHF contains trace amounts of mouse protein (maximum of 0.1 ng/IU rAHF), hamster protein (maximum of 1.5 ng CHO protein/IU rAHF), and bovine protein (maximum of 1 ng BSA/IU rAHF), 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.

Although allergic type hypersensitivity reactions were not observed in any patient receiving RECOMBINATE rAHF on study, such reactions are theoretically possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician if these symptoms occur.

Laboratory Tests

Although dosage can be estimated by the calculations which follow, it is strongly recommended that whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

If the patient's plasma AHF fails to reach expected levels or if bleeding is not controlled after adequate dosage, the presence of inhibitor should be suspected. By performing appropriate laboratory procedures, the presence of an inhibitor can be demonstrated and quantified in terms of AHF International Units neutralized by each mL of plasma or by the total estimated plasma volume. If the inhibitor is present at levels less than 10 Bethesda Units per mL, administration of additional AHF may neutralize the inhibitor. Thereafter, the administration of additional AHF International Units should elicit the

predicted response. The control of AHF levels by laboratory assay is necessary in this situation.

Inhibitor titers above 10 Bethesda Units per mL may make hemostasis control with AHF either impossible or impractical because of the very large dose required. In addition, the inhibitor titer may rise following AHF infusion because of an anamnestic response to the AHF antigen.

Carcinogenesis, Mutagenesis, Impairment of Fertility

RECOMBINATE rAHF was tested for mutagenicity at doses considerably exceeding plasma concentrations of rAHF *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, Antihemophilic Factor (Recombinant) (rAHF) 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

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

Adverse Reactions

During the clinical studies conducted in the previously treated patient group, there were 13 infusion related minor adverse reactions reported out of 10,446 infusions (0.12%).

One patient experienced flushing and nausea during his first infusion which abated on decreasing the infusion rate. A second patient experienced mild fatigue during and following one infusion and a third patient had a series of eleven nose bleeds with a periodicity associated with the infusions.

The protein in greatest concentration in RECOMBINATE rAHF is Albumin (Human). Reactions associated with intravenous administration of albumin are extremely rare, although nausea, fever, chills or urticaria have been reported. Other allergic reactions could theoretically be encountered in the use of this Antihemophilic Factor preparation. See **Information for Patients**.

Dosage and Administration

Each bottle of RECOMBINATE rAHF is labeled with the AHF activity expressed in IU per bottle. 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 AHF 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*⁸ and is supported by the data generated by 419 clinical pharmacokinetic studies with rAHF 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.

Example (Assuming patient's baseline AHF level is at <1%):

- (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 $25 \times 2 = 50$ 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 $70/2 \times 40 = 1400$ 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 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.

The careful control of the substitution therapy is especially important in cases of major surgery or life threatening hemorrhages.

Although dosage can be estimated by the calculations above, it is strongly recommended that whenever possible, appropriate laboratory tests including serial AHF assays be performed on the

patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

Other dosage regimens have been proposed such as that of Schimpf, *et al*, which describes continuous maintenance therapy.⁹

Reconstitution: Use Aseptic Technique

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

NOTE: Do not refrigerate after reconstitution. See **Administration**.

Administration: Use Aseptic Technique

Administer at room temperature.

RECOMBINATE rAHF 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. A colorless to faint yellow appearance is acceptable for RECOMBINATE rAHF.

Plastic syringes are recommended for use with this product since proteins such as AHF tend to stick to the surface of all-glass syringes.

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into the syringe.
2. Insert needle into reconstituted RECOMBINATE rAHF.
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 RECOMBINATE rAHF, the contents of multiple bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. Filter needles are intended to filter the contents of a single bottle of RECOMBINATE rAHF only.

Rate of Administration

Preparations of RECOMBINATE, Antihemophilic Factor (Recombinant) (rAHF) can be administered at a rate of up to 10 mL per minute with no significant reactions.

The pulse rate should be determined before and during administration of RECOMBINATE rAHF. 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 rAHF is available in single-dose bottles which contain nominally 250, 500 and 1000 International Units per bottle. RECOMBINATE rAHF is packaged with

10 mL of Sterile Water for Injection, USP, a double-ended needle, a filter needle, one physician insert and one patient insert.

Storage

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

References

1. 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
2. Kessler CM: An Introduction to Factor VIII Inhibitors: The Detection and Quantitation. **Am J Med** 91 (Suppl 5A):1S-5S, 1991
3. Schwarzinger I, Pabinger I, Korninger C, Haschke F, Kundi M, Niessner H, Lechner K: Incidence of inhibitors in patients with severe and moderate hemophilia A treated with factor VIII concentrates. **Am J Hematology** 24:241-245, 1987
4. Penner JA, Kelly PE: Management of patients with factor VIII or IX inhibitors. **Sem Thromb Hemostasis** 1:386-399, 1975
5. Ehrenforth S, Kreuz W, Scharrer I, *et al*: Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. **Lancet** 339:594-598, 1992
6. McMillan CW, Shapiro SS, Whitehurst D, *et al*: The natural history of factor VIII inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. **Blood** 71:344-348, 1988
7. Addiego JE Jr., 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
8. Abildgaard CF, Simone JV, Corrigan JJ, *et al*: Treatment of hemophilia with glycine-precipitated Factor VIII. **New Eng J Med** 275:471-475, 1966

9. Schimpf K, Rothman P, Zimmermann K: Factor VIII dosis in prophylaxis of hemophilia A; A further controlled study in **Proc XIth Cong W.F.H.** Kyoto, Japan, Academic Press, 1976, pp 363-366
10. Gill FM: The Natural History of Factor VIII Inhibitors in Patients with Hemophilia A. Hoyer LW (ed), Factor VIII Inhibitors, **N.Y. AR Liss**, 1984, pp 19-29
11. Rasi V, Ikkala E: Haemophiliacs with factor VIII inhibitors in Finland: prevalence, incidence and outcome. **Br J Haematol 76**:369-371, 1990
12. Lusher JM, Salzman PM: Viral Safety and Inhibitor Development Associated with Factor VIII Ultra-Purified From Plasma in Hemophiliacs Previously Unexposed to Factor VIII Concentrates. **Seminars in Hematology 27**:1-7, 1990

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

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

DESCRIPTION

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. In culture, the CHO cell line expresses recombinant antihemophilic factor (rAHF) into the cell culture medium. The rAHF is purified from the culture medium using a series of chromatography columns. The cornerstone of the purification process is 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 as Antihemophilic Factor (Human) [AHF (Human)]. Structurally the recombinant protein has a similar combination of heterogeneous heavy and light chains as found in AHF (Human).

ADVATE is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. ADVATE is available in single-dose vials that contain nominally 250, 500, 1000, 1500 and 2000 International Units (IU) per vial. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximal amounts: 38 mg/mL mannitol, 10 mg/mL trehalose, 108 mEq/L sodium, 12 mM histidine, 12 mM Tris, 1.9 mM calcium, 0.15 mg/mL polysorbate-80, and 0.10 mg/mL 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/100 IU rAHF, which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative. Each vial of ADVATE is labeled with the rAHF activity expressed in IU per vial. Biological potency is determined by an in vitro assay, which employs a Factor VIII concentrate standard that is referenced to a World Health Organization (WHO) International Standard for Factor VIII:C concentrates. The specific activity of ADVATE is 4000 to 10000 IU per milligram of protein.

CLINICAL PHARMACOLOGY

The pharmacokinetics of ADVATE were investigated in a Phase 2/3 multicenter pivotal study of previously treated subjects. In addition, an interim analysis comparing the pharmacokinetics of ADVATE at the onset of treatment and after a period of at least 75 exposure days was performed in the context of an ongoing continuation study in subjects who completed treatment in the multicenter pivotal Phase 2/3 study. Post-infusion levels and clearance of Factor VIII during the perioperative period were examined in an interim analysis of subjects from the pivotal and continuation studies who were enrolled in an ongoing Phase 2/3 surgical study. Finally, the pharmacokinetics of ADVATE were investigated in an interim analysis of an ongoing study of pediatric previously treated subjects < 6 years of age (see **PRECAUTIONS**, Pediatric Use).

Pharmacokinetics

A randomized, crossover pharmacokinetic comparison of ADVATE produced at a pilot-scale facility in Orth, Austria (the test article) and RECOMBINATE [Antihemophilic Factor (Recombinant)] (the control article) was conducted in the context of the pivotal Phase 2/3 study. Study subjects were initially infused with one of the two preparations at a dose of 50 ± 5 IU/kg body weight while in a non-bleeding state. The second study preparation was infused in a non-bleeding state at 50 ± 5 IU/kg after a washout period of 72 hours to 4 weeks following the first study infusion. The order in which each study preparation was administered was assigned by randomization. Pharmacokinetic parameters (area under the Factor VIII plasma concentration versus time curve [AUC], maximal post-infusion Factor VIII level [C_{max}], in vivo recovery, half-life, clearance [CL], mean residence time [MRT], and volume of distribution in steady-state [V_{ss}]) were calculated from Factor VIII activity measurements in blood samples obtained immediately before and at standardized time intervals up to 48 hours following each infusion.

A total of 56 study subjects were enrolled and randomized. Of these, 50 (modified intent-to-treat population) received both infusions of study medication and had sufficient pharmacokinetic data for the comparison of ADVATE and RECOMBINATE [Antihemophilic Factor (Recombinant)]. Thirty subjects (per-protocol population) received both pharmacokinetic infusions of study medication and had data for all pharmacokinetic time points. Pharmacokinetic parameters for each study preparation in the per-protocol analysis are presented in Table 1.

Parameter	RECOMBINATE		ADVATE	
	N	Mean ± SD	N	Mean* ± SD
AUC _{0-48h} (IU·h/dL) ^a	30	1530 ± 380	30	1534 ± 436
In vivo recovery (IU/dL/IU/kg) ^b	30	2.59 ± 0.52	30	2.41 ± 0.50
Half-life (h)	30	11.24 ± 2.53	30	11.98 ± 4.28
C _{max} (IU/dL)	30	129 ± 27	30	120 ± 26
MRT (h)	30	14.52 ± 3.81	30	15.68 ± 6.21
V _{ss} (dL/kg)	30	0.46 ± 0.10	30	0.47 ± 0.10
CL (dL/kg/h)	30	0.03 ± 0.01	30	0.03 ± 0.01

^a Area under the plasma Factor VIII concentration x time curve from 0 to 48 hours post-infusion
^b Calculated as (C_{max} - baseline Factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion Factor VIII measurement

For the pharmacokinetic parameters AUC_{0-48h} and in vivo recovery, the 90% confidence intervals for the ratios of the mean values for the test and control articles were within the pre-established limits of 0.80 and 1.25 for the per-protocol (n = 30) study population. This was also true in the intent-to-treat study (n = 50) population for the total AUC and in vivo recovery. In addition, in vivo recovery at the onset of treatment and after 75 exposure days was 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.

Additionally, the pharmacokinetics of ADVATE produced at the Orth facility were compared with those of ADVATE produced at a commercial-scale facility in Neuchâtel, Switzerland. For the pharmacokinetic parameters AUC_{0-48h} and in vivo recovery, the 90% confidence intervals for the ratios of the mean values for the test and control articles were within the pre-established limits of 0.80 and 1.25 for both the per-protocol and intent-to-treat study populations.

The Phase 2/3 continuation study provided a means for examining potential changes in all pharmacokinetic parameters of ADVATE at the onset of treatment and after a period of at least 75 exposure days. This comparison utilized data for ADVATE produced in the Orth facility obtained at the onset of treatment on the pivotal Phase 2/3 study with data for ADVATE produced in the Neuchâtel facility obtained in the continuation study. A total of 13 of 34 eligible subjects were included in an interim per-protocol analysis (Table 2). Ninety-five percent (95%) confidence intervals calculated for the ratios of the mean values for AUC_{0-48h} and in vivo recovery before and after at least 75 exposure days indicated no evidence of a difference in the pharmacokinetics of ADVATE at the two time points.

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

Parameter	Parameters at the Onset of Treatment ^a					Parameters After ≥ 75 Exposure Days ^b				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
AUC _{0-48h} (IU·h/dL)	13	1315	405	876	2314	13	1262	497	831	2731
C _{max} (IU/dL)	13	111	23	77	151	13	111	25	73	151
Adjusted Recovery (IU/dL/IU/kg)	13	2.24	0.47	1.54	3.02	13	2.20	0.51	1.46	3.06
Total AUMC (IU·h ² /dL)	13	21000	14486	8597	63038	13	19171	13171	8478	58978
Half-life (h)	13	11.10	2.72	6.38	17.96	13	10.89	1.37	9.24	13.92
Clearance (dL/kg·h)	13	0.04	0.01	0.02	0.06	13	0.04	0.01	0.01	0.06
Mean residence time (h)	13	13.95	4.02	8.63	23.38	13	13.54	2.98	8.04	19.58
V _{ss} (dL/kg)	13	0.51	0.10	0.37	0.67	13	0.55	0.12	0.32	0.73

^a Data from the Phase 2/3 pivotal study for ADVATE produced in Orth
^b Data from the Phase 2/3 continuation study for ADVATE produced in Neuchâtel

In an interim analysis of data from 10 of 25 planned subjects in the Phase 2/3 surgery study, the target Factor VIII level was met or exceeded in all cases following a single loading dose ranging from 48.0 to 69.8 IU/kg.

Hemostatic Efficacy

In the Phase 2/3 pivotal study, a global assessment of efficacy was rendered by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using an ordinal scale of excellent, good, fair, or none, based on the quality of hemostasis achieved with ADVATE produced in the Orth facility for the treatment of each new bleeding episode. A total of 510 bleeding episodes were reported, with a mean (± SD) of 6.1 ± 8.2 bleeding episodes per subject. Of the 510 new bleeding episodes treated with ADVATE, 439 (86%) were rated excellent or good in their response to treatment, 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%) new 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%) new bleeding episodes occurred spontaneously, 228 (45%) were the result of antecedent trauma, and for 120 (24%) bleeding episodes, the etiology was unknown. The rate of new bleeding episodes during the protocol-mandated 75 exposure day prophylactic regimen (≥ 25 IU/kg body weight 3-4 times per week) was calculated as a function of the etiology of bleeding episodes for 107 evaluable subjects (n = 274 new bleeding episodes). These rates are presented in Table 3.

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

^a Etiology was indeterminate

In a post-hoc analysis, the overall rate of bleeding was correlated inversely with the degree of compliance with the prescribed prophylactic regimen. Subjects who infused less than 25 IU ADVATE per kg per dose for more than 20% of prophylactic infusions or administered less than 3 infusions per week for more than 20% of study weeks (n = 37) experienced a 2.3-fold higher rate of bleeding in comparison with subjects who complied with the prescribed prophylactic regimen at least 80% of the time and for ≥ 80% of doses (n = 70).

The Phase 2/3 continuation study involved subjects previously treated on the pivotal Phase 2/3 study and provided additional efficacy data on ADVATE. An interim analysis of efficacy was conducted for 27 of 82 enrolled subjects who self-administered ADVATE produced in Neuchâtel on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE. As in the pivotal Phase 2/3 study, new bleeding episodes were treated with ADVATE and the outcome of treatment was rated as excellent, good, fair, or none, based on the quality of hemostasis achieved. A total of 51 new bleeding episodes occurred in 13 of the 27 subjects being treated with ADVATE. By etiology, 53% of these bleeding events resulted from trauma and 27% occurred spontaneously; the other 20% had an undetermined etiology. The response to treatment with ADVATE for the majority (63%) of all new bleeding episodes was rated as excellent or good. In addition, 86% of the bleeding episodes resolved with only 1 infusion and an additional 6% were resolved by a second infusion. Thus, 92% of all bleeding episodes required 1 or 2 infusions of study product. An interim analysis of the hemostatic efficacy of ADVATE during the perioperative management of subjects undergoing surgical procedures was conducted for 10 of 25 planned subjects. Ten subjects underwent 10 surgical procedures while receiving ADVATE. Eight subjects received the test product by intermittent bolus infusion and 2 subjects received a combination of continuous and intermittent bolus infusion. Nine of the 10 subjects completed the study. Six of the surgical procedures were classified as major, and 4 were minor. Of the 6 major surgeries, 5 were for orthopedic complications of hemophilia. A brief description of each surgical procedure, along with study duration and study medication exposure, are presented in Table 4.

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

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

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

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

to evaluate control of hemorrhage from a surgical drain placed at the incision site in one subject. The quality of hemostasis achieved with ADVATE was rated as excellent or good for all assessments.

INDICATIONS AND USAGE

ADVATE is indicated in Hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. ADVATE is also indicated in the perioperative management of patients with Hemophilia A. ADVATE can be of therapeutic value in patients with Factor VIII inhibitors not exceeding 10 Bethesda Units (BU) per mL.^{1,2} However, in patients with a known or suspected inhibitor to Factor VIII, the plasma Factor VIII level should be monitored frequently and the dose of ADVATE should be adjusted accordingly. ADVATE is not indicated for the treatment of von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to mouse or hamster proteins may be a contraindication to the use of ADVATE (see **PRECAUTIONS**). Known intolerance or allergic reaction to any of the constituents in the formulation may be a contraindication to the use of ADVATE. ADVATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.

WARNINGS

None.

PRECAUTIONS

General

Identification of the clotting defect as Factor VIII deficiency is essential before the administration of ADVATE. No benefit may be expected from this product in treating other coagulation factor deficiencies.

Formation of Inhibitors to Factor VIII

The formation of neutralizing antibodies to Factor VIII (Factor VIII inhibitors) is a known complication in the management of individuals with Hemophilia A. The reported prevalence of these antibodies in previously untreated patients who were administered rAHF products over several years is 20.7 to 31.7%.^{3,4,5,6,7,8} These inhibitors are invariably of the immunoglobulin G (IgG) isotype, and the Factor VIII inhibitory activity is expressed as BU per mL of plasma. Patients treated with AHF products should be carefully monitored for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests.

Factor VIII inhibitor testing was performed throughout all studies in the rAHF-PFM clinical program. Among 136 treated subjects ≥ 10 years of age, all of whom had ≥ 150 exposure days to Factor VIII products at study entry, 102 had at least 75 exposure days to ADVATE. None of these subjects developed an inhibitor. One subject who had < 50 exposure days to ADVATE while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE 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 RECOMBINATE [Antihemophilic Factor (Recombinant)]. For the group comprising all subjects with at least 75 exposure days to ADVATE and the single subject who developed an inhibitor, the 95% confidence interval (Poisson distribution) for the risk of developing an inhibitor to Factor VIII was 0.02 to 5.4%.

An interim analysis of inhibitor development in 15 of 50 planned pediatric subjects < 6 years of age who had at least 50 prior exposure days to Factor VIII at study entry was conducted. No subject completed 50 exposure days to ADVATE. Ten of the 15 enrolled subjects completed at least 10 exposure days to ADVATE or 120 total days on study; in among this subset, there were no inhibitors.

Formation of Antibodies to Mouse or Hamster Protein

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG; maximum of 0.1 ng/IU ADVATE) and hamster (CHO) proteins (maximum of 1.5 ng/IU ADVATE). As such, there exists a remote possibility that patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

In the Phase 2/3 pivotal study of ADVATE, serum samples were tested by enzyme immunoassays at baseline and after every 15 ± 2 exposure days, for the presence of antibodies to CHO protein and MuIgG. Regression analysis of assay results was conducted to evaluate trends in levels of antibodies to heterologous proteins as a function of time on study. Four study subjects showed a statistically significant increasing trend in the levels of anti-CHO (n = 1) or anti-MuIgG (n = 3) antibody levels over the course of the study. A fifth study subject showed a marked increase in anti-MuIgG antibodies coincident with the 60 and 75 exposure day interval study visits. None of these subjects exhibited adverse experiences (AEs) or other study findings consistent with an allergic or hypersensitivity response.

Information For Patients

Although allergic type hypersensitivity reactions were not observed in any study subjects receiving ADVATE, such reactions are theoretically possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician immediately if these symptoms occur.

Laboratory Tests

Although the dose can be estimated by the calculations that follow, it is highly recommended that, whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate Factor VIII levels have been reached and are maintained.

If the patient's plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after adequate dosing, the presence of an inhibitor should be suspected. By performing the appropriate laboratory procedures, the presence of an inhibitor can be demonstrated and quantified in terms of the number of BU per mL (i.e. the amount of Factor VIII activity neutralized by one mL of patient plasma). If the inhibitor is present at levels less than 10 BU per mL, the administration of additional AHF concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response. The close monitoring of plasma Factor VIII levels by laboratory assays is necessary in this situation. Inhibitor titers above 10 BU per mL are likely to make the control of hemostasis with AHF concentrates either impossible or impractical because of the very large dose required. In addition, the inhibitor titer may rise following AHF 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

No studies were conducted with the active ingredient in ADVATE to assess its mutagenic or carcinogenic potential. The CHO cell line employed in the production of ADVATE is derived from that used in the biosynthesis of RECOMBINATE [Antihemophilic Factor (Recombinant)]. ADVATE has been shown to be comparable to RECOMBINATE with respect to its biochemical and physicochemical properties, as well as its non-clinical in vivo pharmacology and toxicology.⁹ By inference, RECOMBINATE and ADVATE would be expected to have equivalent mutagenic and 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

Patient Package Insert (US)

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

LE-07-06169



Information for Patients

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

Pronounced: ant-eye-hee-mo-fil-lick factor

Please read this leaflet carefully before using ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method]. This leaflet is based on the information provided to your doctor, and is a summary of the important information you need to know about your medicine for your Factor VIII deficiency. This leaflet does not take the place of talking with your doctor, and does not contain all of the information available about ADVATE. **This leaflet should be used only after you have received instructions from your doctor.** If you have any questions after reading this leaflet, ask your doctor or pharmacist.

1. What is ADVATE?

Factor VIII (also called antihemophilic factor) is the clotting factor that people with Hemophilia A are missing. Hemophilia A (classical hemophilia) is a hereditary bleeding disorder that prevents blood from clotting well. All people with Hemophilia A are born with this bleeding tendency, and frequently have a family history of the disorder. Typically, males are affected with the disorder, but in rare instances, females can also exhibit symptoms of the disorder.

ADVATE is a clotting factor (Factor VIII) that helps people with Hemophilia A prevent and control bleeding episodes. The Factor VIII protein is made by inserting the genetic code for Factor VIII into animal cells, which produce the human coagulation Factor VIII protein. In the human Factor VIII is then purified and separated from animal cell components. In the manufacturing process for ADVATE, no raw materials of human or animal origin are added in the cell culture process, purification, or final product formulation. ADVATE has the same clot-promoting effects as Factor VIII protein made from human plasma.

2. What is ADVATE used for?

ADVATE can temporarily correct the blood clotting process, so it helps prevent and control bleeding in people with Hemophilia A (classical hemophilia). However, you must carefully follow your doctor's or other healthcare provider's instructions regarding the dose and schedule for infusing ADVATE in order for your ADVATE treatment to work effectively. Adults and children of all ages, including newborns, may use ADVATE for treatment or prevention of Hemophilia A-related bleeding. ADVATE is not useful for treating other clotting disorders.

3. How does ADVATE work?

ADVATE temporarily raises the level of Factor VIII in the blood to a more normal level, allowing your body's blood clotting process to function properly. You must carefully follow your doctor's or other healthcare provider's instructions regarding the dose and schedule for infusing ADVATE.

4. Who should not use ADVATE?

You should not use ADVATE unless your doctor confirms that you have Hemophilia A. Patients with known allergy-type reactions to mouse or hamster proteins should talk to their doctor before using this product. Pregnant women should use this product only if clearly needed, since it is not known whether ADVATE can harm your unborn child. It is also not known whether ADVATE affects a woman's ability to have children. If you are considering becoming pregnant, you should talk to your doctor.

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

Your body may form inhibitors to Factor VIII. An inhibitor is an antibody (part of your body's normal immune defenses) that forms in response to infusions of Factor VIII that prevents the Factor VIII from working properly. These inhibitors can lead to a reduced response, or to no response to Factor VIII therapy. This is not an uncommon complication in the

treatment of people with Hemophilia A. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to Factor VIII. Contact your doctor if you are not able to prevent or control bleeding episodes with your regular doses of prescribed Factor VIII therapy.

There is a possibility that you could have an allergic reaction to ADVATE. You should be aware of the early signs of allergic reactions. **These include: rash, hives, itching, tightness of the chest, difficulty breathing, throat tightness, and low blood pressure. The signs and symptoms of low blood pressure can include a weak pulse, feeling lightheaded or dizzy when you stand, and possibly shortness of breath. If you experience any of these symptoms, stop the infusion immediately and contact your doctor.** Severe symptoms, including difficulty breathing and (near) fainting require prompt emergency treatment.

6. What are the possible side effects of ADVATE?

Side effects that have been reported with the infusion of ADVATE include a strange taste in the mouth, itching, dizziness, headache, catheter-related infection, cold shivers, hot flushes, diarrhea, sweating, nausea, pain in the upper abdomen, chest pain, prolonged bleeding after postoperative drain removal, decreased hematocrit, swelling of limbs, swelling of joints, shortness of breath, fever, decreased Factor VIII levels and postoperative unspecified blood clot at the site of surgery.

7. How do I use ADVATE?

ADVATE is injected directly into the blood stream. When you are first starting treatment, you must go to a Hemophilia Treatment Center, hospital or to your local healthcare provider to receive your infusions. Many people with hemophilia learn to infuse their Factor VIII concentrates either by themselves or with the help of a family member. Your doctor or other healthcare provider can teach you the proper technique for self-infusion. Once you learn how to self-infuse, you can follow the instructions on this leaflet.

8. How do I know what dose of ADVATE to take?

Your doctor will prescribe a treatment regimen for you that is based on your body weight, the severity of your hemophilia, and the location and severity of bleeding. Your doctor may periodically need to check blood test results following infusion of ADVATE to be sure that the blood level of Factor VIII is high enough to allow satisfactory blood clotting. If your bleeding is not controlled after infusing ADVATE, contact your doctor immediately. ADVATE comes in five different strengths, noted as follows:

L Low	for the Low dosage strength of approximately 250 IU per vial.
M Mid	for the Medium dosage strength of approximately 500 IU per vial.
H High	for the High dosage strength of approximately 1000 IU per vial.
SH Super-high	for the Super-high dosage strength of approximately 1500 IU per vial.
UH Ultra-high	for the Ultra-High dosage strength of approximately 2000 IU per vial.

The actual potency will be imprinted on the label and on the box. Always check the potency printed on the label to make sure you are using the potency prescribed by your doctor. Always check the expiration date printed on the vial or box. You should not use the product after the expiration date printed on the vial or box. Each vial of ADVATE is for single use only. After you add the diluent to the ADVATE, it should be used within 3 hours. You should not refrigerate ADVATE after you add the diluent. Any ADVATE left in the vial at the end of your infusion should be discarded, and you should properly dispose of the needle and syringe as well.

9. How do I store ADVATE?

You must store ADVATE in powder form (without the diluent added). ADVATE should be stored in the refrigerator (2° - 8°C [36° - 46°F]). Alternatively, ADVATE may be stored at room temperature (up to 30°C [86°F]) for a period of up to six months not to exceed the expiration date. You must note the date the product is removed from refrigeration on the outer carton.

Do not use beyond the expiration date printed on the vial or 6 months past the date noted on the product carton, whichever is earliest. DO NOT FREEZE. Once ADVATE is kept at room temperature, it should remain so until infused. After storage at room temperature, the product must not be returned to the refrigerator.

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10. How can I access Baxter's patient resources?

You can contact Baxter to receive more product information:
 Product Information Hotline 1-888-4ADVATE
 Product Website www.advate.com
 You can call Baxter to receive more information on patient assistance programs available to you:
 Reimbursement Support 1-800-548-4448
 FACTOR ASSIST (insurance gap program)

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.

Pediatric Use

Use of ADVATE is being examined in the context of an ongoing study of previously treated subjects under 6 years of age and in a planned study of previously untreated subjects with severe or moderately severe Hemophilia A. In addition, pediatric subjects between 10 and 16 years of age were treated on the Phase 2/3 pivotal study, and those over 5 years of age were eligible for treatment on the ongoing Phase 2/3 surgery study. A total of 54 subjects ≤ 16 years of age have been treated across all studies of ADVATE to date. Interim pharmacokinetic data for 34 subjects (per-protocol analysis population) ≤ 16 years of age were obtained from a combined dataset comprising subjects 10 to 16 years of age treated on the Phase 2/3 pivotal study and subjects enrolled and treated on the ongoing study of pediatric previously treated subjects < 6 years of age. Among these, 0 were neonates (birth to < 1 month of age), 2 were infants (1 month to < 2 years of age), 15 were children (2 to 12 years of age), and 17 were adolescents (12 to ≤ 16 years of age). Pharmacokinetic parameters were not significantly different for the different age categories. A summary of the pharmacokinetic parameters for the 34 subjects ≤ 16 years of age in the per-protocol analysis population are shown in Table 5. The mean (± SD) plasma half-life was 11.21 ± 2.92 hours (range: 8.31- 24.7 hours). The mean AUC_{0-24h} was 1363 ± 440 IU·h/dL. The mean values for C_{max} and adjusted recovery were 109 ± 23 IU/dL and 2.17 ± 0.44 IU/dL / IU/kg, respectively.

	N	Mean	SD	Min	Max
AUC _{0-24h} (IU·h/dL)	34	1363	440	792	2398
C _{max} (IU/dL)	34	109	23	62	181
Adjusted Recovery (IU/dL/IU/kg)	34	2.17	0.44	1.23	3.39
Total AUMC (IU·h ² /dL)	34	22545	18198	7989	109633
Half-life (h)	34	11.21	2.92	8.31	24.7
Clearance (dL/kg·h)	34	0.04	0.01	0.01	0.06
Mean residence time (h)	34	14.24	4.52	8.94	34.25
V _d (dL/kg)	34	0.51	0.10	0.27	0.71

Pregnancy

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

ADVERSE REACTIONS

Adverse reactions were examined among a total of 96 subjects > 16 years of age and 54 subjects ≤ 16 years of age who received at least one infusion of ADVATE. For subjects > 16 years of age, the mean ± SD and median (range) values for time on study per subject were 319 ± 213 days and 403 days (1 to 654); the mean ± SD and median (range) exposure days to ADVATE per subject were 130 ± 84 days and 140 days (1 to 289); and the mean ± SD and median (interquartile range) IU/kg per infusion were 32.0 ± 8.27 IU/kg and 30.7 IU/kg (27.8 to 33.8).

For subjects ≤ 16 years of age, the mean ± SD and median (range) values for time on study per subject were 321 ± 210 days and 428 days (1 to 651); the mean ± SD and median (range) exposure days to ADVATE per subject were 138 ± 93 days and 181 days (1 to 284); and the mean ± SD and median (interquartile range) IU/kg per infusion were 36.5 ± 11.7 IU/kg and 33.4 IU/kg (29.7 to 40.4).

Across all clinical studies, a total of 1304 adverse events were reported among 128 of the 150 subjects who received at least 1 infusion of ADVATE. Of the 1304 adverse events, 696 were reported among 85 subjects > 16 years of age and 608 were reported among 43 subjects ≤ 16 years of age. All adverse events (product-related and unrelated) reported by at least 10% of subjects are shown in Table 6.

MedDRA System Organ Class	MedDRA Preferred Term	Number of Events	Number of Subjects	Percent of Evaluable Subjects*
Gastrointestinal disorders	Pharyngolaryngeal pain	22	17	11.3
General disorders and administration site conditions	Fall	25	19	12.7
	Pyrexia	37	25	16.7
Infections and infestations	Nasopharyngitis	32	22	14.7
Injury, poisoning and procedural complications	Accident nos	62	26	17.3
	Limb injury nos	195	52	34.7
Musculoskeletal and connective tissue disorders	Arthralgia	74	35	23.3
Nervous system disorders	Headache nos	138	44	29.3
Respiratory, thoracic and mediastinal disorders	Cough	37	23	15.3

* Percent relative to 150, the total number of subjects across all studies who received at least one infusion of ADVATE

Eighteen of the 1304 adverse events were deemed serious; none were related to the study medication. There were no deaths. Among the 1286 non-serious adverse events, only 28 in 12 subjects were judged by the investigator to be related to the study drug. Severity ratings among the 28 events were mild in 8 cases, moderate in 16 cases, and severe in 4 cases (Table 7).

Severity	MedDRA Preferred Term	Number of Events
Mild	Dysgeusia	3
	Pruritis	1
	Dizziness	1
	Catheter-related infection	1
	Rigors	1
	Headache nos	1
Moderate	Total	8
	Dysgeusia	1
	Dizziness	2
	Headache nos	1
	Hot flushes	2
	Diarrhoea nos	1
	Oedema lower limb	1
	Sweating increased	1
	Nausea	1
	Dyspnoea nos	1
	Abdominal pain upper	1
Chest pain	1	
Bleeding tendency*	1	
Haematocrit decreased	1	

Severity	MedDRA Preferred Term	Number of Events
Severe	Joint Swelling	1
	Total	16
	Headache nos	1
	Pyrexia	1
	Haematoma nos	1
	Coagulation Factor VIII decreased	1
Total	4	

* Recorded as prolonged bleeding after postoperative drain removal on the case report form

The unexpected decreased coagulation Factor VIII levels occurred in one subject during continuous infusion of ADVATE following surgery (postoperative days 10-14). Hemostasis was maintained at all times during this period and both plasma Factor VIII levels and clearance rates returned to appropriate levels by postoperative day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative.

Factor VIII inhibitor testing was performed throughout all studies in the rAHF-PFM clinical program. Among 136 treated subjects > 10 years of age, all of whom had ≥ 150 exposure days to Factor VIII products at study entry, 102 had at least 75 exposure days to ADVATE. None of these subjects developed an inhibitor. One subject who had < 50 exposure days to ADVATE while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE 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 RECOMBINATE [Antihemophilic Factor (Recombinant)]. For the group comprising all subjects with at least 75 exposure days to ADVATE and the single subject who developed an inhibitor, the 95% confidence interval (Poisson distribution) for the risk of developing an inhibitor to Factor VIII was 0.02 to 5.4%.

DOSE AND ADMINISTRATION

Each vial of ADVATE is labeled with the rAHF activity expressed in IU per vial. This potency assignment employs a Factor VIII concentrate standard that is referenced to a WHO International Standard for Factor VIII:C concentrates, 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 2. This calculation is based on the findings of several pharmacokinetic studies of rAHF concentrates,^{10,11,12,13} and is supported by the data generated by 223 pharmacokinetic studies with ADVATE in 107 Phase 2/3 pivotal study subjects. These pharmacokinetic data demonstrated a peak post-infusion recovery of approximately 1.5-2.5 IU/dL per IU/kg above the pre-infusion baseline.

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

- A dose of 1750 IU ADVATE administered to a 70 kg patient should be expected to result in a peak post-infusion Factor VIII increase of 1750 IU x [(2 IU/dL)/(IU/kg)]/[70 kg] = 50 IU/dL (50% of normal).
- A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be 70 IU/dL / [(2 IU/dL)/(IU/kg)] x 40 kg = 1400 IU.

Recommended Dose Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of hemorrhages is provided in Table 8. A guide for dosing in perioperative management is provided in Table 9. The careful control of replacement therapy is especially important in cases of major surgery or life-threatening hemorrhages.

Degree of Hemorrhage	Required Peak Post-Infusion Factor VIII Activity in the Blood (as % of Normal or IU/dL)	Frequency of Infusion
Early hemarthrosis, muscle bleeding episode, or mild oral bleeding episode.	20-40	Begin infusions every 12 to 24 hours for one to three days until the bleeding episode is resolved (as indicated by relief of pain) or healing is achieved.
More extensive hemarthrosis, muscle bleeding episode, or hematoma.	30-60	Repeat infusions every 12 to 24 hours for (usually) three days or more until pain and disability are resolved.
Life-threatening bleeding episodes such as head injury, throat bleeding episode, or severe abdominal pain.	60-100	Repeat infusions every 8 to 24 hours until resolution of the bleeding episode has occurred.

Type of Procedure	Required Peak Post-Infusion Factor VIII Activity in the Blood (as % of Normal or IU/dL)	Frequency of Infusion
Minor surgery, including tooth extraction	60-100	Give a single bolus infusion beginning within one hour of the operation, with optional additional dosing every 12 to 24 hours as needed to control bleeding. For dental procedures, adjunctive therapy may be considered.
Major surgery	80-120 (pre- and post-operative)	For bolus infusion replacement, repeat infusions every 8 to 24 hours, depending on the desired level of Factor VIII and state of wound healing.

Although dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial Factor VIII activity assays be performed on the patient's plasma at suitable intervals to assure that adequate Factor VIII levels have been reached and are maintained.

Reconstitution: Use Aseptic Technique

- Bring the ADVATE (dry factor concentrate) and Sterile Water for Injection, USP (diluent) to room temperature.
- Remove caps from the factor concentrate and diluent vials.
- Cleanse stoppers with germicidal solution, and allow to dry prior to use.
- Remove protective covering from one end of the double-ended needle and insert exposed needle through the center of the stopper.
- Remove protective covering from the other end of the double-ended needle. Invert diluent bottle over the upright ADVATE bottle, then rapidly insert the free end of the needle through the ADVATE bottle stopper at its center. The vacuum in the bottle will draw in the diluent.
- Disconnect the two bottles by removing the needle from the diluent bottle stopper, then remove the needle from the ADVATE bottle. Swirl gently until all material is dissolved. Be sure that ADVATE is completely dissolved, otherwise active materials will be removed by the filter needle.

NOTE: Do not refrigerate after reconstitution.

Administration: Use Aseptic Technique

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless in appearance. If not, do not use the solution and notify Baxter immediately. ADVATE should be administered at room temperature not more than 3 hours after reconstitution. Plastic syringes must be used with this product, since proteins such as ADVATE tend to stick to the surface of glass syringes.

- Attach filter needle to a disposable syringe and draw back plunger to admit air into the syringe.
- Insert needle into reconstituted ADVATE.
- Inject air into bottle and then withdraw the reconstituted material into the syringe.
- Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under **Administration by bolus infusion**.
- If a patient is to receive more than one bottle of ADVATE, the contents of the multiple bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. Filter needles are intended to filter the contents of a single bottle of ADVATE only.

Administration by bolus infusion

A dose of ADVATE should be administered over a period of ≤ 5 minutes (maximum infusion rate, 10 mL/min). The pulse rate should be determined 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.

HOW SUPPLIED

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

- 250 IU per vial (NDC 0944-2940-01)
- 500 IU per vial (NDC 0944-2940-02)
- 1000 IU per vial (NDC 0944-2940-03)
- 1500 IU per vial (NDC 0944-2940-04)
- 2000 IU per vial (NDC 0944-2940-10)

ADVATE is packaged with 5 mL of Sterile Water for Injection, USP, a double-ended needle, a filter needle, one full prescribing physician insert, and one patient insert.

STORAGE

ADVATE should be refrigerated (2° - 8°C [36° - 46°F]) in powder form. ADVATE may be stored at room temperature (up to 30°C [86°F]) for a period of up to 6 months not to exceed the expiration date. The date that ADVATE is removed from refrigeration should be noted on the carton. Do not use beyond the expiration date printed on the vial or six months after date labeled on the carton, whichever is earliest. After storage at room temperature, the product must not be returned to the refrigerator. Avoid freezing to prevent damage to the diluent vial.

REFERENCES

- Aledort L: Inhibitors in hemophilia patients: Current status and management. Am J Hematol 47:208-217, 1994.
- Kessler CM: An introduction to factor VIII inhibitors: The detection and quantitation. Am J Med 91 (Suppl 5A):1S-5S, 1991.
- Lusher J, Arkin S, Hurst D: Recombinant FVIII (Kogenate) treatment of previously untreated patients (PUPs) with hemophilia A. Update of safety, efficacy and inhibitor development after seven study years. Abstract no. PD-664, ISTH, Florence, Thromb Haemost (suppl.):162, 1997.
- Gruppo R, Chen H, Schroth P, Bray GL: Safety and immunogenicity of recombinant factor VIII (Recombinate) in previously untreated patients (PUPs): A 7.3 year update. Abstract no. 291, XXIII Congress of the World Federation of Haemophilia, The Hague, Haemophilia 4:228, 1998.
- Rothschild C, Laurian Y, Satre EP, et al: French previously untreated patients with severe hemophilia A after exposure to recombinant factor VIII: Incidence of inhibitor and evaluation of immune tolerance. Thromb Haemost 80:779-783, 1998.
- Gringeri A, Kreuz W, Escoriala-Etinghausen C, et al: Anti-FVIII inhibitor incidence in previously untreated patients (PUPs) with hemophilia exposed to Kogenate (G.I.P.S.I.—German-Italian PUP Study on Inhibitor). Abstract no. 2642, ISTH, Florence, Thromb Haemost (suppl.):648, 1997.
- Courter SG, Bedrosian CL: Clinical evaluation of B-domain deleted recombinant factor VIII in previously untreated patients. Semin Hematol 38:52-59, 2001.
- Scharrer I, Bray GL, Neutzing O: Incidence of inhibitors in haemophilia A patients — A review of studies of recombinant and plasma-derived factor VIII concentrates. Haemophilia 5:45-54, 1999.
- Baxter Healthcare Corporation, Westlake Village, CA, U.S.A. Data on file, 2002.
- White II GC, Courter S, Bray GL, et al: A multicenter study of recombinant factor VIII (Recombinate™) in previously treated patients with hemophilia A. Thromb Haemost 77:660-667, 1997.
- Abshire TC, Brackmann H-H, Scharrer I, et al: Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy. Thromb Haemost 83:811-816, 2000.
- Lee CA, Owens D, Bray G, et al: Pharmacokinetics of recombinant factor VIII (Recombinate) using one-stage clotting and chromogenic factor VIII assay. Thromb Haemost 82:1644-1647, 1999.
- Fijnvandraat K, Berntorp E, ten Cate JW, et al: Recombinant, B-domain deleted factor VIII (r-VIII SQ): Pharmacokinetics and initial safety aspects in hemophilia A patients. Thromb Haemost 77:298-302, 1997.

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U.S. Patent Numbers: 6,475,725; 6,100,061; 6,586,573; 6,555,391; 5,198,349; 4,757,006; 5,470,954

Baxter Healthcare Corporation

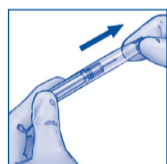
Westlake Village, CA 91362 USA

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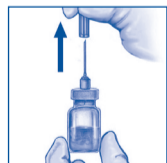
- Remove the protective covering from one end of the double-ended transfer needle.



- Insert the exposed needle through the diluent vial's stopper.



- While keeping the needle in the diluent bottle, remove the protective covering from the other end of the double-ended transfer needle.



- Insert the free end of the needle through the concentrate bottle stopper at its center. The vacuum in the bottle will draw in the diluent. Invert the diluent bottle over the upright concentrate bottle.



- Separate the two bottles by removing the needle from the diluent bottle stopper, then remove the needle from the concentrate bottle. Do not recap the needle and do not dispose in ordinary household trash. Place the needle in a hard-walled Sharps container for proper disposal.



- Swirl the factor concentrate gently and continuously until it is completely dissolved. Do not shake. Check to make sure the factor concentrate is completely dissolved. The solution should be clear and colorless in appearance. If not, do not use the

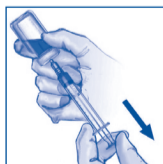
solution and notify Baxter immediately.



- Attach the filter needle to a disposable syringe and draw back the plunger to allow air into the syringe. Insert the needle into the reconstituted Factor VIII concentrate. Inject air into the bottle.



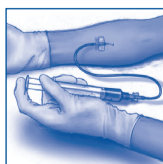
- Withdraw the solution into the syringe. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe. Use a winged infusion set, if available.



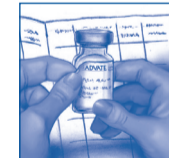
- Apply a tourniquet, and prepare the injection site by wiping the skin well with an alcohol swab (or other suitable solution suggested by your doctor or hemophilia center).



- Insert the needle into the vein, and remove the tourniquet. Infuse the factor concentrate. Do not infuse any faster than 10 mL per minute. Remove the needle from the vein and apply pressure with sterile gauze to the infusion site for several minutes. Do not recap the needle after the infusion, and do not dispose in ordinary household trash. Place it with the used syringe in a hard-walled Sharps container for proper disposal.



- After the infusion, remove the peel-off label from the factor concentrate vial and place it in your factor log book. Clean up any spilled blood with a freshly prepared mixture of 1 part bleach and 9 parts water, soap and water, or any household disinfecting solution.



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Important: Contact your doctor or local Hemophilia Treatment Center if you experience any problems. These instructions are intended as a visual aid only for those patients who have been instructed by their doctor or hemophilia center on the proper way to self-infuse the product. If you have not been taught to self-infuse by your doctor, do not attempt to self-infuse.