

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, 2000 and 3000 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/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.

Table 1.

Pharmacokinetic Parameters for ADVATE and RECOMBINATE (Per-Protocol Analysis)

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

Table 2.

Pharmacokinetic Parameters for ADVATE Before and After at Least 75 Exposure Days

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	8.38	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 (\pm SD) of 6.1 \pm 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.

Table 3.

Rate of New Bleeding Episodes During Prophylaxis

Bleeding Episode Etiology	Mean (\pm SD) New Bleeding Episodes/Subject/Month
Spontaneous	0.34 \pm 0.49
Post-traumatic	0.39 \pm 0.46
Unknown ^a	0.33 \pm 0.34
Overall	0.52 \pm 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 $\geq 80\%$ of doses (n = 70).

Baxter

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.

Table 4.
Surgical Procedures, Study Duration, and Study Medication Exposure

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 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; among this subset, there were no inhibitors.

FORMATION OF ANTIBODIES TO MOUSE OR HAMSTER PROTEIN

ADVATE contains trace amounts of mouse immunoglobulin G (MulgG; 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 MulgG. 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-MulgG ($n = 3$) antibody levels over the course of the study. A fifth study subject showed a marked increase in anti-MulgG 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 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 (\pm SD) plasma half-life was 11.21 ± 2.92 hours (range: 8.31-24.7 hours). The mean AUC_{0-48h} 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.

Table 5.
Pharmacokinetic Parameters with ADVATE in Pediatric Previously Treated Subjects
(Per-protocol Analysis)

	N	Mean	SD	Min	Max
AUC _{0-48h} (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 _{ss} (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.

Table 6.
Summary of All Adverse Experiences (Product-Related and Unrelated)
that Occurred in Greater than or Equal to 10% of Study Subjects

MedDRA System Organ Class	MedDRA Preferred Term	Number of Events	Number of Subjects	Percent of Evaluable Subjects ^a
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

^a 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).

Table 7.
Summary of Non-Serious, Study-Drug Related Adverse Events

Severity	MedDRA Preferred Term	Number of Events
Mild	Dysgeusia	3
	Pruritis	1
	Dizziness	1
	Catheter-related infection	1
	Rigors	1

Table 7.
Summary of Non-Serious, Study-Drug Related Adverse Events

	Headache nos	1
	Total	8
Moderate	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 ^a	1
	Haematocrit decreased	1
	Joint Swelling	1
	Total	16
Severe	Headache nos	1
	Pyrexia	1
	Haematoma nos	1
	Coagulation Factor VIII decreased	1
	Total	4

^a 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%.

DOSAGE 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):

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

Table 8.
Guide to ADVATE Dosing for Treatment of 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.

Table 9.
Guide to ADVATE Dosing for Surgical Procedures

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 using the BAXJECT II Device: Use Aseptic Technique

1. Bring the ADVATE (dry factor concentrate) and Sterile Water for Injection, USP (diluent) to room temperature.
2. Remove caps from the factor concentrate and diluent vials.
3. Cleanse stoppers with germicidal solution, and allow to dry prior to use. Place the vials on a flat surface.
4. Open the BAXJECT II device package by peeling away the lid, without touching the inside (Figure A). **Do not remove the device from the package.**
5. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper (Figure B).
6. Grip the BAXJECT II package at its edge and pull the package off the device (Figure C). **Do not remove the blue cap from the BAXJECT II device.** Do not touch the exposed white plastic spike.
7. Turn the system over, so that the diluent vial is on top. Quickly insert the white plastic spike fully into the ADVATE vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the ADVATE vial.
8. Swirl gently until ADVATE is completely dissolved.

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.

1. Remove the blue cap from the BAXJECT II device. Connect the syringe to the BAXJECT II device (Figure E). **DO NOT INJECT AIR.**
2. Turn the system upside down (factor concentrate vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly (Figure F).
3. Disconnect the syringe; attach a suitable needle and inject intravenously as instructed under **Administration by Bolus Infusion.**

Figure A

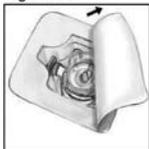


Figure B



Figure C



Figure D



Figure E

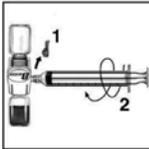
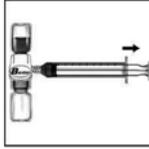


Figure F



4. If a patient is to receive more than one vial of ADVATE, the contents of multiple vials may be drawn into the same syringe. **Please note that the BAXJECT II device is intended for use with a single vial of ADVATE and Sterile Water for Injection only, therefore reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II device.**

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:

Nominal Strength	Factor VIII Potency Range	NDC Number
250 IU per vial	200 – 400 IU/vial	NDC 0944-2941-10
500 IU per vial	401 – 800 IU/vial	NDC 0944-2942-10
1000 IU per vial	801 – 1200 IU/vial	NDC 0944-2943-10
1500 IU per vial	1201 – 1800 IU/vial	NDC 0944-2944-10
2000 IU per vial	1801 – 2400 IU/vial	NDC 0944-2945-10
3000 IU per vial	2401 – 3600 IU/vial	NDC 0944-2946-10

ADVATE is packaged with 5 mL of Sterile Water for Injection, USP, a BAXJECT II Needleless Transfer Device, 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 the date noted 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

1. Aledort L: Inhibitors in hemophilia patients: Current status and management. Am J Hematol 47:208-217, 1994.
2. Kessler CM: An introduction to factor VIII inhibitors: The detection and quantitation. Am J Med 91 (Suppl 5A):1S-5S, 1991.
3. 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.
4. Gruppo R, Chen H, Schroth P, Bray GL: Safety and immunogenicity of recombinant factor VIII (Recombine) 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.
5. 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.
6. Gringeri A, Kreuz W, Escuriola-Ettinghausen C, et al: Anti-FVIII inhibitor incidence in previously untreated patients (PUPs) with hemophilia A exposed to Kogenate (G.L.P.S.I.—German-Italian PUP Study on Inhibitor). Abstract no. 2642, ISTH, Florence. Thromb Haemost (suppl.):648, 1997.
7. Courter SG, Bedrosian CL: Clinical evaluation of B-domain deleted recombinant factor VIII in previously untreated patients. Semin Hematol 38:52-59, 2001.
8. Scharrer I, Bray GL, Neutzling 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.
9. Baxter Healthcare Corporation, Westlake Village, CA. U.S.A. Data on file, 2002.
10. White II GC, Courter S, Bray GL, et al: A multicenter study of recombinant factor VIII (Recombine™) in previously treated patients with hemophilia A. Thromb Haemost 77:660-667, 1997.
11. 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.
12. Lee CA, Owens D, Bray G, et al: Pharmacokinetics of recombinant factor VIII (Recombine) using one-stage clotting and chromogenic factor VIII assay. Thromb Haemost 82:1644-1647, 1999.
13. Fijnvandraat K, Bernthorp E, ten Cate JW, et al: Recombinant, B-domain deleted factor VIII (r-VIII S0): Pharmacokinetics and initial safety aspects in hemophilia A patients. Thromb Haemost 77:298-302, 1997.

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

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

This leaflet summarizes important information about ADVATE. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about ADVATE. If you have any questions after reading this, ask your healthcare provider.



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 doctor or hemophilia center.

You must carefully follow your doctor's or other healthcare provider's instructions regarding the dose and schedule for infusing ADVATE so that your treatment will work best for you.

What is ADVATE?

ADVATE is a medicine used to replace clotting factor (Factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called "classic" hemophilia). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

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

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

Who should not use ADVATE?

You should not use ADVATE if you

- are allergic to mouse or hamster proteins.
- are allergic to any ingredients in ADVATE.

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

How should I use ADVATE?

ADVATE is given directly into the blood stream.

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 hemophilia treatment center or healthcare provider. 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 non-prescription medicines and dietary supplements.
- have any allergies, including allergies to mouse or hamster proteins.
- are nursing.
- are 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 ADVATE?

You could have an allergic reaction to ADVATE.

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

Side effects that have been reported with ADVATE include:

cough	headache	joint swelling
sore throat	fever	itching
unusual taste	dizziness	hematoma
abdominal pain	hot flashes	swelling of legs
diarrhea	chills	
nausea	sweating	

What are the ADVATE dosage strengths?

ADVATE comes in six different dosage strengths. The actual strength will be imprinted on the label and on the box. The six different strengths are coded, as follows:

Light-blue	Nominal dosage strength of approximately 250 IU per vial (200 – 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 – 1200 IU/vial).
Purple	Nominal dosage strength of approximately 1500 IU per vial (1201 – 1800 IU/vial).
Orange	Nominal dosage strength of approximately 2000 IU per vial (1801 – 2400 IU/vial).
Silver	Nominal dosage strength of approximately 3000 IU per vial (2401 – 3600 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 ADVATE?

ADVATE 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 ADVATE at room temperature:

- note the date that the product is removed from refrigeration on the box.
- do not use after six months from this date or the expiration date listed on the vial, whichever is earlier.

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 ADVATE left in the vial at the end of your infusion should be discarded.

What else should I know about ADVATE and hemophilia A?

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

Resources at Baxter available to the patients:

Contact Baxter to receive more product information:

Product Information Hotline 1-888-4ADVATE

Product Website www.advate.com

Information on patient assistance programs:

FACTOR ASSIST (insurance gap program) 1-888-BAXTER9 (1-888-229-8379)

HEMOPHILIA GALAXY (www.hemophilialgalaxy.com)

INSTRUCTIONS FOR USE

ADVATE

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

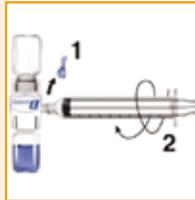
(For intravenous use only)

Do not attempt to do an infusion to yourself unless you have been taught how by your 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 ADVATE concentrate and the Sterile Water for Injection, USP (diluent) warm up to room temperature. Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.



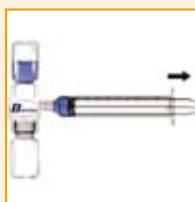
2. Remove caps from the ADVATE concentrate and diluent vials to expose the centers of the rubber stoppers.



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



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.



9. Turn over the connected vials so that the ADVATE vial is on top. Draw the ADVATE solution into the syringe by pulling back the plunger slowly. Disconnect the syringe from the vials. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.



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.**

If you are using more than one vial of ADVATE, 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 ADVATE.



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.**

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).



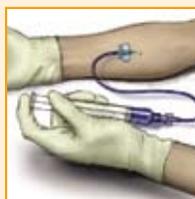
The diluent vial now has the BAXJECT II device connected to it and is ready to be connected to the ADVATE vial.



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



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



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.



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



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

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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