

ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM)

DESCRIPTION

ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM) 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 rAHF-PFM 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 rAHF-PFM is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. ADVATE rAHF-PFM is available in single-dose vials that contain nominally 250, 500, 1000 and 1500 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, 0.17 mg/mL polysorbate-80, and 0.10 mg/mL glutathione. von Willebrand Factor (vWF) is co-expressed with FVIII, 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 rAHF-PFM is labeled with the AHF 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 rAHF-PFM is 4000 to 10,000 IU per milligram of protein.

CLINICAL PHARMACOLOGY

The pharmacokinetics of ADVATE rAHF-PFM were investigated in a Phase 2/3 multicenter pivotal study of previously treated subjects. In addition, an interim analysis comparing the pharmacokinetics of ADVATE rAHF-PFM 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 rAHF-PFM were investigated in an interim analysis of an ongoing study of pediatric previously treated subjects < 6 years of age (see Pediatric Use subsection under "PRECAUTIONS").

Pharmacokinetics

A randomized, crossover pharmacokinetic comparison of ADVATE rAHF-PFM produced at a pilot-scale facility in Orth, Austria (the test article) and RECOMBINATE rAHF (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 rAHF and RECOMBINATE rAHF. 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 rAHF-PFM and RECOMBINATE rAHF (Per-Protocol Analysis)

Parameter	RECOMBINATE rAHF		ADVATE rAHF-PFM	
	N	Mean ± SD	N	Mean ^a ± 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	20.03 ± 7.80	30	22.82 ± 13.94
V _{ss} (dL/kg)	30	0.58 ± 0.15	30	0.60 ± 0.15
CL (dL/kg/hr)	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 both the per-protocol (n = 30) and intent-to-treat study (n = 50) populations. 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 vivo recovery at the onset of treatment and after ≥75 exposure days.

Additionally, the pharmacokinetics of ADVATE rAHF-PFM produced at the Orth facility were compared with those of ADVATE rAHF-PFM produced at a commercial-scale facility in Neuchatel, 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 rAHF-PFM at the onset of treatment and after a period of at least 75 exposure days. This comparison utilized data for ADVATE rAHF-PFM produced in the Orth facility obtained at the onset of treatment on the pivotal Phase 2/3 study with data for ADVATE rAHF-PFM produced in the Neuchatel 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 rAHF-PFM at the two time points.

Table 2.
Pharmacokinetic Parameters for ADVATE rAHF-PFM 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	32995	31768	10527	129569	13	28231	23573	10065	100710
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	19.15	8.40	9.80	40.56	13	18.14	5.32	9.39	29.82
V _{ss} (dL/kg)	13	0.64	0.13	0.42	0.90	13	0.68	0.16	0.43	0.94

^a Data from the Phase 2/3 pivotal study for ADVATE rAHF-PFM produced in Orth

^b Data from the Phase 2/3 continuation study for ADVATE rAHF-PFM 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 rAHF-PFM 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 rAHF-PFM, 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 rAHF-PFM 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 (\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 rAHF-PFM 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 ($n = 70$).

The Phase 2/3 continuation study involved subjects previously treated on the pivotal Phase 2/3 study and provided additional efficacy data on ADVATE rAHF-PFM. An interim analysis of efficacy was conducted for 27 of 82 enrolled subjects who self-administered ADVATE rAHF-PFM produced in Neuchâtel on a routine prophylactic regimen during a minimum period of 50 exposure days to ADVATE rAHF-PFM. As in the pivotal Phase 2/3 study, new bleeding episodes were treated with ADVATE rAHF-PFM 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 rAHF-PFM. 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 rAHF-PFM 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 rAHF-PFM 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 rAHF-PFM. 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 rAHF-PFM Exposure Days	Cumulative ADVATE rAHF-PFM 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 rAHF-PFM 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 rAHF-PFM 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 rAHF-PFM was rated as excellent or good for all assessments.

INDICATIONS AND USAGE

ADVATE rAHF-PFM is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes. ADVATE rAHF-PFM is also indicated in the perioperative management of patients with hemophilia A. ADVATE rAHF-PFM 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 rAHF-PFM should be adjusted accordingly.

ADVATE rAHF-PFM 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 rAHF-PFM (see **PRECAUTIONS**). Known intolerance or allergic reaction to any of the constituents in the formulation may be a contraindication to the use of ADVATE rAHF-PFM. ADVATE rAHF-PFM 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 rAHF-PFM. 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 rAHF-PFM. None of these subjects developed an inhibitor. One subject who had < 50 exposure days to ADVATE rAHF-PFM while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE rAHF-PFM 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 rAHF. For the group comprising all subjects with at least 75 exposure days to ADVATE rAHF-PFM 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 rAHF-PFM. Ten of the 15 enrolled subjects completed at least 10 exposure days to ADVATE rAHF-PFM or 120 total days on study; among this subset, there were no inhibitors.

Formation of Antibodies to Mouse or Hamster Protein

ADVATE rAHF-PFM contains trace amounts of mouse immunoglobulin G (MulgG; maximum of 0.1 ng/IU ADVATE rAHF-PFM) and hamster (CHO) proteins (maximum of 1.5 ng/IU ADVATE rAHF-PFM). 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 rAHF-PFM, 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 rAHF-PFM, 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 rAHF-PFM to assess its mutagenic or carcinogenic potential. The CHO cell line employed in the production of ADVATE rAHF-PFM is derived from that used in the biosynthesis of RECOMBIMATE rAHF. ADVATE rAHF-PFM has been shown to be comparable to RECOMBIMATE rAHF with respect to its biochemical and physicochemical properties, as well as its non-clinical in vivo pharmacology and toxicology.⁹ By inference, RECOMBIMATE rAHF and ADVATE rAHF-PFM would be expected to have equivalent mutagenic and carcinogenic potential.

RECOMBIMATE rAHF 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 rAHF-PFM 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 rAHF-PFM 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_{0-48h} 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.

	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	36823	47250	9749	283097
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	19.79	9.92	10.70	66.66
V _{ss} (dL/kg)	34	0.64	0.12	0.32	0.86

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ADVATE rAHF-PFM. It is not known whether ADVATE rAHF-PFM can cause fetal harm when administered to a pregnant woman, or whether it can affect reproductive capacity. ADVATE rAHF-PFM 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 rAHF-PFM. 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 rAHF-PFM 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 rAHF-PFM 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 rAHF-PFM. 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 ^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 rAHF-PFM

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
	Total	8
	Moderate	Dysgeusia
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 rAHF-PFM 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 rAHF-PFM. None of these subjects developed an inhibitor.

One subject who had < 50 exposure days to ADVATE rAHF-PFM while on study developed an inhibitor. This subject manifested a low titer inhibitor (2.0 BU by the Bethesda assay) after 26 ADVATE rAHF-PFM 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 rAHF. For the group comprising all subjects with at least 75 exposure days to ADVATE rAHF-PFM 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 rAHF-PFM 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 rAHF-PFM 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 1,750 IU ADVATE rAHF-PFM administered to a 70 kg patient should be expected to result in a peak post-infusion Factor VIII increase of $1750 \text{ IU} \times \{[2 \text{ IU/dL}] / [\text{IU/kg}]\} / [70 \text{ kg}] = 50 \text{ IU/dL}$ (50% of normal).
2. A peak level of 70% is required in a 40 kg child. In this situation, the appropriate dose would be $70 \text{ IU/dL} \times \{[2 \text{ IU/dL}] / [\text{IU/kg}]\} \times 40 \text{ kg} = 1400 \text{ IU}$.

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.

Table 9.
Guide to ADVATE rAHF-PFM 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 – 24 hours as needed to control bleeding. For dental procedures, adjunctive 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

1. Bring the ADVATE rAHF-PFM (dry concentrate) and Sterile Water for Injection (diluent) to room temperature.
2. Remove caps from the concentrate and diluent vials.
3. Cleanse stoppers with germicidal solution, and allow to dry prior to use.
4. Remove protective covering from one end of the double-ended needle and insert exposed needle through the center of the stopper.
5. Remove protective covering from the other end of the double-ended needle. Invert diluent bottle over the upright ADVATE rAHF-PFM bottle, then rapidly insert the free end of the needle through the ADVATE rAHF-PFM bottle stopper at its center. The vacuum in the bottle will draw in the diluent.
6. Disconnect the two bottles by removing the needle from the diluent bottle stopper, then remove the needle from the ADVATE rAHF-PFM bottle. Swirl gently until all material is dissolved. Be sure that ADVATE rAHF-PFM 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. A colorless appearance is acceptable for ADVATE rAHF-PFM. ADVATE rAHF-PFM 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 rAHF-PFM tend to stick to the surface of 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 ADVATE rAHF-PFM.
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 **Administration by bolus infusion.**
5. If a patient is to receive more than one bottle of ADVATE rAHF-PFM, 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 rAHF-PFM only.

Administration by bolus infusion

A dose of ADVATE rAHF-PFM 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 rAHF-PFM. 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 rAHF-PFM is available in single-dose vials that contain nominally 250, 500, 1000, and 1500 IU per vial. ADVATE rAHF-PFM is packaged with 5 mL of Sterile Water for Injection, a double-ended needle, a filter needle, infusion set/blood collection set*, 10 mL sterile syringe, alcohol swabs, bandages, one full prescribing physician insert, and one patient insert.

STORAGE

ADVATE rAHF-PFM should be refrigerated (2° - 8°C [36° - 46°F]). Avoid freezing to prevent damage to the diluent vial. ADVATE rAHF-PFM may be stored at room temperature (22° - 28°C [72° - 82°F]) for a period of up to 6 months until the expiration date. Do not use beyond the expiration date printed on the vial.

* Approved for both indications under 510(k).

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