Item Number: LE-07-60786	**Version:** 2		**Swatches**
Profile: 0400374_1_PIL_Drwg **Technical Specification:** LE0400374 **Artwork Dimensions/Size:** 310 x 446 mm			**Front**: PANTONE 259 C, Black **Back**: Black
Graphics House: Perigord **Date:** 01MAR2024			**Visible / Not Printed*:** Dieline, Technical Info
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ADVATE

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

LE-07-60786

ADVATE

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

Product Information

Name of the drug: ADVATE 250 IU, 500 IU, 1000 IU, 1500 IU

Chemical Name: Recombinant Coagulation Factor VIII (rch)
INN: Octocog Alfa
Laboratory Code: Recombinant Antihaemophilic FVIII, Plasma/Albumin Free Method (rAHF-PFM)

Composition: Table 1: **Unit Formulation**
Powder for intravenous injection, after reconstitution with Sterile Water for Injection to 5 mL. The amounts of the inactive ingredients are constant in all strengths.

ADVATE	250 IU	500 IU	1000 IU	1500 IU
Active Ingredient Octocog alfa [Recombinant Coagulation FVIII (rch)]	250 IU	500 IU	1000 IU	1500 IU
Inactive Ingredient:	(mg)	(mg)	(mg)	(mg)
Trehalose	40.0	40.0	40.0	40.0
Histidine	8.0	8.0	8.0	8.0
Trometamol	6.0	6.0	6.0	6.0
Sodium Chloride	26.5	26.5	26.5	26.5
Calcium Chloride	1.0	1.0	1.0	1.0
Glutathione (reduced)	0.4	0.4	0.4	0.4
Polysorbate 80	0.5	0.5	0.5	0.5
Mannitol	160.0	160.0	160.0	160.0

Description

ADVATE is formulated as a sterile, non-pyrogenic, white to off-white, lyophilised powder preparation of Recombinant Antihaemophilic Factor VIII. It is produced from a genetically engineered Chinese Hamster Ovary (CHO) cell-line under conditions, which are free from the use of animal derived protein. ADVATE (rAHF-PFM) is presented in a glass vial accompanied by sterile Water for Injection (5 mL) for reconstitution (see **Dosage and Administration**). The reconstituted product is a clear, colourless solution for intravenous (IV) injection. After reconstitution, the product contains 0.45 mmol (10 mg) sodium per vial.
Trehalose, a disaccharide of two glucose molecules linked by an α, α, glucopyranose of glycoside bond has been used as a stabiliser in the formulation, instead of human albumin as shown in Table 1. The active ingredient, rAHF-PFM, has been manufactured by a method that is free from the use of animal or human derived proteins. This manufacturing process provides a low risk of transmission of bloodborne viruses derived from exogenous human and animal origins.
The molecular integrity and biological activity of rAHF-PFM is indistinguishable from that of the first generation of recombinant Antihaemophilic Factor VIII (rAHF). They differ on the culture media used during the manufacturing process and the cell lines.
In the first generation of rAHF production, the cell lines are grown in a culture medium containing animal/human derived proteins, whereas in the rAHF-PFM production, the cell lines are adapted to grow without using animal/human components. The CHO cells transfected with Factor VIII gene, express Factor VIII within the cell as a glycosylated protein, rAHF-PFM, which is subsequently secreted into the culture medium. The isolation and purification of the rAHF-PFM from the culture medium is basically the same as in the first generation, rAHF, using a series of immunoaffinity chromatography column. In this process, the purification matrix packed into the column was produced by immobilisation of monoclonal antibodies directed to Factor VIII to a carrier, which selectively binds the rAHF-PFM. It is followed by the elution of the bound rAHF-PFM from the matrix and subsequently the eluate is subjected to a series of ion-exchange column chromatography procedures to remove the buffer components.
The potency (IU) is determined using the one-stage clotting assay or by chromogenic method (EP), against an in-house standard that is referenced to the FDA/US Mega I Standard. The latter was calibrated against the third WHO standard.

Chemical Structure

The chemical structure of rAHF-PFM is that of a dimeric glycoprotein, which has been shown to have a similar amino acid sequence with that of the human plasma derived Factor VIII. Amino acid analysis of the purified glycosylated protein demonstrated that it constitutes 2332 amino acids with a molecular mass of approximately 280 kDa. Thus, the rAHF-PFM is a full length Factor VIII.

Pharmacology

General

Under normal physiological conditions, Factor VIII is essential for blood clotting and haemostasis. The activated Factor VIII (FVIIIa) acts as a cofactor for activating Factor IX to IXa cascading to activate Factor X to Xa. By the actions of the activated factors Va and Xa, circulating pro-thrombin is converted into thrombin. Subsequently, thrombin converts fibrinogen to fibrin monomer cascading to formation of linear fibrin polymer.
By the action of Factor XIII the fibrin monomer is cross-linked to form fibrin clots leading to the arrest of bleeding episodes. In patients with haemophilia A (classical haemophilia), a sex-linked hereditary disorder of blood coagulation, the level of circulating Factor VIII is decreased, leading to profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. The use of plasma-derived or recombinant derived Factor VIII has been shown successfully to correct this deficiency. Thus, plasma derived and recombinant derived Factor VIII have the same pharmacological actions.

Pharmacodynamics

Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII activity and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. The plasma levels of Factor VIII are increased by replacement therapy, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendency. The level required to achieve adequate haemostasis varies depending on anatomic location and severity of traumatic insult, if present.

Pharmacokinetics

All pharmacokinetics (PK) studies with ADVATE were conducted in patients with severe to moderately severe haemophilia A (baseline Factor VIII ≤ 2%). A total of 260 subjects provided PK parameters that were included in the full PK analysis set. From this analysis set, 208 subjects provided PK parameters included in the per protocol PK and analysis set. Categories of these analyses for infants (1 month to <2 years of age), children (2 to <12 years of age), adolescents (12 to <16 years of age), and adults (16 years of age and older) were used to summarise PK parameters, where age was defined as age at time of PK infusion.

Table 2
Summary of Pharmacokinetic Parameters of ADVATE per Age Group

Parameter (Mean ± Standard Deviation)	Infants (n = 7)	Children (n = 56)	Adolescents (n = 35)	Adults[a] (n = 162)
Total AUC (IU*.hr/dL)	1240 ± 330	1263.40 ± 470.90	1300 ± 49	1554.88 ± 507.92
Adjusted Incremental Recovery at C_{max} (IU/dL per IU/kg)[b]	2.07 ± 0.54	1.91 ± 0.50	2.05 ± 0.49	2.23 ± 0.61
Half-life (hr)	8.67 ± 1.43	10.22 ± 2.72	12.00 ± 2.92	12.96 ± 4.02
Maximum Plasma Concentration Post Infusion (IU/dL)	104 ± 27	97.16 ± 27.13	103 ± 25	112.35 ± 30.27
Mean Residence Time (hr)	10.42 ± 2.54	12.87 ± 3.70	14.89 ± 4.61	16.37 ± 5.80
Volume of Distribution at Steady State [Vss] (dL/kg)	0.43 ± 0.10	0.55 ± 0.15	0.60 ± 0.14	0.55 ± 0.17
Clearance (mL/kg*hr)	4.26 ± 1.00	4.53 ± 1.51	4.21 ± 1.16	3.56 ± 1.21

[a] 162 subjects provided PK assessments.
[b] Calculated as (Cmax – baseline Factor VIII) divided by the dose in IU/kg, where Cmax is the maximal post-infusion Factor VIII measurement.

Absorption

Refer to Table 2 for a summary of the adjusted recovery, AUC, and Vss in the infant, child, adolescent and adult populations.

Distribution

When infused into a haemophilia patient, ADVATE binds to endogenous von Willebrand factor in the patient's circulation. The Factor VIII/von Willebrand factor complex is distributed primarily in the intravascular space.

Metabolism

Not applicable.

Elimination

Factor VIII clearance is mediated by vascular receptors, including low-density lipoprotein receptor-related protein (LPR) and heparin sulphate proteoglycans (HSPGs), by mechanisms that have been fully elucidated.

Clinical Studies

Original Safety and Efficacy Study: 069901
The safety, haemostatic efficacy and immunogenicity of ADVATE were evaluated in an open label study in 111 subjects aged 10 years and older. The trial is conducted in previously treated subjects (PTPs with ≥ 150 exposure days) diagnosed with moderate to severe haemophilia A (FVIII level ≤ 2% of normal) who were ≥ 10 years of age (20 were 10 to < 13, 22 were 13 to <16, and 69 were 16 years and older). Subjects with a history of, or a detectable FVIII were excluded.
Subjects self-administered ADVATE for routine prophylaxis (≥ 25 IU/kg body weight 3 – 4 times per week) and for the on-demand treatment of bleeding episodes. A global assessment of efficacy was rendered either by the subject (for home treatment) or study site investigator (for treatment under medical supervision) using a scale of excellent, good, fair, or none, based on the quality of haemostasis achieved with ADVATE (rAHF-PFM) 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 the 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%) received 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.

Table 3: Haemostatic Efficacy Results from 069901

End point	Results in 510 new bleeding episodes treated with ADVATE 162 (32%) spontaneous, 228 (45%) antecedent trauma, 120 (24%) unknown etiology
Quality of haemostasis	Excellent or good response: 439 (86%) Fair response: 61 (12%) No response: 1 (0.2%) Unknown response: 9 (2%)
Number of infusion required	Single infusion (1): 411 (81%) Two (2) infusions: 62 (12%) Three (3) infusions: 15 (3%) Four (4) or more infusions: 22 (4%)

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

Table 4: rate of New Bleeding Episodes During Prophylaxis

Bleeding Episode Etiology	Mean (± SD) New Bleeding Episodes/Subjects/Month
Spontaneous	0.34 ± 0.49
Post Traumatic	0.39 ± 0.46
Unknown*)	0.33 ± 0.34
Overall	0.52 ± 0.71

*) Etiology was indeterminate

In a post-hoc analysis, the overall rate of bleeding was correlated 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 prescribed prophylactic regimen at least 80% of the time and at ≥ 80% of the prescribed dose (n=70).
The phase 2/3 continuation study involved subjects previously treated in the pivotal Phase 2/3 study and provided additional data on ADVATE (rAHF-PFM). An interim analysis of efficacy was conducted for 27 of 82 enrolled subjects who self-administered ADVATE (rAHF-PFM) on routine prophylactic regimen during a minimum period of 50 exposures 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 the treatment was rated as excellent, good, fair, or none, based on the quality of haemostasis 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 remaining 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 the bleeding episodes required 1 or 2 infusions of study product.
An interim analysis of the haemostatic 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 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 orthopaedic complications of haemophilia. A brief description of each surgical procedure, along with study duration and study medication exposure, are presented in Table 5.

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

Table 5 Surgical Procedures, Study Duration, and Study Medication Exposure

Surgery Type	Days of Study	ADVATE (rAHF-PHM) 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*	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*	32,334
Wisdom teeth Extraction	14	5	15,257

* 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 haemostasis with ADVATE (rAHF-PFM) was assessed by operating surgeon and study site investigator, respectively, using ordinal scale of excellent, good, fair, or none. The same rating scale was used to evaluate control of haemorrhage from a surgical drain placed at the incision site in one subject. The quality of haemostasis achieved with ADVATE (rAHF-PFM) was rated as excellent or good for all assessments.

Indications

ADVATE is indicated for use in haemophilia A for prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with ADVATE as perioperative management. ADVATE is not indicated in von Willebrand's disease.

Contra-indications

Known hypersensitivity to any active substance, to excipients, or to mouse or hamster proteins.

Precautions

Hypersensitivity reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE and have been manifested by dizziness, paraesthesia, rash, flushing, face swelling, urticaria, and pruritis. If these symptoms occur, patients should be advised to discontinue use of the product immediately and contact their physicians. In the case of anaphylactic shock, the current medical standards for shock treatment should be implemented.

Inhibitor formation

The development of neutralising antibodies (inhibitors) to Factor VIII is a known complication of the treatment of patients with Haemophilia A. In particular when the subject has not been treated with antihaemophilic Factor VIII previously, the chance of antibodies formation is high. These inhibitors are usually IgG immunoglobulins directed against Factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified Bethesda assay.
The risk of developing inhibitors is correlated to the extent of exposure to the Factor VIII, the risk is being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with ADVATE should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. Among 136 treated subjects greater or equal to 10 years of age, all of whom had >150 exposure days to Factor VIII 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 the study developed an inhibitor. This subject manifested a low titre inhibitor (2.0 BU by the Bethesda assay) after 26 exposure days with ADVATE (rAHF-PFM).

Inhibitors have predominantly been reported in previously untreated patients.
In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

Antibodies against Mouse or Hamster (CHO) proteins

ADVATE (rAHF-PFM) contains trace amounts of mouse immunoglobulin G (MuIgG); maximum level of 0.1 ng/IU and hamster (CHO) proteins (maximum levels of 1.5 ng/ IU). As such, there exists a remote possibility that patients treated with this product may develop hypersensitivity to these non-human derived proteins.
In the Phase 2/3 pivotal study of ADVATE (rAHF-PFM), serum samples were tested by enzyme immunoassays at base line and after every 15 ± 2 days for the presence of antibodies to CHO proteins and MuIgG. 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 day interval study visits. None of these subjects exhibited adverse experiences (AEs) or other study findings consistent with an allergic or hypersensitivity response.

Pregnancy, Lactation, and Fertility

The safety of ADVATE for use in pregnant or lactating women has not been established. Animal reproduction studies have not been conducted with ADVATE. It is not known whether ADVATE can cause foetal harm when administered to a pregnant woman, or whether it can affect reproductive capacity. Physicians should balance the potential risks and only prescribe ADVATE if clearly needed.

The effects of ADVATE on fertility have not been established.

Paediatric Patients

The safety and haemostatic efficacy of ADVATE in this population are similar to that of adult patients. Adjusted recovery and terminal half-life was approximately 20% lower in children than in adults. (See **Pharmacokinetics**)

Interactions with other drugs

No interactions studies have been performed with ADVATE.*

*None known based upon the absence of data from clinical trials, current medical/scientific literature, and most marketing safety reports.

Effects on Ability to Drive and Use Machines

There is no information on the effects of ADVATE on the ability to drive or operate an automobile or other heavy machinery.

Adverse Reactions

Adverse Reactions from Clinical Trial

Clinical studies with ADVATE enrolled 450 unique subjects. The safety analysis set included 418 subjects with at least one exposure to ADVATE from 12 clinical studies: 069901, 060102, BLB-200-01, 060101, 060401, 069902, 060201, 060103, 060403, 060702, 060601, and 060801.

A total of 93 adverse reactions (ADR) were reported in 45 of the 418 unique treated subjects. The most common adverse reaction included FVIII inhibition, pyrexia, and headache. Of these, 17 ADRs for FVIII inhibition were considered serious. Factor VIII inhibition was the most frequent ADR that was reported in 4.1% of treated subjects (n=17). Of the 93 ADRs, none were reported in neonates (0 to < 1 month of age), 30 ADRs were reported in 20/60 infants (1 month to <2 years of age), 7 ADRs were reported in 3/68 children (2 to <12 years of age), 10 ADRs were reported in 5/38 adolescents (12 to <16 years of age), and 46 ADRs were reported in 17/147 adults (16 years of age and older).

Table 6
ADVATE CCDS Clinical Study Adverse Reactions[a]

System Organ Class (SOC)	Preferred MedDRA Term (Version 23)	Number of Unique Subjects N = 418	ADR Rate (% of subjects)[b]	Frequency Category
INFECTIONS AND INFESTATIONS	Influenza	1	0.24	Uncommon
	Laryngitis	1	0.24	Uncommon
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Factor VIII inhibition[c]	1 (PTP[d]) 16 (PUPs[d])	0.28 29.09	Uncommon Very Common
	Lymphangitis	1	0.24	Uncommon
NERVOUS SYSTEM DISORDERS	Headache	7	1.67	Common
	Dizziness	4	0.96	Uncommon
	Dysgeusia	1	0.24	Uncommon
	Memory impairment	1	0.24	Uncommon
	Migraine	1	0.24	Uncommon
	Syncope	1	0.24	Uncommon
	Tremor	1	0.24	Uncommon
EYE DISORDERS	Eye inflammation	1	0.24	Uncommon
CARDIAC DISORDERS	Palpitations	1	0.24	Uncommon
VASCULAR DISORDERS	Haematoma	1	0.24	Uncommon
	Hot flush	2	0.48	Uncommon
	Pallor	1	0.24	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnoea	2	0.48	Uncommon
GASTROINTESTINAL DISORDERS	Abdominal pain upper	2	0.48	Uncommon
	Diarrhoea	2	0.48	Uncommon
	Nausea	1	0.24	Uncommon
	Vomiting	1	0.24	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	2	0.48	Uncommon
	Pruritus	2	0.48	Uncommon
	Rash	4	0.96	Uncommon
	Urticaria	1	0.24	Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia	6	1.44	Common
	Chest discomfort	1	0.24	Uncommon
	Chest pain	1	0.24	Uncommon
	Chills	1	0.24	Uncommon
	Felling abnormal	1	0.24	Uncommon
	Peripheral oedema	1	0.24	Uncommon
	Vessel puncture site haematoma	1	0.24	Uncommon
INVESTIGATIONS	Coagulation factor VIII level decreased	1	0.24	Uncommon
	Haematocrit decreased	1	0.24	Uncommon
	Laboratory test abnormal	1	0.24	Uncommon
	Monocyte count increased	1	0.24	Uncommon
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Post procedural complication	1	0.24	Uncommon
	Post procedural haemorrhage	1	0.24	Uncommon
	Procedural site reaction	1	0.24	Uncommon

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)
[a] ADRs are defined as all ADRs related to investigational product: 93.
[b] Percent is based on total number of subjects who received ADVATE: 418.
[c] In study 060103 (PUP), 16 subjects reported an ADR for inhibitor development. In study 060201, one subject reported an ADR for inhibitor development that was not confirmed. In study 069901, one subject had an inhibitor that was not reported as an ADR. In total, there were 17 confirmed inhibitors reported in 17 subjects.
[d] Of the 418 unique subjects, 363 are PTPs and 55 are PUPs

Immunogenicity
A total of 276 patients, diagnosed with severe to moderately severe haemophilia A (FVIII ≤2%), entered studies that required a minimum of 150 exposure days in adults and older children and 50 exposure days in children < 6 years of age to Factor VIII concentrates prior to participation. Among these patients, one displayed evidence of a Factor VIII inhibitor. This subject manifested a low titre inhibitor (2.0 BU by the Bethesda assay) after 26 exposure days. Follow-up inhibitor tests in this subject after withdrawal from the study were negative. Across all studies, median exposure to ADVATE was 97.0 exposure days per subject (range 1 to 709) for previously treated patients. The overall incidence and 95% CI of any FVIII inhibitor development (low or high) was 0.36% (1 of 276), the 95% CIs: 0.009 to 2.002% based on 276 previously treated patients. The incident results for low titre and overall titre (low and high) were the same. The high titre incidence and 95% CI of FVIII inhibitor development was 0.00% (0 of 276), the 95% CIs: 0.000 to 1.328%.

In addition, 16 out of 55 previously untreated patients developed FVIII inhibitors: 7 subjects developed high-titre inhibitors and 9 subjects developed low-titre inhibitors, 1 of which was also classified as a transient inhibitor.

Post-Marketing Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These adverse reactions are listed by preferred MedDRA term in order of severity.

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity (See **Special warnings and precautions for use**)

GENERAL AND ADMINISTRATION SITE CONDITIONS: Injection site reaction, Fatigue, Malaise

Dosage and Administration

Treatment should be initiated under the supervision of a physician experienced in the management of haemophilia.

Dosage:

The dosage and duration of the substitution therapy depend on the severity of Factor VIII deficiency, the location and the extent of the bleeding and on the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening haemorrhages.
The dose of Factor VIII administered is expressed in International Unit (IU), which is related to the WHO standard for Factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IUs (relative to the international Standard for Factor VIII in plasma).
One IU of Factor VIII activity is equivalent to that quantity of Factor VIII in one mL of normal human plasma. The calculation of the required dosage of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by 2 IU/dL. The dose is determined using the following formula and table.

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

Formula: Required units (IU) =
body weight (kg) x desired factor VIII rise (%) x 0.5

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (% or IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage: Early haemorthosis, muscle bleeding or oral bleeding	20 – 40	Repeat infusions every 12 to 24 Hours for at least 1 day, until the bleeding episode, as indicated by pain is resolved or healing is achieved.
More extensive haemorthosis, muscle bleeding or haematoma	30 – 60	Repeat infusions every 12 – 24 hours for 3 – 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60 – 100	Repeat infusions every 8 to 24 hours until threat is resolved.
Surgical:		
Minor, including both extraction	30 – 60	Every 24 hours, at least 1 day until healing is achieved.
Major:	80 – 100 (pre- and postoperative)	Repeat infusions every 8 – 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a Factor VIII activity of 30% to 60% (IU/dL)

In case of the haemorrhagic events as shown in the table, the Factor VIII activity should not fall below the given plasma activity level (in % normal or IU/dL) in the corresponding period. The above table can be used to guide dosing in bleeding episodes and surgery.
The amount and frequency of administration should be adapted to the clinical effectiveness of the product in the individual case. Under certain circumstances (e.g., presence of a low titre inhibitor) doses larger than those recommended may be necessary.
During the course of treatment, appropriate determination of plasma Factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions.
If bleeding is not controlled with the recommended dose, the plasma level of Factor VIII should be determined and with a sufficient dose of ADVATE should be administered to achieve a satisfactory clinical response.
In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of plasma Factor VIII activity assay is indispensable. Individual patients may vary in their response to Factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives.
For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of Factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary. There are data on 13 pediatric patients collected on the use of ADVATE.

Patients with inhibitors

Patients should be evaluated for the development of Factor VIII inhibitors, if the expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose. In patients with high levels of inhibitor, Factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia A. (see **Precautions**, under subheading **Inhibitor formation**)

Laboratory tests

Although dosage 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. If the patient's plasma Factor VIII fails to reach the expected levels or if bleeding is not controlled after adequate dosage, the presence of inhibitor should be suspected. By performing appropriate laboratory investigations, the presence of an inhibitor can be demonstrated and quantified in terms of IU Factor VIII neutralised by each mL of plasma. If the inhibitor is present at a level of less than 10 BU/mL, administration of additional Factor VIII may neutralise the inhibitor. Thereafter, the administration of additional Factor VIII should elicit the predicted response. The control of Factor VIII and inhibitor levels by laboratory assays is necessary in this situation. Inhibitor titres above 10 BU/mL may make haemostatic control with Factor VIII either impossible or impractical because of the large dose required. In addition, the inhibitor titre may rise following AHF infusion because of an anamnestic response to Factor VIII.

Nature and contents of container

ADVATE powder and the solvent come in single-dose 5 mL vials of neutral borosilicate glass hydrolytic type I. The product vials are closed with Teflon coated butyl rubber stoppers and the solvent vials are closed with chlorobutyl or bromobutyl rubber stoppers. Each vial is labelled for potency in IU, and is packaged together with 5 mL of sterilised water for injection, 1 BAXJECT II device for reconstitution, 1 mini-infusion set, 1 of 10 mL sterile disposable syringe for administration, 2 alcohol swabs and 2 plasters.

Instructions for use, handling and disposal

The preparation is to be administered intravenously after reconstitution with the provided sterilised water for injection. Do not use after the expiry date printed on the label. Use within 3 hours after reconstitution. Do not refrigerate the preparation after reconstitution. Discard any unused preparation appropriately.

Reconstitution using the BAXJECT II Device: Use Aseptic Technique

1. Bring the ADVATE (dry factor concentrate) and Sterile Water for Injection (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. A colourless appearance is acceptable for ADVATE. 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. It is strongly recommended that every time ADVATE is administered, the patient name and batch number of the product are recorded to maintain a link between the patient and the batch of the product.

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**.
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 reconstitution 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 reconstitution device.**

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

Administration by Bolus Infusion

A dose of ADVATE should be administered over a period of ≤ 5 minutes. The rate of administration should be a rate that ensures the comfort of the patient, up to a maximum of 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.

Figure A

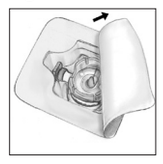


Figure B

Figure C

Figure D

Figure E

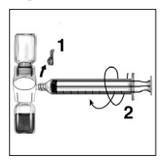
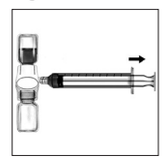


Figure F



Administration by continuous infusion

The 1500, 1000 and 500 IU/vial nominal potency of ADVATE are suitable for use in a continuous infusion mode of administration. Continuous infusion of ADVATE must employ either a syringe pump running at a rate of greater than or equal to 0.4 mL/ hour, or a CADD-1 type infusion pump running at a rate of 1.5 mL/hour.
In vitro studies employing a syringe pump or CADD-1 pump have demonstrated > 80% of the hour 0 potency of ADVATE for up to 48 hours of continuous infusion. For sterility assurance purposes, a fresh supply of reconstituted ADVATE for continuous infusion (prepared under laminar air flow conditions) should be replaced at bedside no less frequently than every 12 hours. The post-reconstitution photostability of ADVATE is acceptable under the conditions of visible and ultra-violet light exposure in a clinical setting. It is highly recommended that Factor VIII levels be checked within 3 to 6 hours after the initiation of continuous infusion in order to document that the desired Factor VIII levels are being maintained. Rates of infusion should be modified based on the levels of plasma Factor VIII activity measured at least once per day thereafter and based on the desired level of Factor VIII.

Overdosage

Of all infusions administered during clinical studies, 0.9% of infusions were >100 IU/kg.
No safety concerns were identified with these infusions. No subject received a dose >208 IU/kg in these studies.

Non-Clinical Studies

Carcinogenesis, Mutagenesis

No studies were conducted with the active ingredient in ADVATE to assess its mutagenic or carcinogenic potential. Its mechanism of action and nature do not suggest that ADVATE interacts directly with the DNA or any other chromosomal material and hence this biological product is not considered to have any genotoxic potential. ADVATE is a recombinant protein and is not considered to be mutagenic nor clastogenic, or have any carcinogenic potential based on the pharmacological based on the pharmacological mode of action. The CHO cell line employed in the production of ADVATE is derived from that used in the biosynthesis of RECOMBINATE rAHF. ADVATE has been shown to be comparable to RECOMBINATE rAHF with respect to its biochemical and physicochemical properties, as well as its non-clinical *in vivo* pharmacology and toxicology. By inference, RECOMBINATE rAHF and ADVATE would be expected to have equivalent mutagenic and carcinogenic potential. RECOMBINATE 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.

Reproductive Toxicology

Animal reproductive studies have not been performed. Due to the immune response to heterologous proteins in animals after repeated dosing and due to the risk of incompatibility reactions based on an antigen-antibody reaction, reproductive and development toxicity studies would not be representative for the situation in humans.

Animal Toxicology and/or Pharmacology

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, acute toxicology, repeated dose toxicology, local toxicology and genotoxicity.

Incompatibilities

ADVATE must not be mixed with other medicinal products or solvents.

Presentation

ADVATE is formulated as a sterile, nonpyrogenic, off-white, lyophilised powder, for intravenous injection. It is supplied in single-dose glass vials containing nominally 250, 500, 1000 or 1500 IU per vial and a diluent for reconstitution. The diluent is sterilised Water for Injection comes in single-dose of 5 mL vials of neutral borosilicate glass hydrolytic type I with nominal volume of 5.4 mL and with a minimum extractable volume of 5 mL.

***Needleless Transfer Device* (BAXJECT II):** the product is accompanied by a needleless transfer device designed for transferring and mixing drugs contained in two vials (product and diluent). Each Needleless Transfer Device has a two-vial holder, a two-sided siliconised piercing plastic spike for penetration into the rubber stoppers of the two vials, a stopcock with an embedded/filter, and a female port designed for connection to a syringe (Fig A-F).

Shelf life: 2 years. The product is stable for the duration of the specified shelf life when stored in the specified temperature storage condition. ADVATE should be administered at room temperature not more than 3 hours after reconstitution. For single use only. Discard unused portion of the product.

***Storage*: ADVATE** should be stored at 2°C – 8°C for the duration of its shelf life. Do not freeze. In the case of a need for ambulatory use, ADVATE may be kept at or below 25°C (room temperature) for a single period of up to 6 months and then discarded.
After ADVATE has been stored at room temperature, it should not be re-refrigerated.
Do not use beyond the expiration date printed on the label. Protect from light.

Product Owner:
Takeda Manufacturing Austria AG,
Vienna, Austria.

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