

# ADVATE

***Recombinant Coagulation Factor VIII (rch)***

***INN: Octocog Alfa***

***Laboratory Code: Recombinant Antihemophilic FVIII***

***Plasma/Albumin-Free Method (rAHF-PFM)***

## NAME OF THE DRUG

ADVATE 250IU powder and diluent for solution for injection.

ADVATE 500IU powder and diluent for solution for injection.

ADVATE 1000IU powder and diluent for solution for injection.

ADVATE 1500IU powder and diluent for solution for injection.

ADVATE 2000IU powder and diluent for solution for injection.

ADVATE 3000IU powder and diluent for solution for injection.

## COMPOSITION

Powder for intravenous injection, after reconstitution with Water for Injection to 5mL. The amounts of the inactive ingredients are constant in all strengths.

<b>Table 1: Unit Formulation</b>						
<b>ADVATE</b>	<b>250IU</b>	<b>500IU</b>	<b>1000IU</b>	<b>1500IU</b>	<b>2000IU</b>	<b>3000IU</b>
<b>Active ingredient:</b> Octocog alfa [Recombinant Coagulation FVIII (rch)]	250IU	500IU	1000IU	1500IU	2000IU	3000IU
<b>Inactive ingredient:</b>	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Trehalose	40.0	40.0	40.0	40.0	40.0	40.0
Histidine	8.0	8.0	8.0	8.0	8.0	8.0
Trometamol	6.0	6.0	6.0	6.0	6.0	6.0
Sodium Chloride	26.5	26.5	26.5	26.5	26.5	26.5
Calcium Chloride	1.3	1.3	1.3	1.3	1.3	1.3
Glutathione (reduced)	0.4	0.4	0.4	0.4	0.4	0.4
Polysorbate 80	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol	160.0	160.0	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 (5mL) for reconstitution (see *Dosage and Administration*). The reconstituted product is a clear, colourless solution for intravenous (IV) injection.

Trehalose, a disaccharide of two glucose molecules linked by an  $\alpha, \alpha$ , 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 blood-borne 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. The specific activity is approximately 4,000 - 10,000IU/mg protein.

## 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 280kDa. 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.

## Pharmacokinetics

A randomized, crossover pharmacokinetic comparison of ADVATE (rAHF-PFM) and RECOMBINATE (rAHF) was conducted in the context of a pivotal Phase 2/3 study. Pharmacokinetic parameters area under the plasma curve versus time (AUC), C<sub>max</sub>, mean residence time (MRT) and volume distribution in steady state [V<sub>ss</sub>] 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. The results are shown in Table 2.

**Table 2: Pharmacokinetic Parameters for ADVATE (rAHF-PFM) and RECOMBINATE (rAHF)**

Parameters	RECOMBINATE (rAHF)		ADVATE (rAHF-PFM)	
	N	Mean ± sd	N	Mean ± sd
AUC <sub>0-48h</sub> (IU·h/dL)	30	1530 ± 380	30	1534 ± 436
<i>In vivo</i> recovery (IU/dL/kg)	30	2.59 ± 0.52	30	2.41 ± 0.50
Half-life (t <sub>1/2</sub> )	30	11.24 ± 2.53	30	11.98 ± 4.28
C <sub>max</sub> (IU/dL)	30	129 ± 27	30	120 ± 26
MRT (h)	30	14.52 ± 3.81	30	15.68 ± 6.21
V <sub>ss</sub> (dL/kg)	30	0.46 ± 0.10	30	0.47 ± 0.10
CL (dL/kg/hr)	30	0.03 ± 0.01	30	0.03 ± 0.01

For the pharmacokinetic parameters AUC (0 - 48h) and the *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 bioequivalence 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 indicated no significant change in the *in vivo* recovery at the onset of treatment and after 75 exposure days.

## CLINICAL TRIALS

In the phase 2/3 pivotal study, a global assessment of efficacy was rendered either 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 haemostasis achieved with ADVATE (rAHF-PFM). 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 (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.

The rate of new bleeding episodes during the protocol-mandated minimum of 75 exposure day prophylactic regimen ( $\geq 25$  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 3.

<b>Bleeding Episode Etiology</b>	<b>Mean (<math>\pm</math> SD) New Bleeding Episodes/Subjects/Month</b>
<b>Spontaneous</b>	$0.34 \pm 0.49$
<b>Post Traumatic</b>	$0.39 \pm 0.46$
<b>Unknown*</b>	$0.33 \pm 0.34$
<b>Overall</b>	$0.52 \pm 0.71$

\* 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  $\geq 80\%$  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, is presented in Table 4.

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

\* 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.

## CONTRAINDICATIONS

Known hypersensitivity to any component 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, paresthesias, rash, flushing, face swelling, urticaria, and pruritis.

Patients should be informed of the signs of hypersensitivity reactions (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis). If these symptoms occur, they 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 formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals 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.

The risk for inhibitor development depends on a number of factors relating to the characteristics of the patient, e.g. type of the Factor VIII gene mutation, family history, ethnicity, which are believed to represent the most significant risk factors for inhibitor formation.

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 titer inhibitor (2.0BU by the Bethesda assay) after 26 exposure days with ADVATE (rAHF-PFM).

### **Antibodies against Mouse or Hamster (CHO) proteins**

ADVATE (rAHF-PFM) contains trace amounts of mouse immunoglobulin G (MuIgG); maximum level of 0.1ng/IU and hamster (CHO) proteins (maximum levels of 1.5ng/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  $15 \pm 2$  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

### **Carcinogenicity, mutagenicity and impairment of fertility**

Mutagenity studies and long-term studies in animals to evaluate carcinogenic potential ADVATE have not been performed. Animal studies examining the effects of ADVATE on fertility have not been conducted.

### **Use in Pregnancy (Category B2)**

Factor VIII deficiency is an X-chromosome linked (male) congenital disease. The safety of ADVATE for use in pregnant women has not been established. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing ADVATE. Animal reproduction studies with recombinant factor VIII, including ADVATE, have not been conducted.

### **Use in lactation**

It is not known if ADVATE or its metabolites are excreted in human milk. The safety of ADVATE for use in lactating women has not been established. Breastfeeding is not

recommended in women being treated with ADVATE. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing ADVATE.

### Interactions with Other Drugs

No interactions of ADVATE with other medicinal products are currently known, based upon the absence of data from clinical trials, current medical/scientific literature, and 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

Although hypersensitivity or allergic reactions were not observed in any subjects participating in the clinical trials with ADVATE, such reactions are theoretically possible. Patients should be informed of the early signs of hypersensitivity reactions, which may include nausea, vomiting, rash, urticaria, dizziness, shortness of breath, hypotension and syncope. Patients should be advised to contact their physician if these symptoms occur.

Across all clinical studies, a total of 1304 adverse reactions 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 5.

<b>Table 5: Summary of all adverse reactions (product related and unrelated) that occurred in greater or equal to 10% of study subjects.</b>				
<b>MedDRA Standard System Organ Class</b>	<b>MedDRA Preferred Term</b>	<b>Number of Events</b>	<b>Number of Subjects</b>	<b>% of evaluable subjects*</b>
<b>Gastrointestinal</b>	Pharyngolaryngeal pain	22	17	11.3
<b>General disorder and administration site conditions</b>	Fall	25	19	12.7
	Pyrexia	37	25	16.7
<b>Infections and infestations</b>	Nasopharyngitis	32	22	14.7
<b>Injury, poisoning, and procedural complications</b>	Accidents nos	62	26	17.3
	Limb injury numbers	195	52	34.7
<b>Muskuloskeletal and connective tissue disorder</b>	Arthralgia	74	35	23.3
<b>Nervous system disorder</b>	Headaches numbers	138	44	29.3
<b>Respiratory, thoracic, mediastinal disorder</b>	Cough	37	23	15.3

Note: Percentage relative to 150, the total number of subjects across all the studies who received at least one infusion of ADVATE rAHF-PFM

Eighteen of the 1304 adverse events were regarded as serious; none were related to the study medication. There was no death. 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 as shown in Table 6.

The unexpected decreased coagulation factor VIII levels occurred in one subject during continuous infusion of rAHF- PFM following surgery (postoperative Days 10 – 14). Haemostasis was maintained at all times during this period and both plasma FVIII 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 the studies in the rAHF-PFM clinical program. Among 136 treated subjects  $\geq 10$  years of age, all of whom had  $\geq 150$  exposure days to Factor VIII products at the 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 (2.0BU 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%.

**Table 6: Summary of Non-serious, Study-Drug Related Adverse Events**

<b>Severity</b>	<b>MedDRA Preferred Term</b>	<b>Number of Events</b>
<b>Mild</b>	Dysgeusia	3
	Pruritis	1
	Dizziness	1
	Catheter-related infection	1
	Rigors	1
	Headaches	1
	<b>Total</b>	<b>8</b>
	<b>Moderate</b>	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*	1
	Haematocrit decreased	1
	Joint swelling	1
	<b>Total</b>	<b>16</b>
<b>Severe</b>	Headache	1
	Pyrexia	1
	Haematoma numbers	1
	Coagulation factor VIII decreased	1
	<b>Total</b>	<b>4</b>
*Recorded as a prolonged bleeding after postoperative drain removal on the case report form.		

## 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.

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction, Hypersensitivity

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Factor VIII inhibition

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. 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 1IU factor VIII per kg body weight raises the plasma factor VIII activity by 2IU/dL. The dose is determined using the following formula and table.

**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)
<b>Haemorrhage</b>		
Early haemarthrosis, 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 haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat infusions every 12 to 24 hours for 3 to 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.
<b>Surgery</b>		
<i>Minor</i> , including tooth extraction	30 - 60	Every 12 hours, at least 1 day, until healing is achieved.
<i>Major</i>	80 - 100 (pre- and postoperative)	Repeat infusions every 8 to 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 cases 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 (presence of a low responder inhibitor) doses larger than the calculated doses 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. 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 40IU 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 paediatric 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 *Warnings and Precautions*, under subheading *Antibody formation*).

### **Laboratory tests**

Although dosage can be estimated by the calculations as described above, it is strongly recommended that, whenever possible, appropriate laboratory tests including serial AHF assays be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and maintained.

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 10BU/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 10BU/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 diluent come in single-dose 5mL vials of neutral borosilicate glass hydrolytic type I. The product vials are closed with Teflon coated butyl rubber stoppers and the diluent vials are closed with chlorobutyl rubber stoppers. Each vial is labelled for potency in IU, and is packaged together with 5mL of sterilized water for injection, 1 BAXJECT II device for reconstitution, 1 mini-infusion set, 1 of 10mL 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 (25°C).
2. Remove caps from the factor concentrate and diluent vials.

3. Cleanse stoppers with a 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.**

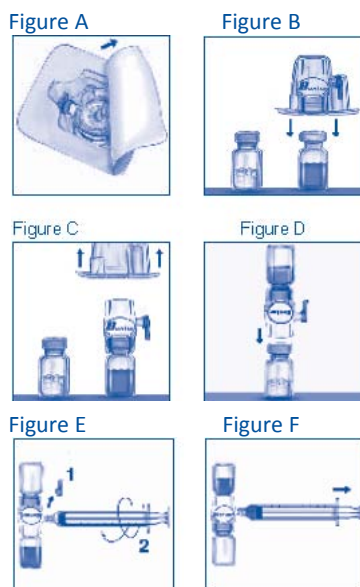
### **Administration: Use Aseptic Technique**

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.

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.

Inject intravenously. The preparation can be administered at a rate of up to 10 mL per minute. The pulse rate should be determined before and during the administration of ADVATE. Should a

significant increase occur, reducing the rate of administration or temporarily interrupting the injection usually allows the symptoms to disappear promptly (see *Warnings and Precautions* and *Adverse Effects* Sections).



### Administration by continuous infusion

The 1500, 1000 and 500IU/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 0.4mL/hour, or a CADD-1 type infusion pump running at a rate of 1.5mL/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 photo stability 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

There has been no reported clinical adverse experience that could be associated with overdosage.

## PRESENTATION

ADVATE is formulated as a sterile, nonpyrogenic, off-white, lyophilized powder, for intravenous injection. It is supplied in single-dose glass vials containing nominally 250, 500, 1000, 1500, 2000 or 3000IU per vial and a diluent for reconstitution.

The diluent is sterilized Water for Injection comes in single-dose of 5mL vials of neutral borosilicate glass hydrolytic type I with nominal volume of 5.4mL and with a minimum extractable volume of 5mL.

### Needleless Transfer Device (BAXJECT)

The product is accompanied by a needleless transfer device designed for transferring and mixing drugs contained in two vials (product and diluent). Each Needles 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

Two 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. Do not use beyond the expiration date printed on the label. Protect from light.

## MEDICINE CLASSIFICATION

General Sale Medicine.

## NAME AND ADDRESS

ADVATE is manufactured by:

BioScience Division  
Baxter AG

Industriestasse 67, A-1221 Vienna  
Austria

ADVATE is distributed in New Zealand by:

Baxter Healthcare Ltd  
33 Vestey Drive  
Mt Wellington  
Auckland 1060

ADVATE is distributed in Australia by:

Baxter Healthcare Pty Ltd  
1 Baxter Drive  
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NSW 2146, Sydney

## **DATE OF PREPARATION**

9 September 2010.

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*Based on Australian PI approved 7 November 2008, most recent amendment 7 September 2010.*