

Baxter

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU powder and solvent for solution for injection.

ADVATE 500 IU powder and solvent for solution for injection.

ADVATE 1000 IU powder and solvent for solution for injection.

ADVATE 1500 IU powder and solvent for solution for injection.

ADVATE 2000 IU powder and solvent for solution for injection.

ADVATE 3000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Octocog alfa (recombinant human coagulation factor VIII produced by recombinant DNA technology in Chinese Hamster Ovary cells) 250, 500, 1000, 1500, 2000 and 3000 IU/vial.

Octocog alfa 250 IU per 5 ml after reconstitution.

The concentration after reconstitution is 50 IU/ml.

Octocog alfa 500 IU per 5 ml after reconstitution.

The concentration after reconstitution is 100 IU/ml.

Octocog alfa 1000 IU per 5 ml after reconstitution.

The concentration after reconstitution is 200 IU/ml.

Octocog alfa 1500 IU per 5 ml after reconstitution.

The concentration after reconstitution is 300 IU/ml.

Octocog alfa 2000 IU per 5 ml after reconstitution.

The concentration after reconstitution is 400 IU/ml.

Octocog alfa 3000 IU per 5 ml after reconstitution.

The concentration after reconstitution is 600 IU/ml.

The potency (IU) is determined using the chromogenic assay against an in-house standard that is referenced to the 6th WHO standard. The specific activity is approximately 4,000-10,000 IU/mg protein.

Prepared without the addition of any (exogenous) human- or animal-derived protein in the cell culture process, purification or final formulation.

Excipients:

Sodium chloride: 90 mmol

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White to off-white friable powder. After reconstitution, the solution has a pH of between 6.7 and 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) – see section 4.2.

ADVATE does not contain von Willebrand factor in pharmacologically effective quantities and is therefore not indicated in von Willebrand's disease.

4.2 Posology and method of administration

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

Posology

The dosage and duration of the substitution therapy depend on the severity of factor VIII deficiency, the location and extent of the bleeding and on the patient's clinical condition.

The dose of factor VIII administered is expressed in International Units (IU), which are 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:

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

In case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage Early haemarthrosis, muscle bleeding or oral bleeding.	20 – 40	Repeat infusions every 12 to 24 hours (8 to 24 hours for patients under the age of 6) 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 (8 to 24 hours for patients under the age of 6) 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 (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery <i>Minor</i> Including tooth extraction.	30 – 60	Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.
<i>Major</i>	80 – 100 (pre- and postoperative)	Repeat infusions every 8 to 24 hours (6 to 24 hours for patients under the age of 6) 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).

The amount and frequency of administration should be adapted to the clinical response in the individual case. Under certain circumstances (e.g. presence of a low titre inhibitor) doses larger than those calculated using the formula 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 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In patients under the age of 6, doses of 20 to 50 IU of factor VIII per kg body weight 3 to 4 times weekly are recommended.

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.

See also section 4.4.

Method of administration

Prepare the product for administration as described in section 6.6. ADVATE should be administered via the intravenous route.

The rate of administration should be determined at a rate that ensures the comfort of the patient up to a maximum of 10 ml/min.

4.3 Contraindications

Hypersensitivity to the active substance, any of the excipients or mouse or hamster proteins.

4.4 Special warnings and special precautions for use

As with any intravenous product, allergic type hypersensitivity reactions are possible. The product contains traces of mouse and hamster proteins.

Patients should be informed of the signs of immediate-type hypersensitivity reactions including hives, pruritus, generalised urticaria, angioedema, hypotension (e.g. dizziness or syncope), shock and acute respiratory distress (e.g. tightness in the chest, wheezing). If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physicians.

In case of anaphylactic shock, the current medical standards for shock treatment should be implemented (see section 4.8).

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. 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 factor VIII, the risk being highest within the first 20 exposure days, and to other genetic and environmental factors. 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. See also section 4.8.

In the interest of patients, it is recommended that, whenever possible, every time that ADVATE is administered to them, the name and batch number of the product should be registered.

This medicinal product contains 90 mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of ADVATE with other medicinal products are known.

4.6 Pregnancy and lactation

Based on the rare occurrence of haemophilia A in women, experience regarding the use of ADVATE during pregnancy is not available. Animal reproduction studies have not been conducted with ADVATE. Therefore, the benefit of using ADVATE during pregnancy must be judged against the risk for the mother and baby and should be used only if clearly needed.

Based on the lack of experience regarding the use of ADVATE during lactation, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

ADVATE has no influence on the ability to drive and to operate machines.

4.8 Undesirable effects

As with any intravenous product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions, which may include hives, pruritus, generalised urticaria, angioedema, hypotension (e.g. dizziness and syncope), shock and acute respiratory distress (e.g. tightness in the chest and wheezing). Patients should be advised to immediately contact their physician if these symptoms occur (see section 4.4).

During clinical studies with ADVATE, a total of 56 adverse drug reactions (ADRs) were reported in 27 of 234 unique treated subjects. The ADRs that occurred in the greatest number of subjects were factor VIII inhibitors (5 subjects), all occurring in previously untreated patients who have elevated risk of inhibitor development, headache (5 subjects), fever and dizziness (3 subjects each). Of the 56 ADRs, none were reported in neonates, 16 were reported in 13/32 infants, 7 were reported in 4/56 children, 8 were reported in 4/31 adolescents and 25 were reported in 14/94 adults.

The following table provides the frequency of subjects with adverse drug reactions in clinical trials:

MedDRA Standard System Organ Class	MedDRA Preferred Term	Number of Subjects	Adverse Experience Rate (% subjects) ^a	ADR Rate Frequency Category ^b
Infections and Infestations	Influenza	1	0.43	Uncommon
	Laryngitis	1	0.43	Uncommon
Blood and Lymphatic System Disorders	Lymphangitis	1	0.43	Uncommon
Nervous System Disorders	Headache	5	2.14	Common
	Dizziness	3	1.28	Common
	Memory Impairment	1	0.43	Uncommon
	Tremor	1	0.43	Uncommon
	Migraine	1	0.43	Uncommon
	Dysgeusia	1	0.43	Uncommon
Eye Disorders	Eye inflammation	1	0.43	Uncommon
Vascular Disorders	Haematoma	1	0.43	Uncommon
	Hot flush	1	0.43	Uncommon
	Pallor	1	0.43	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	1	0.43	Uncommon
Gastrointestinal Disorders	Diarrhoea	2	0.85	Uncommon
	Abdominal pain upper	1	0.43	Uncommon
	Nausea	1	0.43	Uncommon
	Vomiting	1	0.43	Uncommon
Skin and Subcutaneous Tissue Disorders	Pruritus	2	0.85	Uncommon
	Rash	2	0.85	Uncommon
	Hyperhidrosis	1	0.43	Uncommon
	Dermatitis diaper	1	0.43	Uncommon

MedDRA Standard System Organ Class	MedDRA Preferred Term	Number of Subjects Rate	Adverse Experience Category ^a	ADR Rate Frequency (% subjects) ^b
General Disorders and Administration Site Conditions	Pyrexia	3	1.28	Common
	Oedema peripheral	1	0.43	Uncommon
	Chest pain	1	0.43	Uncommon
	Chills	1	0.43	Uncommon
	Feeling Abnormal	1	0.43	Uncommon
Investigations	Anti-factor VIII antibody positive	5	2.14	Common
	Alanine aminotransferase increased	1	0.43	Uncommon
	Coagulation factor VIII level decreased ^c	1	0.43	Uncommon
	Haematocrit decreased	1	0.43	Uncommon
	Laboratory test abnormal	1	0.43	Uncommon
Injury, poisoning and procedural complications	Post procedural complication	1	0.43	Uncommon
	Post procedural haemorrhage	1	0.43	Uncommon
	Procedural site reaction	1	0.43	Uncommon

- a) Percent of subjects calculated based on total number of unique subjects (234).
- b) Frequency has been evaluated using the following criteria: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
- c) The unexpected decrease in coagulation factor VIII levels occurred in one subject during continuous infusion of ADVATE following surgery (postoperative days 10-14). Haemostasis 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.

In patients who develop neutralising antibodies (inhibitors) to factor VIII, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

The immunogenicity of ADVATE was evaluated in previously treated patients. During clinical trials with ADVATE in 145 children (2 years \leq age $<$ 12 years) adolescents (12 years \leq age $<$ 16 years) and adults (age \geq 16 years), diagnosed with severe to moderately severe haemophilia A (FVIII \leq 2%), with previous exposure to factor VIII concentrates \geq 150 days, one subject developed a low-titre inhibitor (2.4 BU in the modified Bethesda assay) after 26 exposure days to ADVATE. Follow-up inhibitor tests in this subject after withdrawal from the study were negative. Also, in 53 paediatric subjects under the age of 6, also diagnosed with severe to moderately severe haemophilia A (FVIII \leq 2%), with previous exposure to factor VIII concentrates \geq 50 days, no FVIII inhibitor was detected.

In previously untreated patients in an ongoing clinical study, 5 (20%) of 25 subjects who received ADVATE developed inhibitors to factor VIII. Of those, 4 were high titre (\geq 5 Bethesda Units) and 1 was low titre ($<$ 5 Bethesda Units). The frequency of factor VIII inhibitors detected so far are within the expected and previously observed range.

The subjects' immune response to trace amounts of contaminating proteins was analyzed by examining titres of antibodies to these proteins, laboratory parameters and reported adverse events. Of the 182 treated subjects who were assessed for antibodies to CHO cell

protein, 3 showed a statistically significant upward trend in titres by linear regression analysis and 4 displayed sustained peaks or transient spikes. 1 subject had both a statistically significant upward trend and displayed a sustained peak in anti-CHO cell protein antibody level, but no other signs or symptoms indicative of an allergic or hypersensitivity response. Of the 182 treated subjects who were assessed for antibodies to murine IgG, 10 showed a statistically significant upward trend by linear regression analysis and 2 displayed a sustained peak or transient spike. 1 subject had both a statistically significant upward trend and displayed a sustained peak in anti-murine IgG antibody level. Four of these subjects reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts amongst numerous repeat study product exposures.

As with other intravenous products, allergic type hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions, have been reported in ADVATE of unknown frequency.

4.9 Overdose

No symptoms of overdose with recombinant human coagulation factor VIII have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factor VIII. ATC code: B02BD02.

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions.

ADVATE contains recombinant coagulation factor VIII, a glycoprotein that has an amino acid sequence comparable to human factor VIII, and post-translational modifications that are similar to those of the plasma-derived molecule.

ADVATE is a glycoprotein consisting of 2332 amino acids with an approximate molecular mass of 280 kD. When infused into a haemophilia patient, factor VIII binds to endogenous von Willebrand factor in the patient's circulation.

Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. 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.

5.2 Pharmacokinetic properties

All pharmacokinetic studies with ADVATE were conducted in patients with severe to moderately severe haemophilia A (baseline factor VIII \leq 2%). The analysis of plasma samples was conducted in a central laboratory using a one-stage clotting assay. The pharmacokinetic parameters derived from a crossover study of ADVATE in 100 previously treated patients greater than or equal to 10 years of age are listed in the table opposite.

Summary of Pharmacokinetic Parameters for ADVATE in 100 Patients with Severe Haemophilia A				
PK Parameter	Mean	SD	Median	Interquartile Range
AUC _{0-∞} (IU•h/dl)	1527*	528	1549	668
Half-life (h)	11.8	3.1	11.1	2.8
Adjusted Recovery (IU/d/IU/kg)	2.38*	0.50	2.42	0.68
C _{max} (IU/dl)	120*	26	119	38
Clearance (dl/kg•h)	0.037	0.030	0.033	0.0147
MRT (h)	15.2	4.8	14.1	4.2
V _{ss} (dl/kg)	0.52	0.39	0.48	0.13

* Geometric mean

Data from single-dose administrations of ADVATE in 53 paediatric patients less than 6 years of age were used to obtain this table.

Summary of Pharmacokinetic Parameters for ADVATE in 53 Paediatric Patients with Severe Haemophilia A		
PK Parameter	Mean	SD
AUC _{0-∞} (IU•h/dl)	1195*	430
Half-life (h)	9.7	1.9
Adjusted Recovery (IU/d/IU/kg)	1.84*	0.42
C _{max} (IU/dl)	93*	22
Clearance (dl/kg•h)	0.044	0.014
MRT (h)	12.2	3.1
V _{ss} (dl/kg)	0.51	0.12

* Geometric Mean

Adjusted recovery was approximately 20% lower than in adults, which is consistent with the known higher plasma volume per kilogram body weight in younger patients. Terminal half-life was also 20% lower than in adults, in agreement with a similar observation by Courter and Bedrosian in patients of the same age group infused with B-domain deleted recombinant factor VIII (Courter SG and Bedrosian CL: Clinical evaluation of B-domain deleted recombinant factor VIII in previously treated patients. *Semin Hematol* 38: 44–51, 2001, Courter SG and Bedrosian CL : Clinical evaluation of B-domain deleted recombinant factor VIII in previously untreated patients. *Semin Hematol* 38: 52–59, 2001).

No Pharmacokinetic data with ADVATE on previously untreated patients are currently available.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Mannitol

Sodium chloride

Histidine

Trehalose

Calcium chloride

Trometamol

Polysorbate 80

Glutathione (reduced).

Solvent:

Sterilised water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or solvents.

6.3 Shelf life

Two years. ADVATE should be administered at room temperature not more than 3 hours after reconstitution. From a microbiological viewpoint, the product should be used immediately after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. During the shelf life the product may be kept at room temperature (up to 25°C) for a single period not exceeding 2 months. Please record the beginning of storage at room temperature on the product carton. The product may not be returned to refrigerated storage after storage at room temperature. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

A single pack contains a powder vial, a 5 ml solvent vial (both type I glass closed with halogenobutyl rubber stopper) and a device for reconstitution (BAXJECT II).

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

The preparation is to be administered intravenously after reconstitution with the provided sterilised water for injections. After reconstitution the solution is clear, colourless and free from foreign particles.

- For reconstitution use only the sterilised water for injections and the reconstitution device provided in the pack. For administration the use of a luer-lock syringe is required.
- Use within three hours after reconstitution.
- Do not refrigerate the preparation after reconstitution.
- Dispose any unused product or waste material in accordance with local requirements.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

Reconstitution: Use Aseptic Technique:

1. Bring ADVATE (powder) and sterilised water for injections (solvent) to 15-25°C.
2. Remove caps from powder and solvent vials.
3. Cleanse stoppers with alcohol swabs. Place the vials on a flat surface.
4. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package.
5. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from BAXJECT II device.
6. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the ADVATE stopper. The vacuum will draw the solvent into the ADVATE vial (Fig. c).
7. Swirl gently until all material is dissolved. Be sure that ADVATE is completely dissolved, otherwise active material will not pass through the device filter. The product dissolves rapidly (usually in less than 1 minute).

Fig. a



Fig. b



Fig. c



Administration: Use Aseptic Technique:

Parenteral drug products should be inspected for particulate matter prior to administration, whenever solution and container permit. Only a clear and colourless solution should be used.

1. Remove the blue cap from BAXJECT II. DO NOT DRAW AIR INTO THE SYRINGE. Connect the syringe to BAXJECT II (Fig. d).
2. Invert the system (with concentrate vial on top). Draw the concentrate into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.
4. Attach the administration set to the syringe. 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 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 sections 4.4 and 4.8).

Fig. d

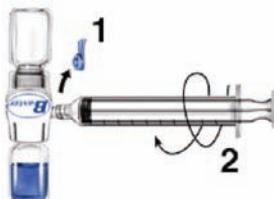
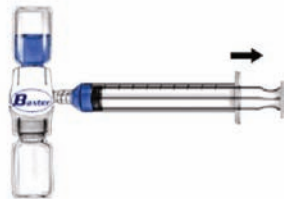


Fig. e



7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/271/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ADVATE 250 IU, 500 IU, 1000 IU, 1500 IU first authorised 2nd March 2004. ADVATE 2000, 3000 IU authorised 22 May 2008.

10. DATE OF REVISION OF THE TEXT

22nd May 2008

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>

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