ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/5 ml powder and solvent for solution for injection
ADVATE 500 IU/5 ml powder and solvent for solution for injection
ADVATE 1 000 IU/5 ml powder and solvent for solution for injection
ADVATE 1 500 IU/5 ml powder and solvent for solution for injection
ADVATE 2 000 IU/5 ml powder and solvent for solution for injection
ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADVATE 250 IU/5 ml powder and solvent for solution for injection

Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 50 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 5 ml solvent.

ADVATE 500 IU/5 ml powder and solvent for solution for injection

Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 100 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 5 ml solvent.

ADVATE 1 000 IU/5 ml powder and solvent for solution for injection

Each vial contains nominally 1 000 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 200 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 5 ml solvent.

ADVATE 1 500 IU/5 ml powder and solvent for solution for injection

Each vial contains nominally 1 500 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 300 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 5 ml solvent.

ADVATE 2 000 IU/5 ml powder and solvent for solution for injection

Each vial contains nominally 2 000 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 400 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 5 ml solvent.

ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

Each vial contains nominally 3 000 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 600 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 5 ml solvent.

The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ADVATE is approximately 4 520 - 11 300 IU/mg protein.
Octocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 2 332 amino acids. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Prepared without the addition of any (exogenous) human- or animal-derived protein in the cell culture process, purification or final formulation.

Excipients with known effect

This medicinal product contains 0.45 mmol sodium (10 mg) and 0.5 mg polysorbate 80 per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: White to off-white friable powder.
Solvent: Clear and colourless solution.

After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.7 to 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ADVATE is indicated in all age groups.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and with resuscitation support immediately available in case of anaphylaxis.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

Posology

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

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment

The calculation of the required dose 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 required dose is determined using the following formula:

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

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness 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.

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 (Table 1) can be used to guide dosing in bleeding episodes and surgery:

Table 1. Guide for 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 injections 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 injections 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 injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor 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.
Major	80 – 100 (pre- and post-operative)	Repeat injections 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).

Prophylaxis

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 dosage intervals or higher doses may be necessary.

Paediatric population

For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. 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 for prophylactic therapy.

Method of administration

Intravenous use. In case of administration by a non-healthcare professional appropriate training is needed.

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to mouse or hamster protein.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE. The product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors

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 the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. 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 haemophilia and factor VIII inhibitors.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Excipient related considerations

Sodium

This medicinal product contains 10 mg sodium per vial, equivalent to 0.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

It is strongly recommended that every time ADVATE is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population

The listed warnings and precautions apply to both adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

ADVATE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical studies with ADVATE included 418 subjects with at least one exposure to ADVATE reporting in total 93 adverse drug reactions (ADRs). The ADRs that occurred in the highest frequency were development of neutralising antibodies to factor VIII (inhibitors), headache and fever.

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Development of antibodies to mouse and/or hamster protein with related hypersensitivity reactions may be observed.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ADVATE (see section 5.1). If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated summary of adverse reactions

Table 2 provides the frequency of adverse reactions in clinical trials and from spontaneous reporting, according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequency has been evaluated according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Frequency of adverse reactions in clinical trials and from spontaneous reports

MedDRA Standard System Organ Class	Adverse reaction	Frequency[a]
Infections and infestations	Influenza	Uncommon
	Laryngitis	Uncommon
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)[b] Very common (PUPs)[b]
	Lymphangitis	Uncommon
Immune system disorders	Anaphylactic reaction[*]	Not known
	Hypersensitivity[c*]	Not known
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
	Memory impairment	Uncommon
	Syncope	Uncommon
	Tremor	Uncommon
	Migraine	Uncommon
	Dysgeusia	Uncommon
Eye disorders	Eye inflammation	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Haematoma	Uncommon
	Hot flush	Uncommon
	Pallor	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon
Gastrointestinal disorders	Diarrhoea	Uncommon
	Abdominal pain upper	Uncommon
	Nausea	Uncommon
	Vomiting	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Hyperhidrosis	Uncommon
	Urticaria	Uncommon
General disorders and administration site conditions	Pyrexia	Common
	Peripheral oedema	Uncommon
	Chest pain	Uncommon
	Chest discomfort	Uncommon
	Chills	Uncommon
	Feeling abnormal	Uncommon
	Vessel puncture site haematoma	Uncommon
	Fatigue[*]	Not known
	Injection site reaction[*]	Not known
	Malaise[*]	Not known
Investigations	Monocyte count increased	Uncommon
	Coagulation factor VIII level decreased[d]	Uncommon
	Haematocrit decreased	Uncommon
	Laboratory test abnormal	Uncommon
Injury, poisoning and procedural complications	Post-procedural complication	Uncommon
	Post-procedural haemorrhage	Uncommon
	Procedural site reaction	Uncommon

a) Calculated based on total number of patients who received ADVATE (418) in clinical trials, except for adverse reactions identified in post-marketing surveillance marked with *.
b) Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.
c) ADR explained in the section below.
d) The unexpected decrease in coagulation factor VIII levels occurred in one patient during continuous infusion of ADVATE following surgery (post-operative 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 post-operative day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative.

Description of selected adverse reactions

ADRs specific to residues from the manufacturing process

Of the 229 treated patients who were assessed for antibodies to Chinese hamster ovary (CHO) cell protein, 3 showed a statistically significant upward trend in titres, 4 displayed sustained peaks or transient spikes and one patient had both but no clinical symptoms. Of the 229 treated patients who were assessed for antibodies to murine IgG, 10 showed a statistically significant upward trend, 2 displayed a sustained peak or transient spike and one patient had both. Four of these patients reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts amongst repeated exposures to the study product.

Hypersensitivity

Allergic type reactions include anaphylaxis and have been manifested by dizziness, paraesthesia, rash, flushing, face swelling, urticaria, and pruritus.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in ADRs were noted in the clinical studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

ADVATE contains recombinant coagulation factor VIII (octocog alfa), a glycoprotein that is biologically equivalent to the factor VIII glycoprotein found in human plasma. Octocog alfa is a glycoprotein consisting of 2 332 amino acids with an approximate molecular mass of 280 kD.

The factor VIII/von Willebrand Factor complex consists of two molecules (factor VIII and von Willebrand Factor) with different physiological functions. When infused into a haemophiliac 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 into 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:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Of note, annualized bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

Clinical efficacy and safety

Data on Immune Tolerance Induction (ITI) in patients with inhibitors have been collected. Within a sub-study of PUP-study 060103, ITI-treatments in 11 PUPs were documented. Retrospective chart review was done for 30 paediatric subjects on ITI (in study 060703). A non-interventional prospective registry (PASS-INT-004) documented ITI in 44 paediatric and adult subjects of whom 36 completed ITI therapy. Data show that immune tolerance may be achieved.

In study 060201 two long-term prophylaxis treatment schemes have been compared in 53 PTPs: an individualized pharmacokinetic guided dosing regimen (within a range of 20 to 80 IU of factor VIII per kg body weight at intervals of 72 ± 6 hours, n=23) with a standard prophylactic dosing regimen (20 to 40 IU/kg every 48 ± 6 hours, n=30). The pharmacokinetic guided dosing regimen (according to a specific formula) was targeted to maintain factor VIII trough levels ≥ 1% at the inter-dosing interval of 72 hours. The data from this study demonstrate that the two prophylactic dosing regimens are comparable in terms of reduction of bleeding rate.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ADVATE in all subsets of the paediatric population in haemophilia A (congenital factor VIII deficiency) in "Immune Tolerance Induction (ITI) in patients with haemophilia A (congenital factor VIII deficiency) who have developed inhibitors to factor VIII" and "treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)" (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

All pharmacokinetic studies with ADVATE were conducted in previously treated patients with severe to moderately severe haemophilia A (baseline factor VIII ≤ 2%). The analysis of plasma samples was conducted in a central laboratory using a one-stage clotting assay.

A total of 195 subjects with severe haemophilia A (baseline factor VIII < 1%) provided pharmacokinetic (PK) parameters that were included in the per-protocol PK analysis set. Categories of these analyses for infants (1 month to < 2 years of age), children (2 to < 5 years of age), older children (5 to < 12 years of age), adolescents (12 to < 18 years of age), and adults (18 years of age and older) were used to summarize PK parameters, where age was defined as age at time of PK infusion.

Table 3. Summary of pharmacokinetic parameters of ADVATE per age group with severe haemophilia A (baseline factor VIII < 1%)

Parameter (mean ± standard deviation)	Infants (n=5)	Children (n=30)	Older children (n=18)	Adolescents (n=33)	Adults (n=109)
Total AUC (IU*·h/dl)	1 362.1 ± 311.8	1 180.0 ± 432.7	1 506.6 ± 530.0	1 317.1 ± 438.6	1 538.5 ± 519.1
Adjusted incremental recovery at C_{max} (IU/dL per IU/kg)[a]	2.2 ± 0.6	1.8 ± 0.4	2.0 ± 0.5	2.1 ± 0.6	2.2 ± 0.6
Half-life (h)	9.0 ± 1.5	9.6 ± 1.7	11.8 ± 3.8	12.1 ± 3.2	12.9 ± 4.3
Maximum plasma concentration post-infusion (IU/dl)	110.5 ± 30.2	90.8 ± 19.1	100.5 ± 25.6	107.6 ± 27.6	111.3 ± 27.1
Mean residence time (h)	11.0 ± 2.8	12.0 ± 2.7	15.1 ± 4.7	15.0 ± 5.0	16.2 ± 6.1
Volume of distribution at steady state (dl/kg)	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2
Clearance (ml/kg*h)	3.9 ± 0.9	4.8 ± 1.5	3.8 ± 1.5	4.1 ± 1.0	3.6 ± 1.2

[a] Calculated as (C_{max} - baseline factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion factor VIII measurement.

Paediatric population

The safety and haemostatic efficacy of ADVATE in the paediatric population are similar to that of adult patients. Adjusted recovery and terminal half-life ($t_{½}$) was approximately 20% lower in young children (less than 6 years of age) than in adults, which may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

Pharmacokinetic data with ADVATE on previously untreated patients are currently not 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 (E421)
Sodium chloride
Histidine
Trehalose
Calcium chloride (E509)
Trometamol
Polysorbate 80 (E433)

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.

6.3 Shelf life

Unopened vial

2 years.

During the shelf life, the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. The end of the 6 months storage at room temperature should be recorded on the product carton. At the end of this period the product shall be used or discarded. The product may not be returned to refrigerated storage again.

After reconstitution

After reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at 25 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

ADVATE with BAXJECT II device: Keep the product vial in the outer carton in order to protect from light.

ADVATE in BAXJECT III system: Keep the sealed blister in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Both the powder vial and the vial containing 5 ml solvent are of type I glass closed with chlorobutyl or bromobutyl rubber stoppers. The product is provided in one of the following configurations:

- ADVATE with BAXJECT II device: Each pack contains a powder vial, a vial containing 5 ml solvent and a device for reconstitution (BAXJECT II).
- ADVATE in BAXJECT III system: Each pack contains a ready to use BAXJECT III system in a sealed blister (the powder vial and the vial containing 5 ml solvent are preassembled with the system for reconstitution).

6.6 Special precautions for disposal and other handling

ADVATE is to be administered intravenously after reconstitution of the product.

The reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear, colourless and free from foreign particles. Do not use solutions that are cloudy or have deposits.

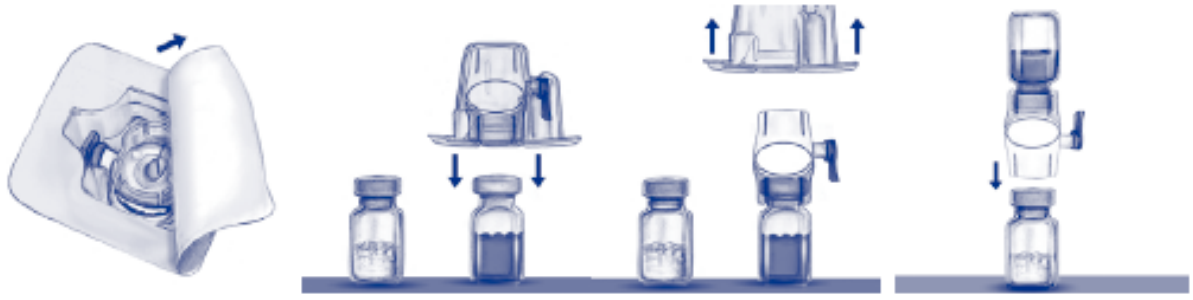
- For administration the use of a luer-lock syringe is required.
- Use within three hours after reconstitution.
- Do not refrigerate the preparation after reconstitution.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution with the BAXJECT II device

- For reconstitution use only the sterilised water for injections and the reconstitution device provided in the pack.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
- Aseptic technique should be used.

1. If the product is still stored in a refrigerator, take both the ADVATE powder and solvent vials from the refrigerator and let them reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. 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. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. 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 the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. 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 powder stopper. The vacuum will draw the solvent into the ADVATE powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. a **Fig. b** **Fig. c**



Reconstitution with the BAXJECT III system

Do not use if the lid is not completely sealed on the blister.

1. If the product is still stored in a refrigerator, take the sealed blister (contains powder and solvent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Open the ADVATE package by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place the ADVATE on a flat surface with the solvent vial on top (Fig. 1). The solvent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
5. With one hand holding the ADVATE in the BAXJECT III system, press down firmly on the solvent vial with the other hand until the system is fully collapsed and the solvent flows down into the ADVATE vial (Fig. 2). Do not tilt the system until the transfer is complete.
6. Verify that the solvent transfer is complete. Swirl gently until all material is dissolved (Fig. 3). Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. 1

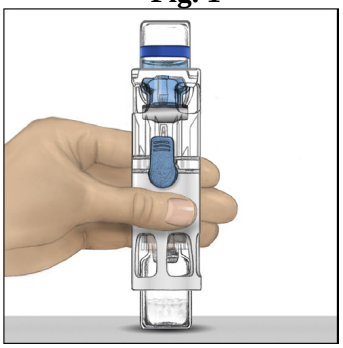


Fig. 2

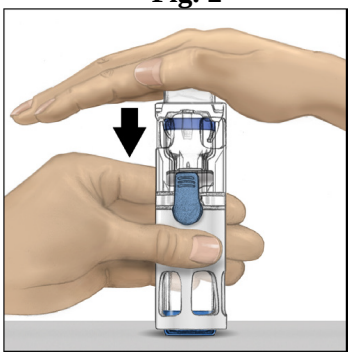
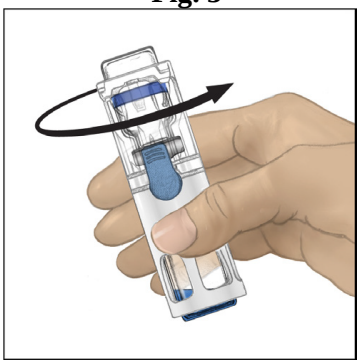


Fig. 3



Administration

Use aseptic technique

Parenteral medicinal 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 / BAXJECT III. **Do not draw air into the syringe**. Connect the syringe to BAXJECT II / BAXJECT III.
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe. Inject intravenously. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 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).

7. MARKETING AUTHORISATION HOLDER

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A-1221 Vienna
Austria
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8. MARKETING AUTHORISATION NUMBERS

EU/1/03/271/001
EU/1/03/271/002
EU/1/03/271/003
EU/1/03/271/004
EU/1/03/271/005
EU/1/03/271/006
EU/1/03/271/011
EU/1/03/271/012
EU/1/03/271/013
EU/1/03/271/014
EU/1/03/271/015
EU/1/03/271/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 20 December 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/2 ml powder and solvent for solution for injection
ADVATE 500 IU/2 ml powder and solvent for solution for injection
ADVATE 1 000 IU/2 ml powder and solvent for solution for injection
ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADVATE 250 IU/2 ml powder and solvent for solution for injection

Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 125 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 2 ml solvent.

ADVATE 500 IU/2 ml powder and solvent for solution for injection

Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 250 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 2 ml solvent.

ADVATE 1 000 IU/2 ml powder and solvent for solution for injection

Each vial contains nominally 1 000 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 500 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 2 ml solvent.

ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

Each vial contains nominally 1 500 IU human coagulation factor VIII (rDNA), octocog alfa. ADVATE contains approximately 750 IU per ml of human coagulation factor VIII (rDNA), octocog alfa after reconstitution with 2 ml solvent.

The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ADVATE is approximately 4 520 - 11 300 IU/mg protein.
Octocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 2 332 amino acids. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Prepared without the addition of any (exogenous) human- or animal-derived protein in the cell culture process, purification or final formulation.

Excipients with known effect

This medicinal product contains 0.45 mmol sodium (10 mg) and 0.5 mg polysorbate 80 per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: White to off-white friable powder.
Solvent: Clear and colourless solution.

After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.7 to 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ADVATE is indicated in all age groups.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and with resuscitation support immediately available in case of anaphylaxis.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

Posology

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

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment

The calculation of the required dose 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 required dose is determined using the following formula:

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

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness 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.

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 (Table 1) can be used to guide dosing in bleeding episodes and surgery:

Table 1. Guide for 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 injections 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 injections 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 injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor 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.
Major	80 – 100 (pre- and post-operative)	Repeat injections 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).

Prophylaxis

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 dosage intervals or higher doses may be necessary.

Paediatric population

For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. 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 for prophylactic therapy.

Method of administration

Intravenous use. In case of administration by a non-healthcare professional appropriate training is needed.

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to mouse or hamster protein.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE. The product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Due to the decrease in injection volume for ADVATE reconstituted in 2 ml sterilised water for injections, if hypersensitivity reactions occur there is less time to react by stopping the injection. Therefore, caution is advised during injection of ADVATE reconstituted in 2 ml sterilised water for injections, especially in children.

Inhibitors

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 the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. 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 haemophilia and factor VIII inhibitors.

Misapplication of ADVATE

For ADVATE reconstituted with 2 ml sterilised water for injections, misapplication (intra-arterially or paravenously) may lead to mild, short term injection site reactions, such as bruising and erythema.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Excipient related considerations

Sodium

This medicinal product contains 10 mg sodium per vial, equivalent to 0.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

It is strongly recommended that every time ADVATE is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population

The listed warnings and precautions apply to both adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

ADVATE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Clinical studies with ADVATE included 418 subjects with at least one exposure to ADVATE reporting in total 93 adverse drug reactions (ADRs). The ADRs that occurred in the highest frequency were development of neutralising antibodies to factor VIII (inhibitors), headache and fever.

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Development of antibodies to mouse and/or hamster protein with related hypersensitivity reactions may be observed.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ADVATE (see section 5.1). If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated summary of adverse reactions

Table 2 provides the frequency of adverse reactions in clinical trials and from spontaneous reporting, according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequency has been evaluated according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Frequency of adverse reactions in clinical trials and from spontaneous reports

MedDRA Standard System Organ Class	Adverse reaction	Frequency[a]
Infections and infestations	Influenza	Uncommon
	Laryngitis	Uncommon
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon (PTPs)[b] Very common (PUPs)[b]
	Lymphangitis	Uncommon
Immune system disorders	Anaphylactic reaction[*]	Not known
	Hypersensitivity[c*]	Not known
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
	Memory impairment	Uncommon
	Syncope	Uncommon
	Tremor	Uncommon
	Migraine	Uncommon
	Dysgeusia	Uncommon
Eye disorders	Eye inflammation	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Haematoma	Uncommon
	Hot flush	Uncommon
	Pallor	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon
Gastrointestinal disorders	Diarrhoea	Uncommon
	Abdominal pain upper	Uncommon
	Nausea	Uncommon
	Vomiting	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Hyperhidrosis	Uncommon
	Urticaria	Uncommon
General disorders and administration site conditions	Pyrexia	Common
	Peripheral oedema	Uncommon
	Chest pain	Uncommon
	Chest discomfort	Uncommon
	Chills	Uncommon
	Feeling abnormal	Uncommon
	Vessel puncture site haematoma	Uncommon
	Fatigue[*]	Not known
	Injection site reaction[*]	Not known
	Malaise[*]	Not known
Investigations	Monocyte count increased	Uncommon
	Coagulation factor VIII level decreased[d]	Uncommon
	Haematocrit decreased	Uncommon
	Laboratory test abnormal	Uncommon

Table 2. Frequency of adverse reactions in clinical trials and from spontaneous reports

MedDRA Standard System Organ Class	Adverse reaction	Frequency[a]
Injury, poisoning and procedural complications	Post-procedural complication	Uncommon
	Post-procedural haemorrhage	Uncommon
	Procedural site reaction	Uncommon

a) Calculated based on total number of patients who received ADVATE (418) in clinical trials, except for adverse reactions identified in post-marketing surveillance marked with *.
b) Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.
c) ADR explained in the section below.
d) The unexpected decrease in coagulation factor VIII levels occurred in one patient during continuous infusion of ADVATE following surgery (post-operative 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 post-operative day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative.

Description of selected adverse reactions

ADRs specific to residues from the manufacturing process

Of the 229 treated patients who were assessed for antibodies to Chinese hamster ovary (CHO) cell protein, 3 showed a statistically significant upward trend in titres, 4 displayed sustained peaks or transient spikes and one patient had both but no clinical symptoms. Of the 229 treated patients who were assessed for antibodies to murine IgG, 10 showed a statistically significant upward trend, 2 displayed a sustained peak or transient spike and one patient had both. Four of these patients reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts amongst repeated exposures to the study product.

Hypersensitivity

Allergic type reactions include anaphylaxis and have been manifested by dizziness, paraesthesia, rash, flushing, face swelling, urticaria, and pruritus.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in ADRs were noted in the clinical studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

ADVATE contains recombinant coagulation factor VIII (octocog alfa), a glycoprotein that is biologically equivalent to the factor VIII glycoprotein found in human plasma. Octocog alfa is a glycoprotein consisting of 2 332 amino acids with an approximate molecular mass of 280 kD.

The factor VIII/von Willebrand Factor complex consists of two molecules (factor VIII and von Willebrand Factor) with different physiological functions. When infused into a haemophiliac 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 into 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:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Of note, annualized bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

Clinical efficacy and safety

Data on Immune Tolerance Induction (ITI) in patients with inhibitors have been collected. Within a sub-study of PUP-study 060103, ITI-treatments in 11 PUPs were documented. Retrospective chart review was done for 30 paediatric subjects on ITI (in study 060703). A non-interventional prospective registry (PASS-INT-004) documented ITI in 44 paediatric and adult subjects of whom 36 completed ITI therapy. Data show that immune tolerance may be achieved.

In study 060201 two long-term prophylaxis treatment schemes have been compared in 53 PTPs: an individualized pharmacokinetic guided dosing regimen (within a range of 20 to 80 IU of factor VIII per kg body weight at intervals of 72 ± 6 hours, n=23) with a standard prophylactic dosing regimen (20 to 40 IU/kg every 48 ± 6 hours, n=30). The pharmacokinetic guided dosing regimen (according to a specific formula) was targeted to maintain factor VIII trough levels ≥ 1% at the inter-dosing interval of 72 hours. The data from this study demonstrate that the two prophylactic dosing regimens are comparable in terms of reduction of bleeding rate.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ADVATE in all subsets of the paediatric population in haemophilia A (congenital factor VIII deficiency) in "Immune Tolerance Induction (ITI) in patients with haemophilia A (congenital factor VIII deficiency) who have developed inhibitors to factor VIII" and "treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)" (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

All pharmacokinetic studies with ADVATE were conducted in previously treated patients with severe to moderately severe haemophilia A (baseline factor VIII ≤ 2%). The analysis of plasma samples was conducted in a central laboratory using a one-stage clotting assay.

A total of 195 subjects with severe haemophilia A (baseline factor VIII < 1%) provided pharmacokinetic (PK) parameters that were included in the per-protocol PK analysis set. Categories of these analyses for infants (1 month to < 2 years of age), children (2 to < 5 years of age), older children (5 to < 12 years of age), adolescents (12 to < 18 years of age), and adults (18 years of age and older) were used to summarize PK parameters, where age was defined as age at time of PK infusion.

Table 3. Summary of pharmacokinetic parameters of ADVATE per age group with severe haemophilia A (baseline factor VIII < 1%)

Parameter (mean ± standard deviation)	Infants (n=5)	Children (n=30)	Older children (n=18)	Adolescents (n=33)	Adults (n=109)
Total AUC (IU*·h/dl)	1 362.1 ± 311.8	1 180.0 ± 432.7	1 506.6 ± 530.0	1 317.1 ± 438.6	1 538.5 ± 519.1
Adjusted incremental recovery at C_{max} (IU/dL per IU/kg)[a]	2.2 ± 0.6	1.8 ± 0.4	2.0 ± 0.5	2.1 ± 0.6	2.2 ± 0.6
Half-life (h)	9.0 ± 1.5	9.6 ± 1.7	11.8 ± 3.8	12.1 ± 3.2	12.9 ± 4.3
Maximum plasma concentration post-infusion (IU/dl)	110.5 ± 30.2	90.8 ± 19.1	100.5 ± 25.6	107.6 ± 27.6	111.3 ± 27.1
Mean residence time (h)	11.0 ± 2.8	12.0 ± 2.7	15.1 ± 4.7	15.0 ± 5.0	16.2 ± 6.1
Volume of distribution at steady state (dl/kg)	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2
Clearance (ml/kg*h)	3.9 ± 0.9	4.8 ± 1.5	3.8 ± 1.5	4.1 ± 1.0	3.6 ± 1.2

[a] Calculated as (C_{max} - baseline factor VIII) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion factor VIII measurement.

Paediatric population

The safety and haemostatic efficacy of ADVATE in the paediatric population are similar to that of adult patients. Adjusted recovery and terminal half-life ($t_{½}$) was approximately 20% lower in young children (less than 6 years of age) than in adults, which may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

Pharmacokinetic data with ADVATE on previously untreated patients are currently not 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.

A local tolerance study in rabbits showed that ADVATE reconstituted with 2 ml of sterilised water for injections is well tolerated after intravenous administration. Slight transient reddening at the administration site was observed after intraarterial application and after paravenous administration. However, no correlating adverse histopathological changes could be observed indicating a transient nature of this finding.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol (E421)

Sodium chloride
Histidine
Trehalose
Calcium chloride (E509)
Trometamol
Polysorbate 80 (E433)
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.

6.3 Shelf life

Unopened vial

2 years.

During the shelf life, the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. The end of the 6 months storage at room temperature should be recorded on the product carton. At the end of this period the product shall be used or discarded. The product may not be returned to refrigerated storage again.

After reconstitution

After reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 3 hours at 25 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

ADVATE with BAXJECT II device: Keep the product vial in the outer carton in order to protect from light.

ADVATE in BAXJECT III system: Keep the sealed blister in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Both the powder vial and the vial containing 2 ml solvent are of type I glass closed with chlorobutyl or bromobutyl rubber stoppers. The product is provided in one of the following configurations:

- ADVATE with BAXJECT II device: Each pack contains a powder vial, a vial containing 2 ml solvent and a device for reconstitution (BAXJECT II).
- ADVATE in BAXJECT III system: Each pack contains a ready to use BAXJECT III system in a sealed blister (the powder vial and the vial containing 2 ml solvent are preassembled with the system for reconstitution).

6.6 Special precautions for disposal and other handling

ADVATE is to be administered intravenously after reconstitution of the product.
The reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear, colourless and free from foreign particles. Do not use solutions that are cloudy or have deposits.

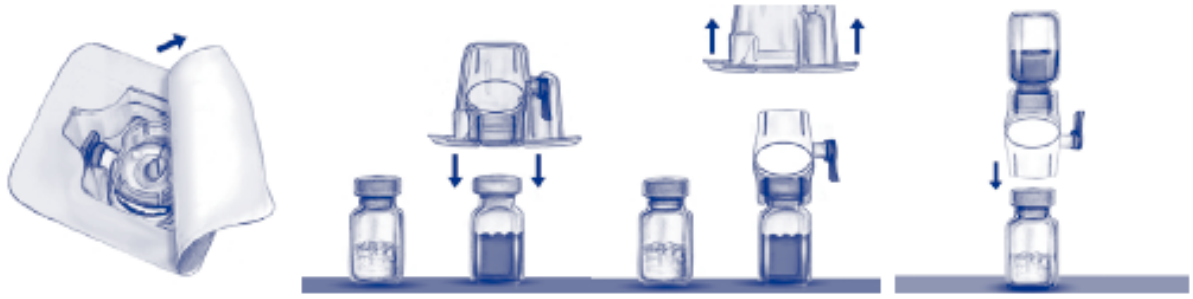
- For administration the use of a luer-lock syringe is required.
- Use within three hours after reconstitution.
- Do not refrigerate the preparation after reconstitution.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

<u>Reconstitution with the BAXJECT II device</u>

- For reconstitution use only the sterilised water for injections and the reconstitution device provided in the pack.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
- Aseptic technique should be used.

1. If the product is still stored in a refrigerator, take both the ADVATE powder and solvent vials from the refrigerator and let them reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. 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. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. 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 the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. 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 powder stopper. The vacuum will draw the solvent into the ADVATE powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. a **Fig. b** **Fig. c**



Reconstitution with the BAXJECT III system

Do not use if the lid is not completely sealed on the blister.

1. If the product is still stored in a refrigerator, take the sealed blister (contains powder and solvent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Open the ADVATE package by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place the ADVATE on a flat surface with the solvent vial on top (Fig. 1). The solvent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
5. With one hand holding the ADVATE in the BAXJECT III system, press down firmly on the solvent vial with the other hand until the system is fully collapsed and the solvent flows down into the ADVATE vial (Fig. 2). Do not tilt the system until the transfer is complete.
6. Verify that the solvent transfer is complete. Swirl gently until all material is dissolved (Fig. 3). Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. 1

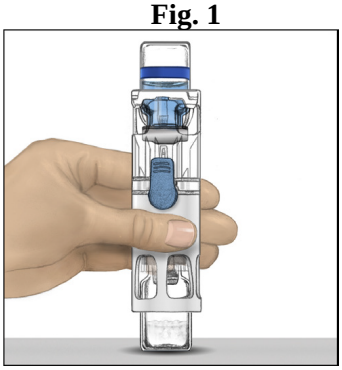


Fig. 2

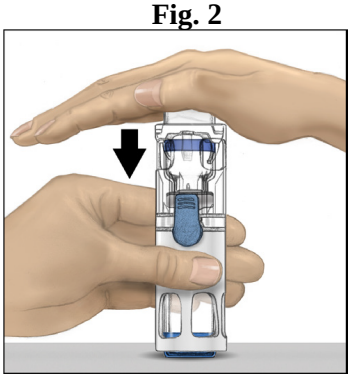
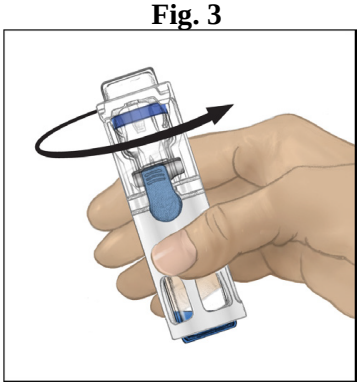


Fig. 3



Administration

Use aseptic technique

Parenteral medicinal 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 / BAXJECT III. **Do not draw air into the syringe**. Connect the syringe to BAXJECT II / BAXJECT III.
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe. Inject intravenously. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 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).

7. MARKETING AUTHORISATION HOLDER

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A-1221 Vienna
Austria
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBERS

EU/1/03/271/007
EU/1/03/271/008
EU/1/03/271/009
EU/1/03/271/010
EU/1/03/271/017
EU/1/03/271/018
EU/1/03/271/019
EU/1/03/271/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 20 December 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Baxalta Manufacturing Sàrl
Route de Pierre-à-Bot 111
CH-2000 Neuchâtel
Switzerland

Takeda Manufacturing Singapore Pte. Ltd.
2A Woodlands Industrial Park D Street 2
Singapore 737779
Singapore

Name and address of the manufacturer responsible for batch release

Baxalta Belgium Manufacturing SA
Boulevard René Branquart 80
B-7860 Lessines
Belgium

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder (MAH) shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 250 IU octocog alfa, approx. 50 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 250 IU octocog alfa, 1 vial with 5 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 250 IU/5 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 250 IU octocog alfa, approx. 50 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 250 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/5 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 5 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

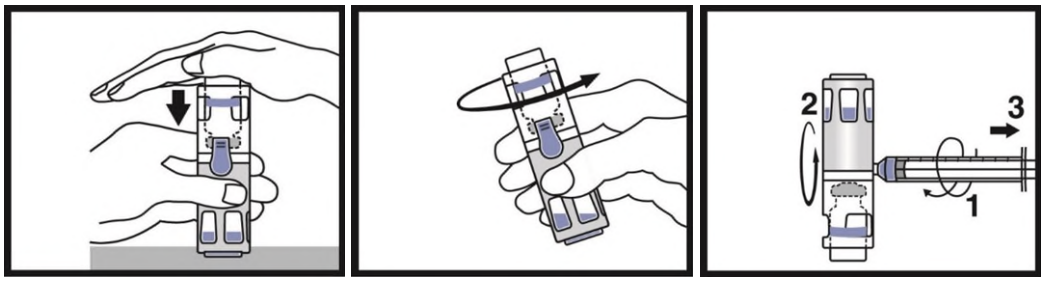
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 250

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 500 IU octocog alfa, approx. 100 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 500 IU octocog alfa, 1 vial with 5 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 500 IU/5 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 500 IU octocog alfa, approx. 100 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 500 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU/5 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 5 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

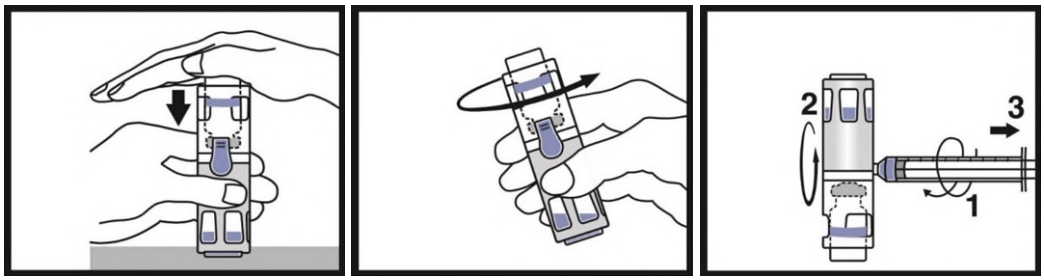
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 500

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 000 IU octocog alfa, approx. 200 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 000 IU octocog alfa, 1 vial with 5 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 000 IU/5 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 000 IU octocog alfa, approx. 200 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 000 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000 IU/5 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 5 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

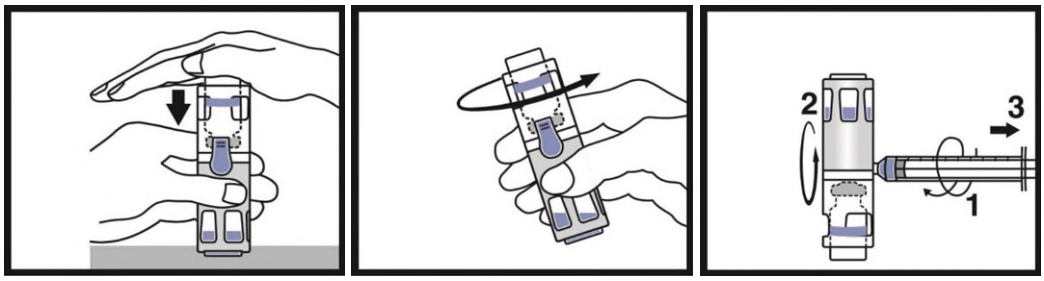
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 500 IU octocog alfa, approx. 300 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 500 IU octocog alfa, 1 vial with 5 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 500 IU/5 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 500 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 500 IU octocog alfa, approx. 300 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 500 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500 IU/5 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 5 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

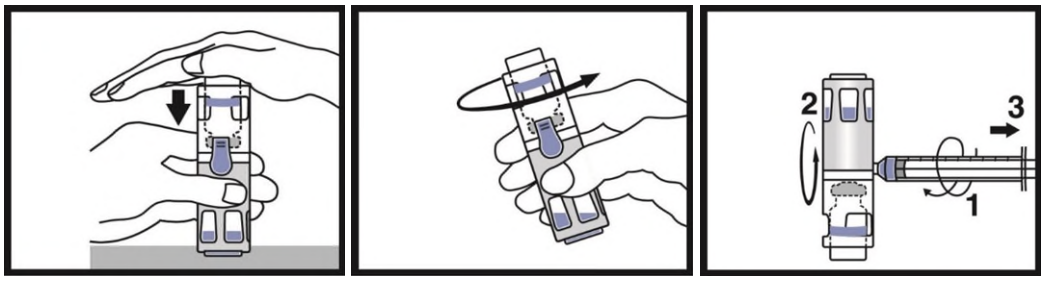
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 500

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 2 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 2 000 IU octocog alfa, approx. 400 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 2 000 IU octocog alfa, 1 vial with 5 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 2 000 IU/5 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 000 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 2 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 2 000 IU octocog alfa, approx. 400 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 2 000 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 2 000 IU/5 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 5 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 2 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

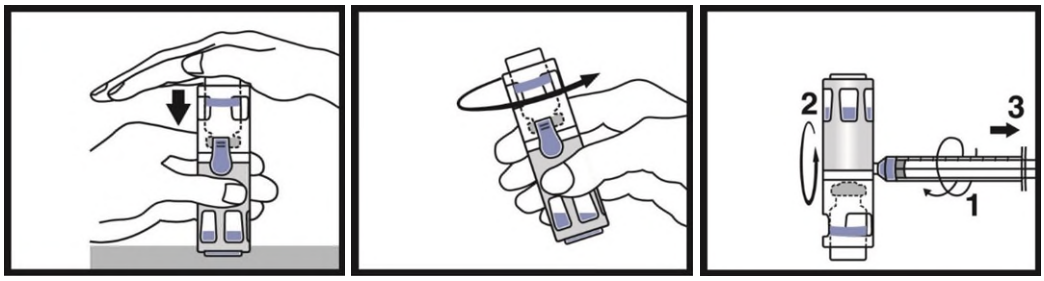
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 2 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 3 000 IU octocog alfa, approx. 600 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 3 000 IU octocog alfa, 1 vial with 5 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 3 000 IU/5 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 000 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 3 000 IU octocog alfa, approx. 600 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 3 000 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 5 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 3 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

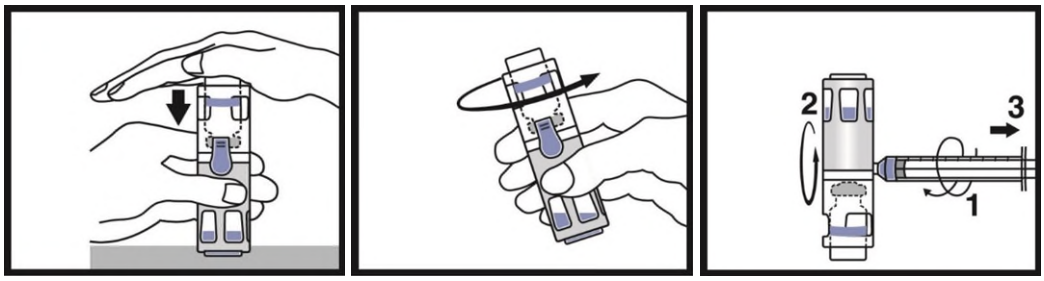
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 3 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 250 IU octocog alfa, approx. 125 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 250 IU octocog alfa, 1 vial with 2 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 250 IU/2 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 250 IU octocog alfa, approx. 125 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 250 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU/2 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 2 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

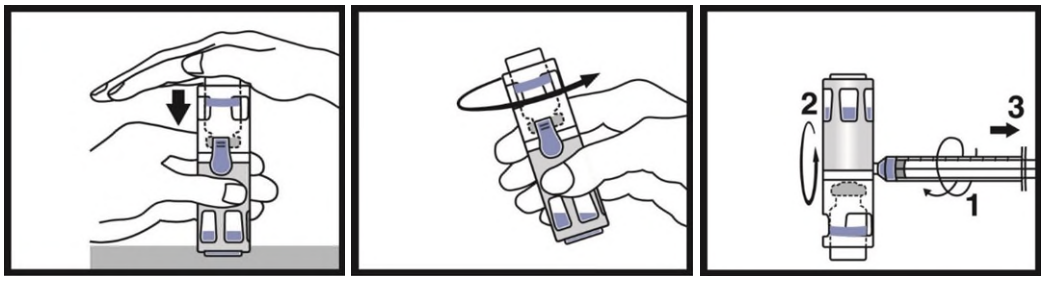
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 250

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 500 IU octocog alfa, approx. 250 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 500 IU octocog alfa, 1 vial with 2 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 500 IU/2 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 500 IU octocog alfa, approx. 250 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 500 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU/2 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 2 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

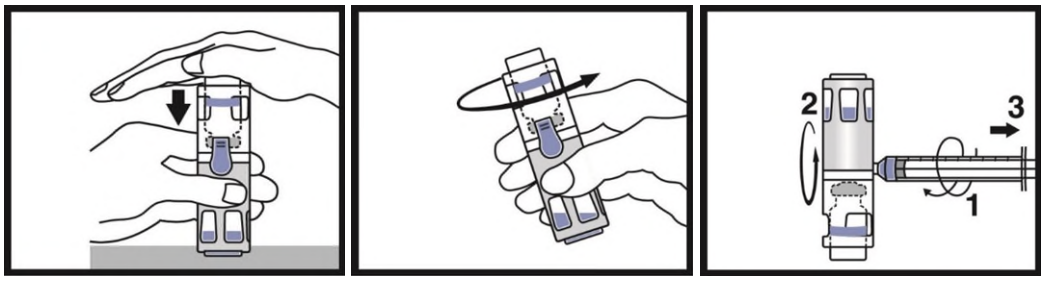
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 500

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 000 IU octocog alfa, approx. 500 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 000 IU octocog alfa, 1 vial with 2 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 000 IU/2 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 000 IU octocog alfa, approx. 500 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 000 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1 000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000 IU/2 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 2 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 000

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

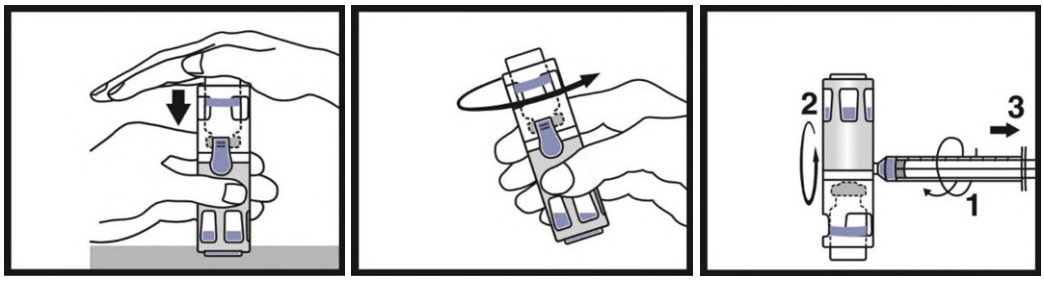
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 000

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 500 IU octocog alfa, approx. 750 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 500 IU octocog alfa, 1 vial with 2 ml sterilised water for injections,
1 BAXJECT II device.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 500 IU/2 ml powder for solution for injection

octocog alfa
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 500 IU octocog alfa

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial: 1 500 IU octocog alfa, approx. 750 IU/ml after reconstitution.

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), glutathione (reduced). Solvent: sterilised water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1 500 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 25 °C) for a single period up to 6 months.

End of 6 month period, if stored at room temperature:
Do not use after the expiry date.

Use immediately or within 3 hours of reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/03/271/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADVATE 1500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

octocog alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intravenous use, after reconstitution.
Use immediately or within 3 hours of reconstitution.
Do not use if packaging is opened or damaged.
Powder vial and 2 ml solvent preassembled in BAXJECT III system.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1 500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

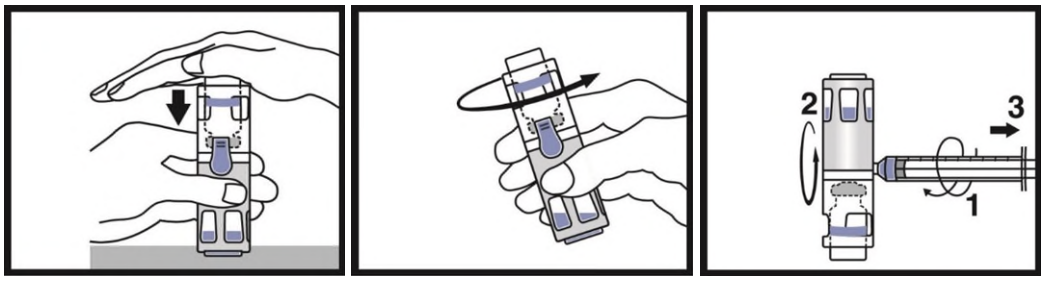
3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADVATE 1 500

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ADVATE 250 IU/5 ml powder and solvent for solution for injection
ADVATE 500 IU/5 ml powder and solvent for solution for injection
ADVATE 1 000 IU/5 ml powder and solvent for solution for injection
ADVATE 1 500 IU/5 ml powder and solvent for solution for injection
ADVATE 2 000 IU/5 ml powder and solvent for solution for injection
ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADVATE is and what it is used for

ADVATE contains the active substance octocog alfa, human coagulation factor VIII produced by recombinant DNA technology. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADVATE is used for the treatment and prevention of bleeding in patients of all age groups with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

ADVATE is prepared without the addition of any human- or animal-derived protein in the entire manufacturing process.

2. What you need to know before you use ADVATE

Do not use ADVATE
- if you are allergic to octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor before using ADVATE. You should tell your doctor if you have been previously treated with factor VIII products, especially if you developed inhibitors, since there might be a higher

risk that it happens again. Inhibitors are blocking antibodies against factor VIII that reduce the efficacy of ADVATE to prevent or control bleeding. Development of inhibitors is a known complication in the treatment of haemophilia A. If your bleeding is not controlled with ADVATE, tell your doctor immediately.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADVATE. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These symptoms can constitute an early symptom of an anaphylactic shock, manifestations of which may additionally include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you have a catheter (central venous access device) where this medicine can be administered into your bloodstream, you may be at risk of developing catheter-related infections or blood clots.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child's bleeding is not being controlled with ADVATE, tell your doctor immediately.

Children and adolescents

The listed warnings and precautions apply to both adults and children (from 0 to 18 years of age).

Other medicines and ADVATE

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

ADVATE has no or negligible influence on your ability to drive or to use machines.

ADVATE contains sodium

This medicine contains 10 mg sodium (main component of cooking salt) per vial. This is equivalent to 0.5% of the recommended maximum daily dietary intake of sodium for an adult.

ADVATE contains polysorbate 80

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.1 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

3. How to use ADVATE

Treatment with ADVATE will be started by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADVATE (in international units or IU) depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADVATE is working for you. Usually, the replacement therapy with ADVATE is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding

The usual dose of octocog alfa is 20 to 40 IU per kg body weight, administered every 2 to 3 days. However, in some cases, especially in younger patients, more frequent injections or higher doses may be necessary.

Treatment of bleeding

The dose of octocog alfa is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

Dose (IU) = body weight (kg) x desired factor VIII rise (% of normal) x 0.5

If you have the impression that the effect of ADVATE is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

For the treatment of bleeding the dosing in children does not differ from adult patients. For the prevention of bleeding in children under the age of 6, doses of 20 to 50 IU per kg body weight 3 to 4 times weekly are recommended. The administration of ADVATE in children (intravenously) does not differ from the administration in adults. A central venous access device (CVAD) may become necessary to allow frequent infusions of factor VIII products.

How ADVATE is given

ADVATE is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADVATE as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADVATE than you should

Always take ADVATE exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADVATE than recommended, tell your doctor as soon as possible.

If you forget to use ADVATE

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADVATE

Do not stop using ADVATE without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 people); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 people). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Factor VIII inhibitors (for children not previously treated with factor VIII medicines).

Common side effects (may affect up to 1 in 10 people)
headache and fever.

Uncommon side effects (may affect up to 1 in 100 people)
Factor VIII inhibitors (for patients who have received previous treatment with factor VIII (more than 150 days of treatment)), dizziness, flu, fainting, abnormal heartbeat, red itchy bumps on the skin, chest discomfort, injection site bruise, injection site reaction, itching, increased sweating, unusual taste in the mouth, hot flushes, migraines, memory impairment, chills, diarrhoea, nausea, vomiting, shortness of breath, sore throat, bruise, tremor, decreased coagulation factor VIII level, complications or bruising after medical procedure, feeling abnormal, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, foot and leg swelling, reduced percentage of red blood cells, increase in a type of white blood cells (monocytes), and pain in the upper abdomen or lower chest.

Related to surgery
catheter-related infection, decreased red cell blood count, swelling of limbs and joints, prolonged bleeding after drain removal, decreased factor VIII level and post-operative bruise.

Related to central venous access devices (CVAD)
catheter-related infection, systemic infection and local blood clot at the catheter site.

Side effects with unknown frequency (frequency cannot be estimated from the available data)
potentially life-threatening reactions (anaphylaxis) and other allergic reactions (hypersensitivity), general disorders (tiredness, lack of energy).

Additional side effects in children

Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in side effects were noted in the clinical studies.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADVATE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and on the carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

During the shelf life the powder vial may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. In this case, this medicine expires at the end of this 6 month period or the expiration date printed on the product vial, whichever is earlier. Please record the end of the 6 months 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.

This product is for single use only. Discard any unused solution appropriately.

Use the product immediately once the powder is completely dissolved.

Do not refrigerate the solution after preparation.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADVATE contains
- The active substance is octocog alfa (human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1 000, 1 500, 2 000, or 3 000 IU octocog alfa.
- The other ingredients are mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), and glutathione (reduced). See section 2 "ADVATE contains sodium" and "ADVATE contains polysorbate 80".
- The solvent vial contains 5 ml sterilised water for injections.

What ADVATE looks like and contents of the pack

ADVATE is a white to off-white friable powder. After reconstitution, the solution is clear, colourless and free from foreign particles.
Each pack also contains a device for reconstitution (BAXJECT II).

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Manufacturer
Baxalta Belgium Manufacturing SA
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/

Instructions for preparation and administration

Aseptic technique is required during preparation of the solution and administration.

Use only the sterilised water for injections and the reconstitution device for preparation of the solution that are provided with each package of ADVATE. ADVATE must not be mixed with other medicinal products or solvents.

It is strongly recommended that every time ADVATE is administered, the name and batch number of the product are recorded.

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration as indicated by the symbol:  .
- Do not refrigerate the solution after preparation.

1. If the product is still stored in a refrigerator, take both the ADVATE powder and solvent vials from the refrigerator and let them reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. 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. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. 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 the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. 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 powder stopper. The vacuum will draw the solvent into the ADVATE powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. a

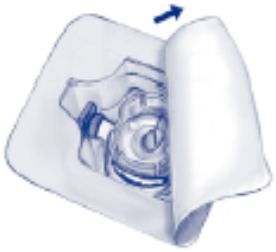


Fig. b

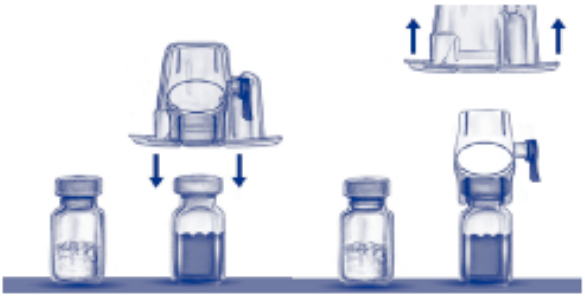


Fig. c

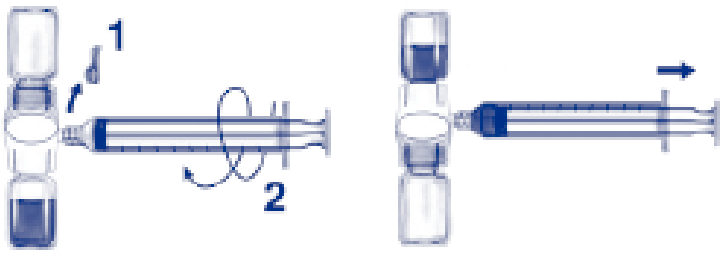
Instructions for injection
For administration the use of a luer-lock syringe is required.

Important note:

- Do not try to administer the injection unless you have received special training from your doctor or nurse.
- Inspect the prepared solution for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from foreign particles).
  Do not use ADVATE if the solution is not fully clear or not completely dissolved.

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 (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe and inject the reconstituted solution into a vein. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. (See section 4 "Possible side effects").
5. Discard any unused solution appropriately.

Fig. d **Fig. e**



The following information is intended for healthcare professionals only:

On demand treatment
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.

The dose 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.

Table 1. Guide for 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 injections 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 injections 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 injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.

Degree of haemorrhage/type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/duration of therapy (days)
Surgery *Minor* 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.
Major	80 – 100 (pre- and post-operative)	Repeat injections 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).

Prophylaxis
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 dosage intervals or higher doses may be necessary.

Paediatric population
For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. 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 for prophylactic therapy.

Package leaflet: Information for the user

ADVATE 250 IU/5 ml powder and solvent for solution for injection
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ADVATE 1 000 IU/5 ml powder and solvent for solution for injection
ADVATE 1 500 IU/5 ml powder and solvent for solution for injection
ADVATE 2 000 IU/5 ml powder and solvent for solution for injection
ADVATE 3 000 IU/5 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADVATE is and what it is used for

ADVATE contains the active substance octocog alfa, human coagulation factor VIII produced by recombinant DNA technology. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADVATE is used for the treatment and prevention of bleeding in patients of all age groups with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

ADVATE is prepared without the addition of any human- or animal-derived protein in the entire manufacturing process.

2. What you need to know before you use ADVATE

Do not use ADVATE
- if you are allergic to octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor before using ADVATE. You should tell your doctor if you have been previously treated with factor VIII products, especially if you developed inhibitors, since there might be a higher

risk that it happens again. Inhibitors are blocking antibodies against factor VIII that reduce the efficacy of ADVATE to prevent or control bleeding. Development of inhibitors is a known complication in the treatment of haemophilia A. If your bleeding is not controlled with ADVATE, tell your doctor immediately.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADVATE. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These symptoms can constitute an early symptom of an anaphylactic shock, manifestations of which may additionally include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you have a catheter (central venous access device) where this medicine can be administered into your bloodstream, you may be at risk of developing catheter-related infections or blood clots.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child's bleeding is not being controlled with ADVATE, tell your doctor immediately.

Children and adolescents

The listed warnings and precautions apply to both adults and children (from 0 to 18 years of age).

Other medicines and ADVATE

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

ADVATE has no or negligible influence on your ability to drive or to use machines.

ADVATE contains sodium

This medicine contains 10 mg sodium (main component of cooking salt) per vial. This is equivalent to 0.5% of the recommended maximum daily dietary intake of sodium for an adult.

ADVATE contains polysorbate 80

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.1 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

3. How to use ADVATE

Treatment with ADVATE will be started by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADVATE (in international units or IU) depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADVATE is working for you. Usually, the replacement therapy with ADVATE is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding

The usual dose of octocog alfa is 20 to 40 IU per kg body weight, administered every 2 to 3 days. However, in some cases, especially in younger patients, more frequent injections or higher doses may be necessary.

Treatment of bleeding

The dose of octocog alfa is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

Dose (IU) = body weight (kg) x desired factor VIII rise (% of normal) x 0.5

If you have the impression that the effect of ADVATE is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

For the treatment of bleeding the dosing in children does not differ from adult patients. For the prevention of bleeding in children under the age of 6, doses of 20 to 50 IU per kg body weight 3 to 4 times weekly are recommended. The administration of ADVATE in children (intravenously) does not differ from the administration in adults. A central venous access device (CVAD) may become necessary to allow frequent infusions of factor VIII products.

How ADVATE is given

ADVATE is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADVATE as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADVATE than you should

Always take ADVATE exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADVATE than recommended, tell your doctor as soon as possible.

If you forget to use ADVATE

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADVATE

Do not stop using ADVATE without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 people); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 people). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Factor VIII inhibitors (for children not previously treated with factor VIII medicines).

Common side effects (may affect up to 1 in 10 people)
headache and fever.

Uncommon side effects (may affect up to 1 in 100 people)
Factor VIII inhibitors (for patients who have received previous treatment with factor VIII (more than 150 days of treatment)), dizziness, flu, fainting, abnormal heartbeat, red itchy bumps on the skin, chest discomfort, injection site bruise, injection site reaction, itching, increased sweating, unusual taste in the mouth, hot flushes, migraines, memory impairment, chills, diarrhoea, nausea, vomiting, shortness of breath, sore throat, bruise, tremor, decreased coagulation factor VIII level, complications or bruising after medical procedure, feeling abnormal, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, foot and leg swelling, reduced percentage of red blood cells, increase in a type of white blood cells (monocytes), and pain in the upper abdomen or lower chest.

Related to surgery
catheter-related infection, decreased red cell blood count, swelling of limbs and joints, prolonged bleeding after drain removal, decreased factor VIII level and post-operative bruise.

Related to central venous access devices (CVAD)
catheter-related infection, systemic infection and local blood clot at the catheter site.

Side effects with unknown frequency (frequency cannot be estimated from the available data)
potentially life-threatening reactions (anaphylaxis) and other allergic reactions (hypersensitivity), general disorders (tiredness, lack of energy).

Additional side effects in children

Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in side effects were noted in the clinical studies.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADVATE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and on the carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

During the shelf life the blister with the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. In this case, this medicine expires at the end of this 6 month period or the expiration date printed on the blister, whichever is earlier. Please record the end of the 6 months storage at room temperature on the product carton. The product may not be returned to refrigerated storage after storage at room temperature.

Keep the blister with the product in the outer carton in order to protect from light.

This product is for single use only. Discard any unused solution appropriately.

Use the product immediately once the powder is completely dissolved.

Do not refrigerate the solution after preparation.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADVATE contains
- The active substance is octocog alfa (human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1 000, 1 500, 2 000, or 3 000 IU octocog alfa.
- The other ingredients are mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), and glutathione (reduced). See section 2 "ADVATE contains sodium" and "ADVATE contains polysorbate 80".
- The solvent vial contains 5 ml sterilised water for injections.

What ADVATE looks like and contents of the pack

ADVATE is a white to off-white friable powder. After reconstitution, the solution is clear, colourless and free from foreign particles.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/

Instructions for preparation and administration

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

It is strongly recommended that every time ADVATE is administered, the name and batch number of the product are recorded.

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the lid is not completely sealed on the blister.
- Do not refrigerate the solution after preparation.

1. If the product is still stored in a refrigerator, take the sealed blister (contains powder and solvent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Open the ADVATE package by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place the ADVATE on a flat surface with the solvent vial on top (Fig. 1). The solvent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
5. With one hand holding the ADVATE in the BAXJECT III system, press down firmly on the solvent vial with the other hand until the system is fully collapsed and the solvent flows down into the ADVATE vial (Fig. 2). Do not tilt the system until the transfer is complete.
6. Verify that the solvent transfer is complete. Swirl gently until all material is dissolved (Fig. 3). Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. 1

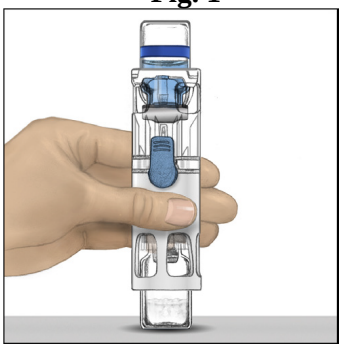


Fig. 2

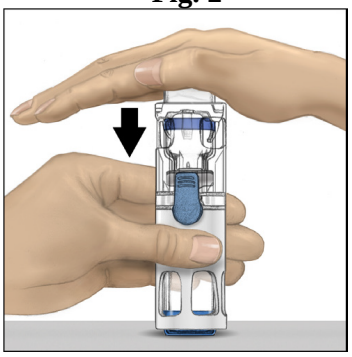
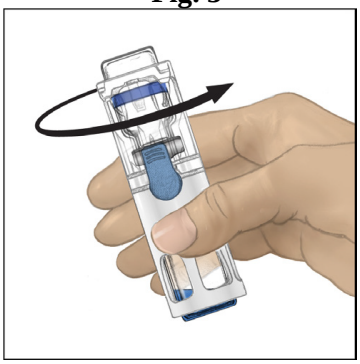


Fig. 3



Instructions for injection

Aseptic technique is required during administration.
For administration the use of a luer-lock syringe is required.

Important note:

- Do not try to administer the injection unless you have received special training from your doctor or nurse.
- Inspect the prepared solution for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from foreign particles).
  Do not use ADVATE if the solution is not fully clear or not completely dissolved.

1. Remove the blue cap from BAXJECT III. **Do not draw air into the syringe**. Connect the syringe to BAXJECT III.
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe and inject the reconstituted solution into a vein. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. (See section 4 "Possible side effects").
5. Discard any unused solution appropriately.

The following information is intended for healthcare professionals only:

On demand treatment
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.

The dose 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.

Table 1. Guide for 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 injections 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 injections 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 injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor 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.
Major	80 – 100 (pre- and post-operative)	Repeat injections 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).

Prophylaxis
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 dosage intervals or higher doses may be necessary.

Paediatric population
For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. 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 for prophylactic therapy.

Package leaflet: Information for the user

ADVATE 250 IU/2 ml powder and solvent for solution for injection
ADVATE 500 IU/2 ml powder and solvent for solution for injection
ADVATE 1 000 IU/2 ml powder and solvent for solution for injection
ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADVATE is and what it is used for

ADVATE contains the active substance octocog alfa, human coagulation factor VIII produced by recombinant DNA technology. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADVATE is used for the treatment and prevention of bleeding in patients of all age groups with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

ADVATE is prepared without the addition of any human- or animal-derived protein in the entire manufacturing process.

2. What you need to know before you use ADVATE

Do not use ADVATE
- if you are allergic to octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor before using ADVATE. You should tell your doctor if you have been previously treated with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again. Inhibitors are blocking antibodies against factor VIII that reduce the efficacy of ADVATE to prevent or control bleeding. Development of inhibitors is a known complication in the

treatment of haemophilia A. If your bleeding is not controlled with ADVATE, tell your doctor immediately.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADVATE. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These symptoms can constitute an early symptom of an anaphylactic shock, manifestations of which may additionally include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you have a catheter (central venous access device) where this medicine can be administered into your bloodstream, you may be at risk of developing catheter-related infections or blood clots.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child's bleeding is not being controlled with ADVATE, tell your doctor immediately.

Children and adolescents

The listed warnings and precautions apply to both adults and children (from 0 to 18 years of age).

Other medicines and ADVATE

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

ADVATE has no or negligible influence on your ability to drive or to use machines.

ADVATE contains sodium

This medicine contains 10 mg sodium (main component of cooking salt) per vial. This is equivalent to 0.5% of the recommended maximum daily dietary intake of sodium for an adult.

ADVATE contains polysorbate 80

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.25 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

Misapplication of ADVATE

Misapplication (injection into the artery or outside the vein) should be avoided as mild, short term injection site reactions, such as bruising and redness, may occur.

3. How to use ADVATE

Treatment with ADVATE will be started by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADVATE (in international units or IU) depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADVATE is working for you. Usually, the replacement therapy with ADVATE is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding

The usual dose of octocog alfa is 20 to 40 IU per kg body weight, administered every 2 to 3 days. However, in some cases, especially in younger patients, more frequent injections or higher doses may be necessary.

Treatment of bleeding

The dose of octocog alfa is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

Dose (IU) = body weight (kg) x desired factor VIII rise (% of normal) x 0.5

If you have the impression that the effect of ADVATE is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

For the treatment of bleeding the dosing in children does not differ from adult patients. For the prevention of bleeding in children under the age of 6, doses of 20 to 50 IU per kg body weight 3 to 4 times weekly are recommended. The administration of ADVATE in children (intravenously) does not differ from the administration in adults. A central venous access device (CVAD) may become necessary to allow frequent infusions of factor VIII products.

Due to the decrease in injection volume for ADVATE reconstituted in 2 ml, the time to react to hypersensitivity reactions during an injection is further reduced. Therefore, caution is advised during injection of ADVATE reconstituted in 2 ml, especially in children.

How ADVATE is given

ADVATE is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADVATE as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADVATE than you should

Always take ADVATE exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADVATE than recommended, tell your doctor as soon as possible.

If you forget to use ADVATE

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADVATE

Do not stop using ADVATE without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:
- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 people); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 people). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Factor VIII inhibitors (for children not previously treated with factor VIII medicines).

Common side effects (may affect up to 1 in 10 people)
headache and fever.

Uncommon side effects (may affect up to 1 in 100 people)
Factor VIII inhibitors (for patients who have received previous treatment with factor VIII (more than 150 days of treatment)), dizziness, flu, fainting, abnormal heartbeat, red itchy bumps on the skin, chest discomfort, injection site bruise, injection site reaction, itching, increased sweating, unusual taste in the mouth, hot flushes, migraines, memory impairment, chills, diarrhoea, nausea, vomiting, shortness of breath, sore throat, bruise, tremor, decreased coagulation factor VIII level, complications or bruising after medical procedure, feeling abnormal, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, foot and leg swelling, reduced percentage of red blood cells, increase in a type of white blood cells (monocytes), and pain in the upper abdomen or lower chest.

Related to surgery
catheter-related infection, decreased red cell blood count, swelling of limbs and joints, prolonged bleeding after drain removal, decreased factor VIII level and post-operative bruise.

Related to central venous access devices (CVAD)
catheter-related infection, systemic infection and local blood clot at the catheter site.

Side effects with unknown frequency (frequency cannot be estimated from the available data) potentially life-threatening reactions (anaphylaxis) and other allergic reactions (hypersensitivity), general disorders (tiredness, lack of energy).

Additional side effects in children

Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in side effects were noted in the clinical studies.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADVATE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and on the carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

During the shelf life the powder vial may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. In this case, this medicine expires at the end of this 6 month period or the expiration date printed on the product vial, whichever is earlier. Please record the end of the 6 months 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.

This product is for single use only. Discard any unused solution appropriately.

Use the product immediately once the powder is completely dissolved.

Do not refrigerate the solution after preparation.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADVATE contains
- The active substance is octocog alfa (human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1 000, or 1 500 IU octocog alfa.
- The other ingredients are mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), and glutathione (reduced). See section 2 "ADVATE contains sodium" and "ADVATE contains polysorbate 80".
- The solvent vial contains 2 ml sterilised water for injections.

What ADVATE looks like and contents of the pack

ADVATE is a white to off-white friable powder. After reconstitution, the solution is clear, colourless and free from foreign particles.
Each pack also contains a device for reconstitution (BAXJECT II).

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/

Instructions for preparation and administration

Aseptic technique is required during preparation of the solution and administration.

Use only the sterilised water for injections and the reconstitution device for preparation of the solution that are provided with each package of ADVATE. ADVATE must not be mixed with other medicinal products or solvents.

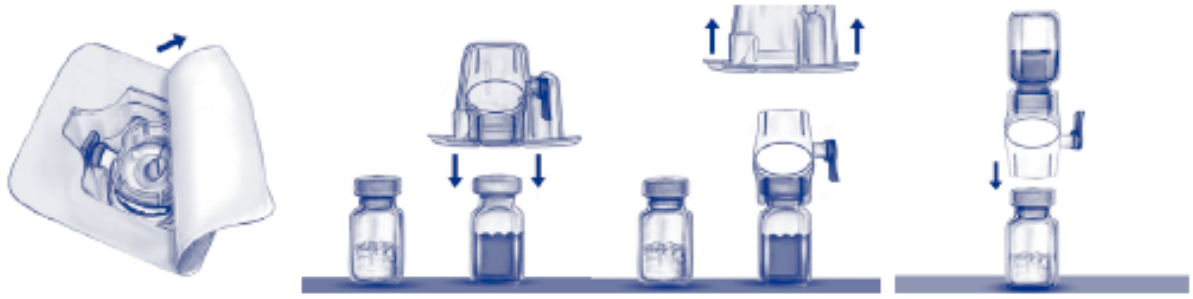
It is strongly recommended that every time ADVATE is administered, the name and batch number of the product are recorded.

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration as indicated by the symbol:  .
- Do not refrigerate the solution after preparation.

1. If the product is still stored in a refrigerator, take both the ADVATE powder and solvent vials from the refrigerator and let them reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. 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. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. 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 the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. 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 powder stopper. The vacuum will draw the solvent into the ADVATE powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. a **Fig. b** **Fig. c**



Instructions for injection

For administration the use of a luer-lock syringe is required.

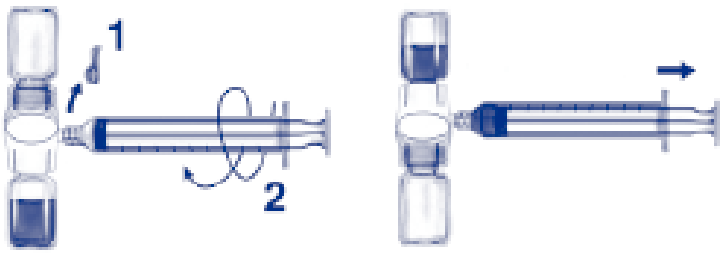
Important note:

- Do not try to administer the injection unless you have received special training from your doctor or nurse.
- Inspect the prepared solution for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from foreign particles).
  Do not use ADVATE if the solution is not fully clear or not completely dissolved.

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 (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe and inject the reconstituted solution into a vein. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. (See section 4 "Possible side effects").
5. Discard any unused solution appropriately.

Fig. d **Fig. e**



The following information is intended for healthcare professionals only:

On demand treatment
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.

The dose 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.

Table 1. Guide for 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 injections 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 injections 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 injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor 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.

Degree of haemorrhage/type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/duration of therapy (days)
Major	80 – 100 (pre- and post-operative)	Repeat injections 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).

Prophylaxis
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 dosage intervals or higher doses may be necessary.

Paediatric population
For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. 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 for prophylactic therapy.

Package leaflet: Information for the user

ADVATE 250 IU/2 ml powder and solvent for solution for injection
ADVATE 500 IU/2 ml powder and solvent for solution for injection
ADVATE 1 000 IU/2 ml powder and solvent for solution for injection
ADVATE 1 500 IU/2 ml powder and solvent for solution for injection

octocog alfa (recombinant human coagulation factor VIII)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADVATE is and what it is used for

ADVATE contains the active substance octocog alfa, human coagulation factor VIII produced by recombinant DNA technology. Factor VIII is necessary for the blood to form clots and stop bleedings. In patients with haemophilia A (inborn lack of factor VIII), it is missing or not working properly.

ADVATE is used for the treatment and prevention of bleeding in patients of all age groups with haemophilia A (an inherited bleeding disorder caused by lack of factor VIII).

ADVATE is prepared without the addition of any human- or animal-derived protein in the entire manufacturing process.

2. What you need to know before you use ADVATE

Do not use ADVATE
- if you are allergic to octocog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor before using ADVATE. You should tell your doctor if you have been previously treated with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again. Inhibitors are blocking antibodies against factor VIII that reduce the efficacy of ADVATE to prevent or control bleeding. Development of inhibitors is a known complication in the

treatment of haemophilia A. If your bleeding is not controlled with ADVATE, tell your doctor immediately.

There is a rare risk that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ADVATE. You should be aware of the early signs of allergic reactions such as rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, general feeling of being unwell, and dizziness. These symptoms can constitute an early symptom of an anaphylactic shock, manifestations of which may additionally include extreme dizziness, loss of consciousness, and extreme difficulty in breathing.

If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

If you have a catheter (central venous access device) where this medicine can be administered into your bloodstream, you may be at risk of developing catheter-related infections or blood clots.

If you suffer from cardiac disease, please inform your doctor, as there is an increased risk of blood clotting (coagulation) complications.

Patients developing factor VIII inhibitors
The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child's bleeding is not being controlled with ADVATE, tell your doctor immediately.

Children and adolescents

The listed warnings and precautions apply to both adults and children (from 0 to 18 years of age).

Other medicines and ADVATE

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

ADVATE has no or negligible influence on your ability to drive or to use machines.

ADVATE contains sodium

This medicine contains 10 mg sodium (main component of cooking salt) per vial. This is equivalent to 0.5% of the recommended maximum daily dietary intake of sodium for an adult.

ADVATE contains polysorbate 80

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.25 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

Misapplication of ADVATE

Misapplication (injection into the artery or outside the vein) should be avoided as mild, short term injection site reactions, such as bruising and redness, may occur.

3. How to use ADVATE

Treatment with ADVATE will be started by a doctor who is experienced in the care of patients with haemophilia A.

Your doctor will calculate your dose of ADVATE (in international units or IU) depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. The frequency of administration will depend on how well ADVATE is working for you. Usually, the replacement therapy with ADVATE is a life-long treatment.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Prevention of bleeding

The usual dose of octocog alfa is 20 to 40 IU per kg body weight, administered every 2 to 3 days. However, in some cases, especially in younger patients, more frequent injections or higher doses may be necessary.

Treatment of bleeding

The dose of octocog alfa is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

Dose (IU) = body weight (kg) x desired factor VIII rise (% of normal) x 0.5

If you have the impression that the effect of ADVATE is insufficient, talk to your doctor.
Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Use in children and adolescents

For the treatment of bleeding the dosing in children does not differ from adult patients. For the prevention of bleeding in children under the age of 6, doses of 20 to 50 IU per kg body weight 3 to 4 times weekly are recommended. The administration of ADVATE in children (intravenously) does not differ from the administration in adults. A central venous access device (CVAD) may become necessary to allow frequent infusions of factor VIII products.

Due to the decrease in injection volume for ADVATE reconstituted in 2 ml, the time to react to hypersensitivity reactions during an injection is further reduced. Therefore, caution is advised during injection of ADVATE reconstituted in 2 ml, especially in children.

How ADVATE is given

ADVATE is usually injected into a vein (intravenously) by your doctor or nurse. You or someone else might also administer ADVATE as an injection, but only after receiving adequate training. Detailed instructions for self-administration are given at the end of this package leaflet.

If you use more ADVATE than you should

Always take ADVATE exactly as your doctor has told you. You should check with your doctor if you are not sure. If you inject more ADVATE than recommended, tell your doctor as soon as possible.

If you forget to use ADVATE

Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using ADVATE

Do not stop using ADVATE without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If **severe, sudden allergic reactions** (anaphylactic) occur, the injection **must be stopped immediately**. You must **contact your doctor immediately** if you have any of the following early symptoms of allergic reactions:
- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

Severe symptoms, including difficulty in breathing and (nearly) fainting, require prompt emergency treatment.

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 people); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 people). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
Factor VIII inhibitors (for children not previously treated with factor VIII medicines).

Common side effects (may affect up to 1 in 10 people)
headache and fever.

Uncommon side effects (may affect up to 1 in 100 people)
Factor VIII inhibitors (for patients who have received previous treatment with factor VIII (more than 150 days of treatment)), dizziness, flu, fainting, abnormal heartbeat, red itchy bumps on the skin, chest discomfort, injection site bruise, injection site reaction, itching, increased sweating, unusual taste in the mouth, hot flushes, migraines, memory impairment, chills, diarrhoea, nausea, vomiting, shortness of breath, sore throat, bruise, tremor, decreased coagulation factor VIII level, complications or bruising after medical procedure, feeling abnormal, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, foot and leg swelling, reduced percentage of red blood cells, increase in a type of white blood cells (monocytes), and pain in the upper abdomen or lower chest.

Related to surgery
catheter-related infection, decreased red cell blood count, swelling of limbs and joints, prolonged bleeding after drain removal, decreased factor VIII level and post-operative bruise.

Related to central venous access devices (CVAD)
catheter-related infection, systemic infection and local blood clot at the catheter site.

Side effects with unknown frequency (frequency cannot be estimated from the available data) potentially life-threatening reactions (anaphylaxis) and other allergic reactions (hypersensitivity), general disorders (tiredness, lack of energy).

Additional side effects in children

Other than the development of inhibitors in previously untreated paediatric patients (PUPs), and catheter-related complications, no age-specific differences in side effects were noted in the clinical studies.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADVATE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the label and on the carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

During the shelf life the blister with the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. In this case, this medicine expires at the end of this 6 month period or the expiration date printed on the blister, whichever is earlier. Please record the end of the 6 months storage at room temperature on the product carton. The product may not be returned to refrigerated storage after storage at room temperature.

Keep the blister with the product in the outer carton in order to protect from light.

This product is for single use only. Discard any unused solution appropriately.

Use the product immediately once the powder is completely dissolved.

Do not refrigerate the solution after preparation.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADVATE contains

- The active substance is octocog alfa (human coagulation factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1 000, or 1 500 IU octocog alfa.
- The other ingredients are mannitol (E421), sodium chloride, histidine, trehalose, calcium chloride (E509), trometamol, polysorbate 80 (E433), and glutathione (reduced). See section 2 "ADVATE contains sodium" and "ADVATE contains polysorbate 80".
- The solvent vial contains 2 ml sterilised water for injections.

What ADVATE looks like and contents of the pack

ADVATE is a white to off-white friable powder. After reconstitution, the solution is clear, colourless and free from foreign particles.

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Takeda Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

Manufacturer
Baxalta Belgium Manufacturing SA
Boulevard René Branquart 80
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Instructions for preparation and administration

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

It is strongly recommended that every time ADVATE is administered, the name and batch number of the product are recorded.

Instructions for reconstitution

- Do not use after the expiry date stated on the labels and carton.
- Do not use if the lid is not completely sealed on the blister.
- Do not refrigerate the solution after preparation.

1. If the product is still stored in a refrigerator, take the sealed blister (contains powder and solvent vials preassembled with the system for reconstitution) from the refrigerator and let it reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Open the ADVATE package by peeling away the lid. Remove the BAXJECT III system from the blister.
4. Place the ADVATE on a flat surface with the solvent vial on top (Fig. 1). The solvent vial has a blue stripe. Do not remove the blue cap until instructed in a later step.
5. With one hand holding the ADVATE in the BAXJECT III system, press down firmly on the solvent vial with the other hand until the system is fully collapsed and the solvent flows down into the ADVATE vial (Fig. 2). Do not tilt the system until the transfer is complete.
6. Verify that the solvent transfer is complete. Swirl gently until all material is dissolved (Fig. 3). Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

Fig. 1

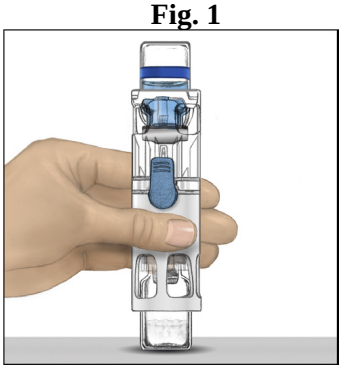


Fig. 2

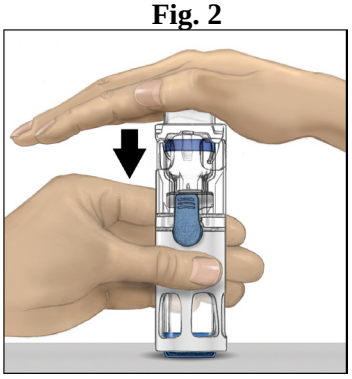
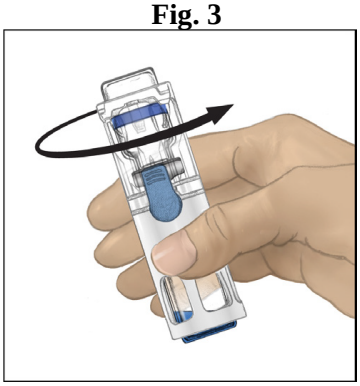


Fig. 3



Instructions for injection

Aseptic technique is required during administration.
For administration the use of a luer-lock syringe is required.

Important note:

- Do not try to administer the injection unless you have received special training from your doctor or nurse.
- Inspect the prepared solution for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from foreign particles).
  Do not use ADVATE if the solution is not fully clear or not completely dissolved.

1. Remove the blue cap from BAXJECT III. **Do not draw air into the syringe**. Connect the syringe to BAXJECT III.
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly.
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe and inject the reconstituted solution into a vein. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute. (See section 4 "Possible side effects").
5. Discard any unused solution appropriately.

The following information is intended for healthcare professionals only:

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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.

The dose 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.

Table 1. Guide for 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 injections 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 injections 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 injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor 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.
Major	80 – 100 (pre- and post-operative)	Repeat injections 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).

Prophylaxis
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 dosage intervals or higher doses may be necessary.

Paediatric population
For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. 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 for prophylactic therapy.