1. NAME OF THE MEDICINAL PRODUCT

ADVATE 500 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ADVATE is approximately 4,000-10,000 IU/mg protein.
Octocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 2332 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) 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.

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.

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 is expressed in International Units (IU), which are related to the WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IUs (relative to the international standard for factor VIII in plasma).

One 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

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 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 postoperative)	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).

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.

During the course of treatment, appropriate determination of plasma factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of plasma factor VIII activity assay is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

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.

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
ADVATE should be administered via the intravenous route. In case of administration by a non health care 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.

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

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 or to mouse or hamster proteins.

4.4 Special warnings and precautions for use

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 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently 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.

Catheter-related complications in treatment
If central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia 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 interaction studies have been performed with ADVATE.

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 breast-feeding only if clearly indicated.

4.7 Effects on ability to drive and use machines

ADVATE has no 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. 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

The following table 2 provides the frequency of adverse drug reactions in clinical trials and from spontaneous reporting. The table is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequency categories are defined 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, undesirable effects are presented in order of decreasing seriousness.

Table 2 Frequency of adverse drug reactions (ADRs) 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)[d] Very common (PUPs)[d]
	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[b]	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).
b) The unexpected decrease in coagulation factor VIII levels occurred in one patient during continuous infusion of ADVATE following surgery (postoperative days 10-14). Haemostasis was maintained at all times during this period and both plasma factor VIII levels and clearance rates returned to appropriate levels by postoperative day 15. Factor VIII inhibitor assays performed after completion of continuous infusion and at study termination were negative.
c) ADR explained in the section below.
d) Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

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, paresthesias, rash, flushing, face swelling, urticaria, and pruritus.

Paediatric population
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.

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.

The factor VIII/von Willebrand Factor complex consists of two molecules (factor VIII and von Willebrand Factor) with different physiological functions. ADVATE contains recombinant coagulation factor VIII (octocog alfa), a glycoprotein that is biologically equivalent to the factor VIII glycoprotein found in human plasma.

Octocog alfa is a glycoprotein consisting of 2332 amino acids with an approximate molecular mass of 280 kD. When infused into a haemophilia patient, octocog alfa binds to endogenous von Willebrand Factor in the patient's circulation. Activated factor VIII acts as a Cofactor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X. Activated Factor X converts prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII activity and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. The plasma levels of factor VIII are increased by replacement therapy, thereby enabling a temporary correction of the factor VIII deficiency and correction of the bleeding tendency.

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.

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 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)	1362.1 ± 311.8	1180.0 ± 432.7	1506.6 ± 530.0	1317.1 ± 438.6	1538.5 ± 519.1
Adjusted Incremental Recovery at Cmax (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 (Cmax - baseline Factor VIII) divided by the dose in IU/kg, where Cmax is the maximal post-infusion Factor VIII measurement.

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
Sodium chloride
Histidine
Trehalose
Calcium chloride
Trometamol
Polysorbate 80
Glutathione (reduced)

Solvent

Sterilised water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

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.

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. The product may not be returned to refrigerated storage again.

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 toppers. 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 solution should be inspected visually for any foreign particulate matter and/or discoloration.

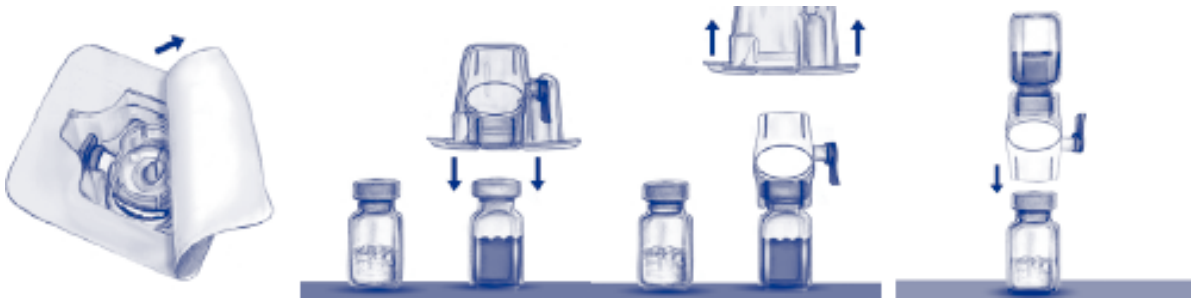
After reconstitution the solution should be clear, colourless and free from foreign particles.
Do not use solutions that are cloudy or have deposits.

- 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**



<u>Reconstitution with the BAXJECT III system</u>

- 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. 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

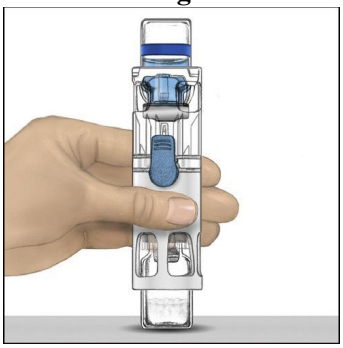


Fig. 2

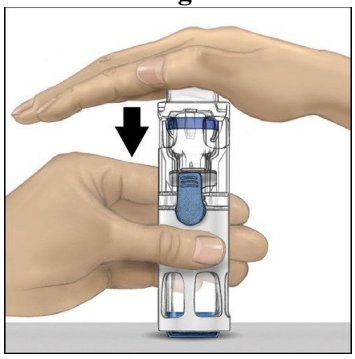
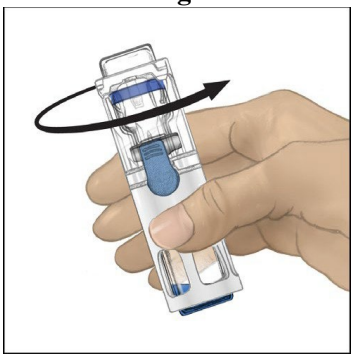


Fig. 3



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

Takeda (Thailand), Ltd.
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 15038/63 (NB)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 2020
Date of latest renewal: 20 September 2021

10. DATE OF REVISION OF THE TEXT

08 Aug 2024