ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 250 IU powder and solvent for solution for injection.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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.

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>

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.

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

*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 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.

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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

* 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 (t½) 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
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 5 ml solvent are of type I glass closed with chlorobutyl 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 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.

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.
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. 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.

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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/271/001
EU/1/03/271/011

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 http://www.ema.europa.eu.
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 100 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 IU (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) * desired factor VIII rise (%) * 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>
<thead>
<tr>
<th>Degree of haemorrhage/hemorrhage type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemorrhosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemorrhosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major</td>
<td>80 – 100 (pre- and postoperative)</td>
<td>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).</td>
</tr>
</tbody>
</table>

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.

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.
**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>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Influenza</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laryngitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor VIII inhibition</td>
<td>Uncommon (PTPs)³</td>
</tr>
<tr>
<td></td>
<td>Lymphangitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity²</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Memory impairment</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eye inflammation</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hot flush</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hyperhidrosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Peripheral oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chest discomfort</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Feeling abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vessel puncture site haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Injection site reaction</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>Not known</td>
</tr>
<tr>
<td>Investigations</td>
<td>Monocyte Count increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Coagulation factor VIII level decreased⁶</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laboratory test abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural complication</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Procedural site reaction</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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 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.

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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU*·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

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 (t₁/₂) 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
- 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 5 ml solvent are of type I glass closed with chlorobutyl 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 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.

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.
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. 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.

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.
2. Connect the syringe to BAXJECT II / BAXJECT III.
3. 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.
4. 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 AUTHORITY

Takeda Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORITY NUMBER(S)

EU/1/03/271/002
EU/1/03/271/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

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 http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT
ADVATE 1000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains nominally 1000 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.

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Including tooth extraction.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
</tr>
</tbody>
</table>

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.

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

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.

ADR explained in the section below.

c) Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

d) Description of selected adverse reactions

ADR 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 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.

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 kDa. 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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)²</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dL)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg·h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

² 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 (t½) 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
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 5 ml solvent are of type I glass closed with chlorobutyl 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 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.

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.
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. 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.

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.
2. Connect the syringe to BAXJECT II / BAXJECT III.
3. 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.
4. 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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/271/003
EU/1/03/271/013

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 http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1500 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 1500 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.

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major</td>
<td>80 – 100 (pre- and postoperative)</td>
<td>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).</td>
</tr>
</tbody>
</table>

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.
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.

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.
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

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Influenza</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laryngitis</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
| 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\(^e\) | 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 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.

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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU*·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

* 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 ($t_{1/2}$) 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
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 5 ml solvent are of type I glass closed with chlorobutyl 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 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.

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.
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. 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.

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.**
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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/03/271/004
EU/1/03/271/014

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**

1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 2000 IU powder and solvent for solution for injection.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains nominally 2000 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.

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Including tooth extraction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>80 – 100 (pre- and postoperative)</td>
<td>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).</td>
</tr>
</tbody>
</table>

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.

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

- 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 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.

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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU*·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)³</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

³ 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 (t½) 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
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 5 ml solvent are of type I glass closed with chlorobutyl 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 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.

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.
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. 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.

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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/03/271/005
EU/1/03/271/015

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 http://www.ema.europa.eu.
1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 3000 IU powder and solvent for solution for injection.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains nominally 3000 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.

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:

\[
\text{Required units (IU)} = \text{body weight (kg)} \times \text{desired factor VIII rise (%) x 0.5}
\]

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>

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.

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

\(^a\) 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

ADR 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
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.

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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg·h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

* 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 ($t_{1/2}$) 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
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 5 ml solvent are of type I glass closed with chlorobutyl 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 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.

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.
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. 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.

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.**
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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/271/006
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 http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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:

\[
\text{Required units (IU)} = \text{body weight (kg)} \times \text{desired factor VIII rise (\%)} \times 0.5
\]

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Influenza</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laryngitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor VIII inhibition</td>
<td>Uncommon (PTPs)*d</td>
</tr>
<tr>
<td></td>
<td>Lymphangitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity*</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Memory impairment</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eye inflammation</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hot flush</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hyperhidrosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Peripheral oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chest discomfort</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Feeling abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vessel puncture site haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Injection site reaction</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>Not known</td>
</tr>
</tbody>
</table>
Table 2 Frequency of adverse drug reactions (ADRs) in clinical trials and from spontaneous reports

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Monocyte Count increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Coagulation factor VIII level decreased b</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Laboratory test abnormal</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural complication</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural haemorrhage</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Procedural site reaction</td>
<td></td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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 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.
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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
</tbody>
</table>
Table 3 Summary of Pharmacokinetic Parameters of ADVATE per Age Group with severe haemophilia A (baseline factor VIII < 1%)

<table>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IU/dL per IU/kg)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

* 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 (t1/2) 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 toxicity, 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 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 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.

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.

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. 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.
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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/03/271/007
EU/1/03/271/017

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 http://www.ema.europa.eu.
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:

\[
\text{Required units (IU)} = \text{body weight (kg)} \times \text{desired factor VIII rise (%) x 0.5}
\]

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>

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 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.

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>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Influenza</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laryngitis</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
| Blood and lymphatic system disorders | Factor VIII inhibition   | Uncommon (PTPs)
|                                    |                           | Very common (PUPs)
|                                    | Lymphangitis              | Uncommon                                       |
| Immune system disorders            | Anaphylactic reaction     | Not known                                      |
|                                    | Hypersensitivity           | Not known                                      |
| Nervous system disorders           | Headache                  | Common                                         |
|                                    | Dizziness                 | Uncommon                                       |
|                                    | Memory impairment         | Uncommon                                       |
|                                    | Syncope                   | Uncommon                                       |
|                                    | Tremor                    | Uncommon                                       |
|                                    | Migraine                  | Uncommon                                       |
|                                    | Migraine                  | Uncommon                                       |
| Dental disorders                   | Tooth pain                | Uncommon                                       |
|                                    | Hamatoma                  | Uncommon                                       |
|                                    | Hot flush                 | Uncommon                                       |
|                                    | Pallor                    | Uncommon                                       |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea               | 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                                      |

83
Table 2 Frequency of adverse drug reactions (ADRs) in clinical trials and from spontaneous reports

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Monocyte Count increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Coagulation factor VIII level decreaseda</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laboratory test abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural complication</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Procedural site reaction</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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 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.
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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
</tbody>
</table>
Table 3 Summary of Pharmacokinetic Parameters of ADVATE per Age Group with severe haemophilia A (baseline factor VIII < 1%)

<table>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IU/dL per IU/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dL)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

* 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 ($t_1/2$) 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 toxicity, 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 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 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.

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.

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. 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.
**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 Manufacturing Austria AG
    Industriestrasse 67
    A-1221 Vienna
    Austria

8. **MARKETING AUTHORISATION NUMBER(S)**

    EU/1/03/271/008
    EU/1/03/271/018

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**

1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 1000 IU powder and solvent for solution for injection.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains nominally 1000 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.

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 IU/s (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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Including tooth extraction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>80 – 100 (pre- and postoperative)</td>
<td>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).</td>
</tr>
</tbody>
</table>

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 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.

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* |
| Infections and infestations | Influenza | Uncommon |
| | Laryngitis | Uncommon |
| Blood and lymphatic system disorders | Factor VIII inhibition | Uncommon (PTPs) |
| | Lymphangitis | Uncommon |
| Immune system disorders | Anaphylactic reaction | Not known |
| | Hypersensitivity | 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 | Haemotoma | 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 |
Table 2 Frequency of adverse drug reactions (ADRs) in clinical trials and from spontaneous reports

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Monocyte Count increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Coagulation factor VIII level</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>decreased²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laboratory test abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural complication</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Procedural site reaction</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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 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.
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>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax (IU/dL per IU/kg)</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
</tbody>
</table>
The safety and haemostatic efficacy of ADVATE in the paediatric population are similar to that of adult patients. Adjusted recovery and terminal half-life (t½) 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 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 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.

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.

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**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. 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.
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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/271/009
EU/1/03/271/019

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 http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1500 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 1500 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.

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:

\[
\text{Required units (IU)} = \text{body weight (kg)} \times \text{desired factor VIII rise (%) x 0.5}
\]

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major</td>
<td>80 – 100 (pre- and postoperative)</td>
<td>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).</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Influenza</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Laryngitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor VIII inhibition</td>
<td>Uncommon (PTPs)*</td>
</tr>
<tr>
<td>道</td>
<td>Lymphangitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>Not known</td>
</tr>
<tr>
<td>道</td>
<td>Hypersensitivity</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td>道</td>
<td>Dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Memory impairment</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Syncope</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Tremor</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Migraine</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Dysgeusia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eye inflammation</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Hot flush</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Pallor</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Abdominal pain upper</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Nausea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Vomiting</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Hyperhidrosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Urticaria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>Common</td>
</tr>
<tr>
<td>道</td>
<td>Peripheral oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Chest pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Chest discomfort</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Chills</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Feeling abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Vessel puncture site haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td>道</td>
<td>Fatigue</td>
<td>Not known</td>
</tr>
<tr>
<td>道</td>
<td>Injection site reaction</td>
<td>Not known</td>
</tr>
<tr>
<td>道</td>
<td>Malaise</td>
<td>Not known</td>
</tr>
</tbody>
</table>
Table 2 Frequency of adverse drug reactions (ADRs) in clinical trials and from spontaneous reports

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Monocyte Count increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Coagulation factor VIII level</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>decreased^b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Laboratory test abnormal</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Post procedural complication</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Procedural site reaction</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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 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.
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.

<p>| Table 3 Summary of Pharmacokinetic Parameters of ADVATE per Age Group with severe haemophilia A (baseline factor VIII &lt; 1%) |</p>
<table>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AUC (IU*·h/dl)</td>
<td>1362.1 ± 311.8</td>
<td>1180.0 ± 432.7</td>
<td>1506.6 ± 530.0</td>
<td>1317.1 ± 438.6</td>
<td>1538.5 ± 519.1</td>
</tr>
<tr>
<td>Adjusted Incremental Recovery at Cmax</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
</tr>
</tbody>
</table>
### Table 3 Summary of Pharmacokinetic Parameters of ADVATE per Age Group with severe haemophilia A (baseline factor VIII < 1%)

<table>
<thead>
<tr>
<th>Parameter (mean ± standard deviation)</th>
<th>Infants (n=5)</th>
<th>Children (n=30)</th>
<th>Older Children (n=18)</th>
<th>Adolescents (n=33)</th>
<th>Adults (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IU/dL per IU/kg)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9.0 ± 1.5</td>
<td>9.6 ± 1.7</td>
<td>11.8 ± 3.8</td>
<td>12.1 ± 3.2</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>Maximum Plasma Concentration Post Infusion (IU/dl)</td>
<td>110.5 ± 30.2</td>
<td>90.8 ± 19.1</td>
<td>100.5 ± 25.6</td>
<td>107.6 ± 27.6</td>
<td>111.3 ± 27.1</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>11.0 ± 2.8</td>
<td>12.0 ± 2.7</td>
<td>15.1 ± 4.7</td>
<td>15.0 ± 5.0</td>
<td>16.2 ± 6.1</td>
</tr>
<tr>
<td>Volume of Distribution at Steady State (dl/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Clearance (ml/kg*h)</td>
<td>3.9 ± 0.9</td>
<td>4.8 ± 1.5</td>
<td>3.8 ± 1.5</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.2</td>
</tr>
</tbody>
</table>

* 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 (t½) 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 toxicity, 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 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 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.

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](image1.jpg) ![Fig. b](image2.jpg) ![Fig. c](image3.jpg)

**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. 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.
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 Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/271/010
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 http://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

Baxalta Manufacturing SARL
Singapore Branch
2A Woodlands Industrial Park D Street 2
Singapore 737779
Singapore

Name and address of the manufacturers 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 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 powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU octocog alfa, approx. 50 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced).
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(S) 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:
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.
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.

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(S)

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:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

ADVATE 250 IU 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)**

<table>
<thead>
<tr>
<th></th>
<th>NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sterilised water for injections</td>
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<table>
<thead>
<tr>
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<th>METHOD OF ADMINISTRATION</th>
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<table>
<thead>
<tr>
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<tbody>
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<table>
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<td>Lot:</td>
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<tr>
<th></th>
<th>CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<td>5 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>OTHER</th>
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</thead>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1.  NAME OF THE MEDICINAL PRODUCT

ADVATE 250 IU powder and solvent for solution for injection
octocog alfa (recombinant human coagulation factor VIII)

2.  STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU octocog alfa, approx. 50 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3.  LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
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(S) 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:
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.
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.

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(S)

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: 
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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</thead>
<tbody>
<tr>
<td>BLISTER LABEL (BAXJECT III SYSTEM)</td>
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</table>

1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 250 IU 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

![Diagram of assembly label](image)
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(S) 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(S) 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 powder and solvent for solution for injection
oxoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU octocog alfa, approx. 100 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
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(S) 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:
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.
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.

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(S)

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:
### 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(S) OF ADMINISTRATION**

   ADVATE 500 IU 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(S) 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 powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU octocog alfa, approx. 100 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). 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(S) 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: 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.
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.

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(S)

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:
1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 500 IU 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)

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
<th>ADVATE 500</th>
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<tbody>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
<td>Takeda Manufacturing Austria AG</td>
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<tr>
<td>3. EXPIRY DATE</td>
<td>EXP:</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
<td>Lot:</td>
</tr>
<tr>
<td>5. OTHER</td>
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### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)**

<table>
<thead>
<tr>
<th></th>
<th>NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>1</td>
<td>ADVATE 500</td>
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<th>METHOD OF ADMINISTRATION</th>
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<tr>
<th></th>
<th>EXPIRY DATE</th>
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<td>3</td>
<td>EXP:</td>
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<th>BATCH NUMBER</th>
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<td>4</td>
<td>Lot:</td>
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<table>
<thead>
<tr>
<th></th>
<th>CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tr>
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<th></th>
<th>OTHER</th>
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<tr>
<td>6</td>
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</table>
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(S) 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
141

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1000 IU powder and solvent for solution for injection
octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1000 IU octocog alfa, approx. 200 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1000 IU octocog alfa, 1 vial with 5 ml sterilised water for
injections, 1 BAXJECT II device.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

#### VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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</thead>
<tbody>
<tr>
<td>ADVATE 1000 IU powder for solution for injection</td>
</tr>
<tr>
<td>octocog alfa</td>
</tr>
<tr>
<td>IV use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Single use only.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
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</thead>
<tbody>
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<td>EXP:</td>
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<tr>
<th>4. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Lot:</td>
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<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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</thead>
<tbody>
<tr>
<td>1000 IU octocog alfa</td>
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<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
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</table>
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(S) 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 1000 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 vial: 1000 IU octocog alfa, approx. 200 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. **LIST OF EXCIPIENTS**

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced).
See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

Contents: 1 vial with 1000 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. **METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
<table>
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<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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</thead>
<tbody>
<tr>
<td>BLISTER LABEL (BAXJECT III SYSTEM)</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 1000 IU 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.
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSEMBLY LABEL (BAXJECT III SYSTEM)</td>
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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<table>
<thead>
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<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<td>Takeda Manufacturing Austria AG</td>
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<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<tr>
<th>4. BATCH NUMBER</th>
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<td>Lot:</td>
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<table>
<thead>
<tr>
<th>5. OTHER</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /> <img src="image2.png" alt="Diagram" /> <img src="image3.png" alt="Diagram" /></td>
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</tbody>
</table>
**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(S) OF ADMINISTRATION**

   ADVATE 1000

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(S) 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 1500 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1500 IU octocog alfa, approx. 300 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1500 IU octocog alfa, 1 vial with 5 ml sterilised water for injections, 1 BAXJECT II device.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)**

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:
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<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
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<tbody>
<tr>
<td>VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)</td>
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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>ADVATE 1500 IU powder for solution for injection</td>
</tr>
<tr>
<td>octocog alfa</td>
</tr>
<tr>
<td>IV use</td>
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<table>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Read the package leaflet before use.</td>
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<td>Single use only.</td>
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<th>3. EXPIRY DATE</th>
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<td>EXP:</td>
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<th>4. BATCH NUMBER</th>
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<td>Lot:</td>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<td>1500 IU octocog alfa</td>
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<tr>
<th>6. OTHER</th>
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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(S) 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 1500 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1500 IU octocog alfa, approx. 300 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1500 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) 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: 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.
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.

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(S)

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:
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1500 IU 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)

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
<th>ADVATE 1500</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
<td>Takeda Manufacturing Austria AG</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
<td>EXP:</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
<td>Lot:</td>
</tr>
<tr>
<td>5. OTHER</td>
<td><img src="image" alt="Instructions" /></td>
</tr>
</tbody>
</table>
1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**
   
   ADVATE 1500

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(S) 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 2000 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 2000 IU octocog alfa, approx. 400 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 2000 IU octocog alfa, 1 vial with 5 ml sterilised water for injections, 1 BAXJECT II device.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
**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(S) OF ADMINISTRATION**

   ADVATE 2000 IU 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**

   2000 IU octocog alfa

6. **OTHER**
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)</strong></td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Sterilised water for injections</td>
</tr>
<tr>
<td>2. METHOD OF ADMINISTRATION</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP:</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot:</td>
</tr>
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<td>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</td>
</tr>
<tr>
<td>5 ml</td>
</tr>
<tr>
<td>6. OTHER</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 2000 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 2000 IU octocog alfa, approx. 400 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
Contents: 1 vial with 2000 IU octocog alfa and 1 vial with 5 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER LABEL (BAXJECT III SYSTEM)</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 2000 IU 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)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
<td>ADVATE 2000</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
<td>Takeda Manufacturing Austria AG</td>
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<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP:</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td>Lot:</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
<td>![Diagram of assembly process]</td>
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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(S) OF ADMINISTRATION

ADVATE 2000

2. METHOD OF ADMINISTRATION


3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT


6. OTHER
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) 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**
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTER CARTON (BAXJECT II DEVICE)</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 3000 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 vial: 3000 IU octocog alfa, approx. 600 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. **LIST OF EXCIPIENTS**

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

Contents: 1 vial with 3000 IU octocog alfa, 1 vial with 5 ml sterilised water for injections, 1 BAXJECT II device.

5. **METHOD AND ROUTE(S) 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: 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.
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.

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(S)

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:
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(S) OF ADMINISTRATION

ADVATE 3000 IU 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

3000 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(S) 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 3000 IU powder and solvent for solution for injection
octocog alfa (recombinant human coagulation factor VIII)

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 3000 IU octocog alfa, approx. 600 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

### 3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
See leaflet for further information.

### 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 3000 IU octocog alfa and 1 vial with 5 ml sterilised water for
injections preassembled in BAXJECT III system.

### 5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
### BLISTER LABEL (BAXJECT III SYSTEM)

1. **NAME OF THE MEDICINAL PRODUCT**

   ADVATE 3000 IU 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 3000

2. **NAME OF THE MARKETING AUTHORITY SCHOOL**

   Takeda Manufacturing Austria AG

3. **EXPIRY DATE**

   EXP:

4. **BATCH NUMBER**

   Lot:

5. **OTHER**

   ![Assembly Diagrams]
### 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(S) OF ADMINISTRATION**

   ADVATE 3000

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(S) 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 powder and solvent for solution for injection
octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU octocog alfa, approx. 125 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
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(S) 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:
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.
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.

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(S)

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:
1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADVATE 250 IU 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(S) 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 powder and solvent for solution for injection
octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU octocog alfa, approx. 125 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
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(S) 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:
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.
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.

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(S)

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:
1. **NAME OF THE MEDICINAL PRODUCT**

ADVATE 250 IU 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)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Takeda Manufacturing Austria AG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>

![Diagram of assembly process]
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(S) 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(S) 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 powder and solvent for solution for injection
octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU octocog alfa, approx. 250 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol,
polysorbate 80, glutathione (reduced).
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(S) 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:
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.
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.

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(S)**

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:
### 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(S) OF ADMINISTRATION**

   ADVATE 500 IU 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)**

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</td>
<td>Sterilised water for injections</td>
</tr>
<tr>
<td>2. METHOD OF ADMINISTRATION</td>
<td></td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
<td>EXP:</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
<td>Lot:</td>
</tr>
<tr>
<td>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</td>
<td>2 ml</td>
</tr>
<tr>
<td>6. OTHER</td>
<td></td>
</tr>
</tbody>
</table>
## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

### OUTER CARTON (BAXJECT III SYSTEM)

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVATE 500 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vial: 500 IU octocog alfa, approx. 250 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder and solvent for solution for injection</td>
</tr>
<tr>
<td>Contents: 1 vial with 500 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous use, after reconstitution. Single use only. Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP: 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.</td>
</tr>
</tbody>
</table>
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.

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(S)

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:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER LABEL (BAXJECT III SYSTEM)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVATE 500 IU powder and solvent for solution for injection octocog alfa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORIZATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda Manufacturing Austria AG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>ASSEMBLY LABEL (BAXJECT III SYSTEM)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVATE 500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda Manufacturing Austria AG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>

![Instructions Diagram](image)
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>ADVATE 500</td>
</tr>
<tr>
<td>2. METHOD OF ADMINISTRATION</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP:</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot:</td>
</tr>
<tr>
<td>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</td>
</tr>
<tr>
<td>6. OTHER</td>
</tr>
</tbody>
</table>
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**VIAL LABEL FOR THE SOLVENT (BAXJECT III SYSTEM)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td>Sterilised water for injections</td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP:</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td>Lot:</td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
<td></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT II DEVICE)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1000 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1000 IU octocog alfa, approx. 500 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1000 IU octocog alfa, 1 vial with 2 ml sterilised water for injections, 1 BAXJECT II device.

5. METHOD AND ROUTE(S) 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:
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.
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.

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 AUTHORIZATON NUMBER(S)

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:
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(S) OF ADMINISTRATION

ADVATE 1000 IU 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

1000 IU octocog alfa

6. OTHER
<table>
<thead>
<tr>
<th>Minimum Particulars to Appear on Small Immediate Packaging Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Label for the Solvent (Baxject II Device)</td>
</tr>
</tbody>
</table>

1. **Name of the Medicinal Product and Route(s) 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 1000 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1000 IU octocog alfa, approx. 500 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1000 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTER LABEL (BAXJECT III SYSTEM)**

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVATE 1000 IU powder and solvent for solution for injection octocog alfa</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda Manufacturing Austria AG</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. EXPIRY DATE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>4. BATCH NUMBER</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. OTHER</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT
ADVATE 1000

2. NAME OF THE MARKETING AUTHORISATION HOLDER
Takeda Manufacturing Austria AG

3. EXPIRY DATE
EXP:

4. BATCH NUMBER
Lot:

5. OTHER

---

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---
| **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(S) OF ADMINISTRATION**

   ADVATE 1000

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(S) 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 1500 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1500 IU octocog alfa, approx. 750 IU/ml after reconstitution.
Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
Contents: 1 vial with 1500 IU octocog alfa, 1 vial with 2 ml sterilised water for injections, 1 BAXJECT II device.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**VIAL LABEL FOR THE POWDER (BAXJECT II DEVICE)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVATE 1500 IU powder for solution for injection</td>
</tr>
<tr>
<td>octocog alfa</td>
</tr>
<tr>
<td>IV use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Single use only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 IU octocog alfa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL FOR THE SOLVENT (BAXJECT II DEVICE)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilised water for injections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1500 IU powder and solvent for solution for injection octocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1500 IU octocog alfa, approx. 750 IU/ml after reconstitution. Specific activity: approx. 4,000 – 10,000 IU/mg protein

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, glutathione (reduced). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 vial with 1500 IU octocog alfa and 1 vial with 2 ml sterilised water for injections preassembled in BAXJECT III system.

5. METHOD AND ROUTE(S) 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:
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.
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.

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(S)

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:
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER LABEL (BAXJECT III SYSTEM)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
<td>ADVATE 1500 IU powder and solvent for solution for injection octocog alfa</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
<td>Takeda Manufacturing Austria AG</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP:</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td>Lot:</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ASSEMBLY LABEL (BAXJECT III SYSTEM)

1. NAME OF THE MEDICINAL PRODUCT

ADVATE 1500

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIAL LABEL FOR THE POWDER (BAXJECT III SYSTEM)</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**
   
   ADVATE 1500

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)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong>&lt;br&gt;Sterilised water for injections</td>
</tr>
<tr>
<td>2</td>
<td><strong>METHOD OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td>3</td>
<td><strong>EXPIRY DATE</strong></td>
</tr>
<tr>
<td></td>
<td>EXP:</td>
</tr>
<tr>
<td>4</td>
<td><strong>BATCH NUMBER</strong></td>
</tr>
<tr>
<td></td>
<td>Lot:</td>
</tr>
<tr>
<td>5</td>
<td><strong>CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
</tr>
<tr>
<td>6</td>
<td><strong>OTHER</strong></td>
</tr>
</tbody>
</table>
Package leaflet: Information for the user

ADVATE 250 IU powder and solvent for solution for injection
ADVATE 500 IU powder and solvent for solution for injection
ADVATE 1000 IU powder and solvent for solution for injection
ADVATE 1500 IU powder and solvent for solution for injection
ADVATE 2000 IU powder and solvent for solution for injection
ADVATE 3000 IU powder and solvent for solution for injection

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
2. What you need to know before you use ADVATE
3. How to use ADVATE
4. Possible side effects
5. How to store ADVATE
6. Contents of the pack and other information

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.

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 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.

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 (from 0 to 18 years of age)
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, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, excessive sweating, 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 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, 1000, 1500, 2000, or 3000 IU octocog alfa.
- The other ingredients are mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, and glutathione (reduced).

Solvent vial: 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).

Marketing Authorisation Holder
Takeda Manufacturing Austria AG
Industriestrasse 67
A-1221 Vienna
Tel: +800 66838470
e-mail: medinfoEMEA@shire.com

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

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://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.

---

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td>Degree of haemorrhage/type of surgical procedure</td>
<td>Factor VIII level required (% or IU/dl)</td>
<td>Frequency of doses (hours)/duration of therapy (days)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Including tooth extraction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>80 – 100 (pre- and postoperative)</td>
<td>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).</td>
</tr>
</tbody>
</table>
package leaflet: information for the user

advate 250 iu powder and solvent for solution for injection
advate 500 iu powder and solvent for solution for injection
advate 1000 iu powder and solvent for solution for injection
advate 1500 iu powder and solvent for solution for injection
advate 2000 iu powder and solvent for solution for injection
advate 3000 iu powder and solvent for solution for injection

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
2. what you need to know before you use advate
3. how to use advate
4. possible side effects
5. how to store advate
6. contents of the pack and other information

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,
whels, 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.

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 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.

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 (from 0 to 18 years of age)
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, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, excessive sweating, 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-threatenning 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 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, 1000, 1500, 2000, or 3000 IU octocog alfa.
- The other ingredients are mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, and glutathione (reduced).

Solvent vial: 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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Manufacturer
Baxalta Belgium Manufacturing SA
Boulevard René Branquart 80
B-7860 Lessines
Belgium

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://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. 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.

**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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>
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
2. What you need to know before you use ADVATE
3. How to use ADVATE
4. Possible side effects
5. How to store ADVATE
6. Contents of the pack and other information

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.

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 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.

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 (from 0 to 18 years of age)
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, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, excessive sweating, 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 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, 1000, or 1500 IU octocog alfa.
- The other ingredients are mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, and glutathione (reduced).

Solvent vial: 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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Belgium

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://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.

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.

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Minor</em> Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td><em>Major</em> (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>
Package leaflet: Information for the user

ADVATE 250 IU powder and solvent for solution for injection
ADVATE 500 IU powder and solvent for solution for injection
ADVATE 1000 IU powder and solvent for solution for injection
ADVATE 1500 IU powder and solvent for solution for injection

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
2. What you need to know before you use ADVATE
3. How to use ADVATE
4. Possible side effects
5. How to store ADVATE
6. Contents of the pack and other information

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.

*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 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.

*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 (from 0 to 18 years of age)
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, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, excessive sweating, 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 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, 1000, or 1500 IU octocog alfa.
- The other ingredients are mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, and glutathione (reduced).

Solvent vial: 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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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://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. 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.

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>
<thead>
<tr>
<th>Degree of haemorrhage/type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours)/duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding.</td>
<td>20 – 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30 – 60</td>
<td>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.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages.</td>
<td>60 – 100</td>
<td>Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Including tooth extraction.</td>
<td>30 – 60</td>
<td>Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 – 100</td>
<td>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).</td>
</tr>
</tbody>
</table>