SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADVATE 250 IU powder and solvent for solution for injection.

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

ADVATE 500 IU powder and solvent for solution for injection.

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

ADVATE 1000 IU powder and solvent for solution for injection.

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 with 5 ml solvent.

ADVATE 1500 IU powder and solvent for solution for injection.

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 with 5 ml solvent.

ADVATE 2000 IU powder and solvent for solution for injection.

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 with 5 ml solvent.

ADVATE 3000 IU powder and solvent for solution for injection.

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 with 5 ml solvent.

The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ADVATE is approximately 4,520-11,300 IU/mg protein.
Octocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 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) and 0.5 mg polysorbate 80 per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Treatment monitoring

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

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

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

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

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

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

The amount to be administrated and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. Under certain circumstances (e.g. presence of a low-titre inhibitor), doses larger than those calculated using the formula may be necessary.

In case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table (Table 1) can be used to guide dosing in bleeding episodes and surgery:

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/type of surgical procedure	**Factor VIII level required (% or IU/dl)**	**Frequency of doses (hours)/duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding.	20 – 40	Repeat injections every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for at least 1 day, until the bleeding episode, as indicated by pain, is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma.	30 – 60	Repeat injections every 12 to 24 hours (8 to 24 hours for patients under the age of 6) for 3 – 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages.	60 – 100	Repeat injections every 8 to 24 hours (6 to 12 hours for patients under the age of 6) until threat is resolved.
Surgery		
Minor Including tooth extraction.	30 – 60	Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	Repeat injections every 8 to 24 hours (6 to 24 hours for patients under the age of 6) until adequate wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

Prophylaxis
For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days.
In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Paediatric population
For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients. In patients under the age of 6, doses of 20 to 50 IU of factor VIII per kg body weight 3 to 4 times weekly are recommended for prophylactic therapy.

Method of administration

Intravenous use. In case of administration by a non 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.

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

4.3 Contraindications

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

Known allergic reaction to mouse or hamster protein.

4.4 Special warnings and precautions for use

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

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

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

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

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

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Cardiovascular events

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

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

Excipient related considerations

Sodium

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

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

Paediatric population:

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

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

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

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

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

a) Calculated based on total number of patients who received ADVATE (418) in clinical trials, except for adverse reactions identified in post-marketing surveillance marked with *.

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

Description of selected adverse reactions

ADRs specific to residues from the manufacturing process

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

Hypersensitivity

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

Paediatric population

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

The factor VIII/von Willebrand Factor complex consists of two molecules (factor VIII and von Willebrand Factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to endogenous von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to

activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

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

Clinical efficacy and safety

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

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

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

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

Parameter (mean ± standard deviation)	Infants (n=5)	Children (n=30)	Older children (n=18)	Adolescents (n=33)	Adults (n=109)
Total AUC (IU·h/dl)	1362.1 ± 311.8	1180.0 ± 432.7	1506.6 ± 530.0	1317.1 ± 438.6	1538.5 ± 519.1
Adjusted incremental recovery at Cmax (IU/dL	2.2 ± 0.6	1.8 ± 0.4	2.0 ± 0.5	2.1 ± 0.6	2.2 ± 0.6

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

Parameter (mean ± standard deviation)	Infants (n=5)	Children (n=30)	Older children (n=18)	Adolescents (n=33)	Adults (n=109)
per IU/kg)[a]					
Half-life (h)	9.0 ± 1.5	9.6 ± 1.7	11.8 ± 3.8	12.1 ± 3.2	12.9 ± 4.3
Maximum plasma concentration post infusion (IU/dl)	110.5 ± 30.2	90.8 ± 19.1	100.5 ± 25.6	107.6 ± 27.6	111.3 ± 27.1
Mean residence time (h)	11.0 ± 2.8	12.0 ± 2.7	15.1 ± 4.7	15.0 ± 5.0	16.2 ± 6.1
Volume of distribution at steady state (dl/kg)	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2
Clearance (ml/kg*h)	3.9 ± 0.9	4.8 ± 1.5	3.8 ± 1.5	4.1 ± 1.0	3.6 ± 1.2

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

Paediatric population

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

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

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol (E421)
Trehalose

Sodium chloride
Histidine
Tris (hydroxymethyl) aminoethane
Calcium chloride (E509)

Polysorbate 80 (E433)
Glutathione (reduced)

Solvent
Sterilised water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

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.

After reconstitution

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
ADVATE with BAXJECT II device: Keep the product vial in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

ADVATE with BAXJECT II device: Each pack contains a powder vial, a vial containing 5 ml solvent and a device for reconstitution (BAXJECT II).

6.6 Special precautions for disposal and other handling

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

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

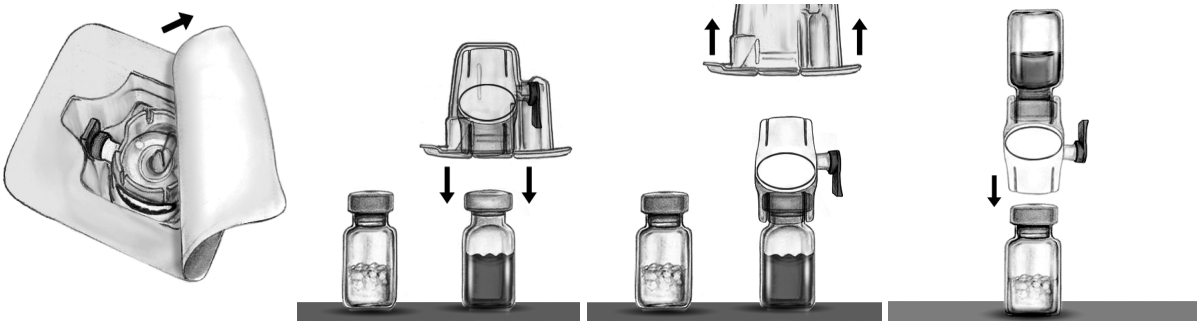
Reconstitution with the BAXJECT II device

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

1. If the product is still stored in a refrigerator, take both the ADVATE powder and solvent vials from the refrigerator and let them reach room temperature (between 15°C and 25°C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.

5. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the ADVATE powder stopper. The vacuum will draw the solvent into the ADVATE powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

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



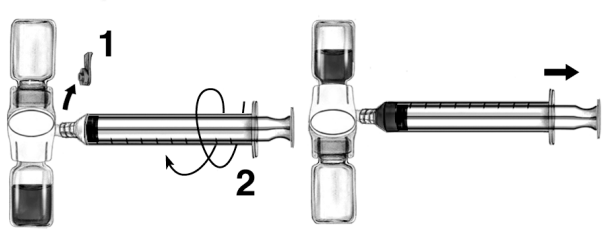
Administration

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. **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. 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).

Fig. d **Fig. e**



7. REGISTRATION NUMBERS:

ADVATE 250 IU powder and solvent for solution for injection.: 150 77 33649 00
ADVATE 500 IU powder and solvent for solution for injection.: 150 78 33665 00
ADVATE 1000 IU powder and solvent for solution for injection.: 150 79 33664 00
ADVATE 1500 IU powder and solvent for solution for injection.: 150 80 33663 00
ADVATE 2000 IU powder and solvent for solution for injection.: 150 81 33662 00
ADVATE 3000 IU powder and solvent for solution for injection.: 150 82 33661 00

8. LICENCE HOLDER AND IMPORTER

Takeda Israel Ltd.
25 Efal St., Petach Tikva 4951125

Revised in July 2025 according to MOHs guidelines