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

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 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 Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. 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: +44 (0)3333 000181
e-mail: medinfoemea@takeda.com

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

This leaflet was last revised in 06/2024.

Instructions for preparation and administration

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

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

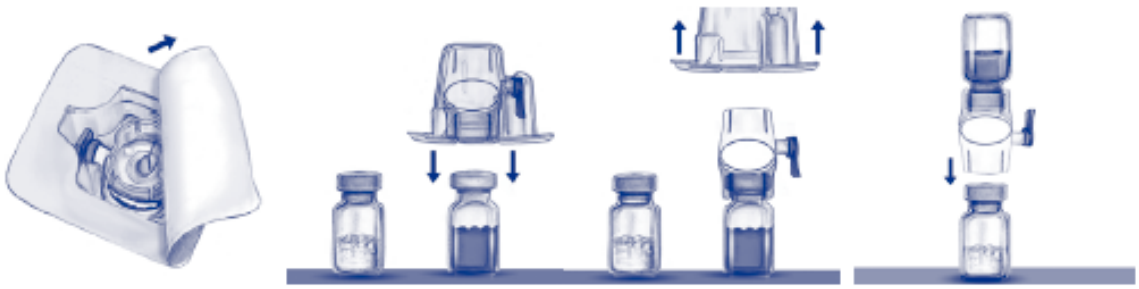
It is strongly recommended that every time ADVATE is administered, the name and batch number of the product are recorded.

Instructions for reconstitution

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

1. If the product is still stored in a refrigerator, take both the ADVATE powder and solvent vials from the refrigerator and let them reach room temperature (between 15 °C and 25 °C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package. Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
6. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from the BAXJECT II device.
7. For reconstitution only the sterilised water for injections and the reconstitution device provided in the pack should be used. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the ADVATE powder stopper. The vacuum will draw the solvent into the ADVATE powder vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that the ADVATE powder is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. The product dissolves rapidly (usually in less than 1 minute). After reconstitution the solution should be clear, colourless and free from foreign particles.

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

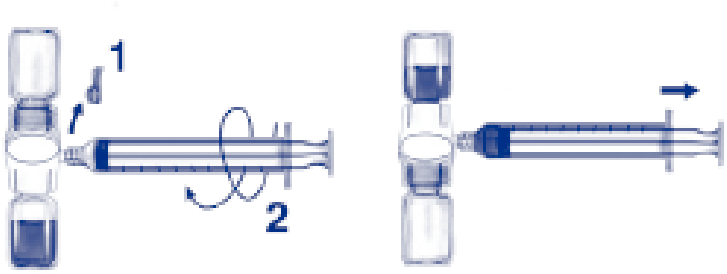


Instructions for injection
For administration the use of a luer-lock syringe is required.

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

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

Fig. d **Fig. e**



The following information is intended for healthcare professionals only:

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

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

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

Degree of haemorrhage/type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/duration of therapy (days)
		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).