ADVATE 250, 500, 1000, 1500 IU

octocog alfa (recombinant human coagulation factor VIII)

What is in this leaflet

What *ADVATE is* used for

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).

How *ADVATE works*

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.

Before you use *ADVATE*

When you must not use it

Do not take *ADVATE* if you:

- are allergic to octocog alfa or any of the other ingredients of this medicine. See the end of this leaflet for a complete list of ingredients in *ADVATE*.
- Are allergic to mouse or hamster proteins.

If you are unsure about this, ask your doctor.

Before you start to use it

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).

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.

Taking other medicines

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

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.

ADVATE is usually injected into a vein (intravenously) by 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 as below:

Instruction 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.

Instruction 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, colorless and free from foreign particles.

Fig. a

Fig. b

Fig. c

Instruction for injection
For administration the use of the 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 matters and discoloration prior to administration (the solution should be clear, colorless 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.
5. Discard any unused solution appropriately.

Fig. d

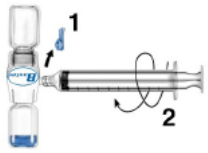
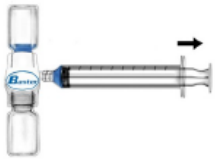


Fig. e



How much to use

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.

When to use it

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 long to use it

Do not stop using *ADVATE* without consulting your doctor. If you have any further questions on the use of this medicine, ask your doctor.

If you forget to use it

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 use too much (overdose)

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.

While you are using *ADVATE*

Things you must not do

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.

Things to be careful of

- *ADVATE* has no influence on your ability to drive or to use machines.
- This medicine contains 0.45 mmol sodium (10 mg) per vial. To be taken into consideration by patients on a controlled sodium diet.

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 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.

Common side effects (may affect up to 1 in 10 people)
Factor VIII inhibitors (for children not previously treated with Factor VIII medicines), 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), flu, sore throat, infection of the lymphatic vessels, dizziness, memory impairment, fainting, muscle contraction, migraines, unusual taste in mouth, eye inflammation, abnormal heartbeat, injection site bruise, hot flushes, diarrhea, pain in the upper abdomen or lower chest, nausea, vomiting, itching, rashes, excessive sweating, red itchy bumps on the skin, foot and leg swelling, chest pain and discomfort, chills, feeling abnormal, increase in a type of white blood cells (monocytes), coagulation factor VIII level decreased, reduced percentage of red blood cells.

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), injection site reactions.

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.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by calling

Tel: 03-78835490, or visiting the website www.npra.gov.my [Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].

Storage and Disposal of *ADVATE*

Storage

- 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 months 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.

Disposal

- 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.

Product Description

What it looks like

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

Ingredients

Active ingredient
octocog alfa (human coagulation Factor VIII produced by recombinant DNA technology). Each powder vial contains nominally 250, 500, 1000, or 1500 IU octocog alfa.

Inactive ingredients
mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, and glutathione (reduced).

MAL number(s):
ADVATE 250IU: MAL20081762AZ
ADVATE 500IU: MAL20081763AZ
ADVATE 1000IU: MAL20081764AZ
ADVATE 1500IU: MAL20081765AZ

Manufacturer
Baxalta Belgium Manufacturing SA
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