ADVATE 250

LE-07-07450

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ADVATE

PACKAGE LEAFLET: INFORMATION FOR THE USER

ADVATE 250 IU powder and solvent for solution for injection

Octocog alfa (recombinant coagulation Factor VIII)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ADVATE IS AND WHAT IT IS USED FOR

ADVATE belongs to a pharmacotherapeutic group called blood coagulation Factor VIII.

ADVATE is prepared without the addition of any human- or animal-derived protein in the cell culture process, purification or final formulation.

The Octocog alfa (recombinant human coagulation Factor VIII produced by recombinant DNA technology in Chinese Hamster Ovary cells) in ADVATE replaces the Factor VIII which is lacking or is not functioning properly in haemophilia A. Haemophilia A is a sex-linked, hereditary blood coagulation defect due to reduced Factor VIII levels. This results in severe bleeding in joints, muscles and internal organs, either spontaneously or as a consequence of accidental or surgical trauma. The administration of ADVATE temporarily corrects the Factor VIII deficiency and reduces the bleeding tendency.

This medicine is used in patients with haemophilia A (congenital Factor VIII deficiency) for
- prevention of bleeding
- treatment of bleeding (e.g. muscle bleeding, oral bleeding, bleeding at the site of surgery).

This preparation does not contain von Willebrand Factor and is therefore not to be used in von Willebrand's disease.

2. BEFORE YOU USE ADVATE

You must not use ADVATE
- if you are allergic (hypersensitive) to octocog alfa or any of the other ingredients of ADVATE including mouse or hamster protein.

If you are unsure about this, ask your doctor.

Take special care with ADVATE

When allergic reactions occur:
- There is a rare chance 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/infusion immediately and contact your doctor. Severe symptoms, including difficulty in breathing and (near) fainting, require prompt emergency treatment.

When monitoring is required:
- Your doctor may wish to carry out tests to ensure that your current dose is sufficient to reach and maintain adequate Factor VIII levels.

When bleeding is still occurring:
- If your bleeding is not controlled with ADVATE, consult your doctor immediately. You may have developed Factor VIII inhibitors and your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood that block the Factor VIII you are using. This makes Factor VIII less effective in controlling bleeding.

Taking other medicines
No interaction with other medicinal products are currently known. Nevertheless, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines without a prescription and dietary supplements.

Pregnancy and breast-feeding
Inform your doctor if you are pregnant or breast-feeding. Your doctor will decide if ADVATE may be used during pregnancy and lactation.

Driving and using machines
ADVATE has no influence on your ability to drive or to operate machines.

Important information about some of the ingredients of ADVATE
This medicinal product contains 90 mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE ADVATE

ADVATE is intended for intravenous administration (infusion into a vein). It is given to you under close supervision of your doctor who is experienced in the care of patients with haemophilia A. Dosage will vary depending on your condition and your body weight. Always use ADVATE exactly as your doctor has told you. You should check with your doctor if you are not sure.

Dosage for prophylaxis of bleeding
If you are using ADVATE to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. He/she will do this according to your particular needs. The usual dose will be between 20 to 40 IU of octocog alfa per kilogramme of body weight, administered at intervals of 2 to 3 days. However, in some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

If you have the impression that the effect of ADVATE is insufficient, talk to your doctor.

Dosage for treatment of bleeding
If you are receiving ADVATE for treatment of bleeding, your doctor will calculate the dose for you. He/she will do this according to your particular needs using the formula below:

Required IU = body weight (kilogramme) x desired Factor VIII rise (% of normal) x 0.5

The following table is intended for your doctor only and provides a guide for Factor VIII minimal blood levels. In the case of the haemorrhagic events listed, the Factor VIII activity should not fall below the given level (in % of normal) during the corresponding period.
Under certain circumstances, larger amounts than those calculated may be required, especially in the case of a low titre inhibitor.

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 infusions 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 infusions 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 infusions 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	Infusion 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 infusions 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).

Monitoring by 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.

Patients with Factor VIII inhibitors
If the Factor VIII level of your plasma fails to reach expected levels, or if bleeding is not adequately controlled following dose increase, the presence of Factor VIII inhibitors should be suspected. The presence of Factor VIII inhibitors will be checked by your doctor.

If you have developed Factor VIII inhibitors, you will possibly need a larger amount of ADVATE to control bleeding. If this dose does not control your bleeding, your doctor may consider the use of a different product. Do not increase the total dose of ADVATE to control your bleeding without consulting your doctor.

Method and route of administration
ADVATE is administered into a vein (intravenously) after preparing the solution with the solvent provided, either
- by injection by your doctor or nurse, or by yourself or another appropriate person after proper training
- by infusion by your doctor or nurse.

The rate of administration should be determined by the patient's comfort level. The preparation can be administered at a rate of up to 10 ml per minute.

Follow the directions given by your doctor closely and use the step-by step instructions given at the end of this package leaflet.

Frequency of administration
Your doctor will tell you how often and at what intervals ADVATE is to be administered. He will do this according to the effectiveness in your individual case.

Duration of treatment
Usually, the replacement therapy with ADVATE is life-long treatment.

If you use more ADVATE than you should
- It is recommended that you adhere to the dose level and frequency of administration as recommended by your doctor. In case you administered more ADVATE than recommended, please inform your doctor as soon as possible.

If you forget to use ADVATE
- Do not take a double dose to make up for a forgotten dose.
- Proceed with the next regular administration immediately and continue at regular intervals 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ADVATE can cause side effects, although not everybody gets them.

- The following side effects were commonly observed during the clinical studies with ADVATE (more than 1 in 100 patients and less than 1 in 10 patients): dizziness, headache and fever. The other side effects were uncommonly observed (more than 1 in 1000 patients and less than 1 in 100 patients): itching, increased sweating, unusual taste in the mouth, hot flushes, migraines, memory impairment, chills, diarrhoea, nausea, vomiting, shortness of breath, laryngitis, infection of the lymphatic vessels, whitening of skin, eye inflammation, rashes, excessive sweating, foot and leg swelling, increase in enzymes that track liver function, decrease in haematocrit and pain in the upper abdomen or lower chest. The following uncommon side effects have been observed during surgery (more than 1 in 1000 patients and less than 1 in 100 patients): 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 haematoma. Most of these events were reported once and did not re-occur upon further exposure to ADVATE. Only headache (5 patients), fever, dizziness (3 patients each), itching and diarrhea (2 patients each) were reported by more than 1 patient.
- Since the drug has been on the market, there have been rare reports of severe and potentially life threatening reactions (anaphylaxis) and other allergic reactions.
  You should be aware of the early symptoms of allergic reactions such as rash, hives, wheals and generalised itching, swelling of the lips or 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 allergic or anaphylactic reactions occur, stop the injection/infusion immediately and contact your doctor.

The formation of neutralising antibodies to Factor VIII (inhibitors) is a known complication in the management of individuals with haemophilia A. During clinical trials with ADVATE there was one low titre inhibitor seen among 198 previously treated patients. In previously untreated patients, 5 (20%) of 25 patients who received ADVATE developed inhibitors to Factor VIII in an ongoing clinical study. The frequency of FVIII inhibitors detected so far is within the expected and previously observed range. If your bleeding is not controlled with ADVATE, you could have developed an inhibitor to coagulation Factor VIII. In such case, please contact your doctor immediately.

If any of these side effects are serious, worsen or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ADVATE

- Keep out of the reach and sight of children.
- Do not use ADVATE 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.
- Keep the vial in the outer carton in order to protect from light.

During the shelf life the product may be kept at room temperature (up to 25°C) for a single period not exceeding 2 months. Please record the beginning of storage at room temperature on the product carton. The product may not be returned to refrigerated storage after storage at room temperature.

Storing after preparation:
- This product is for single use only. Use the product immediately once the powder is completely dissolved.
- Do not refrigerate the solution after preparation.
- Discard any unused solution appropriately.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ADVATE contains

Powder:
- The active substance is 250 IU Octocog alfa (recombinant human coagulation Factor VIII produced by recombinant DNA technology in Chinese Hamster Ovary cells).
- The other ingredients are mannitol, sodium chloride, histidine, trehalose, calcium chloride, trometamol, polysorbate 80, and glutathione (reduced).

Solvent:
- Sterilised water for injections

What ADVATE looks like and contents of the pack

ADVATE is provided as a powder and solvent for solution for injection and 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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Manufacturer:
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This leaflet was last approved in January 2007.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

Instructions for preparation and administration

Aseptic conditions (meaning clean and germ free) are 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. For administration the use of a luer-lock syringe is required.
ADVATE must not be mixed with other medicinal products or solvents.

Instructions for preparing the solution

1. Take ADVATE (powder vial) and sterilised water for injections (solvent vial) from the refrigerator and bring them to room temperature (15°C - 25°C).
2. Wash your hands thoroughly.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat 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.
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 BAXJECT II device.
7. 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 stopper. The vacuum will draw the solvent into the ADVATE vial (Fig. c).
8. Swirl gently until all material is dissolved. Be sure that ADVATE is completely dissolved, otherwise active material will not pass through the device filter. The product dissolves rapidly (usually in less than 1 minute).

Fig. a

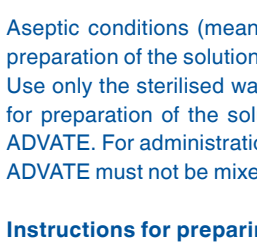


Fig. b

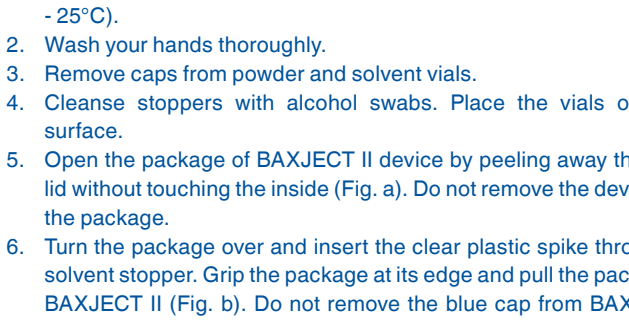


Fig. c

Instructions for administration of the injection

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.
- Do not use ADVATE if the solution is turbid 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 (with concentrate vial on top). Draw the concentrate into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.
4. Attach mini-infusion set to the syringe. Inject intravenously. The preparation can be administered at a rate of up to 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 Section 2 “Before you use ADVATE” and Section 4 “Possible side effects”).

Fig. d

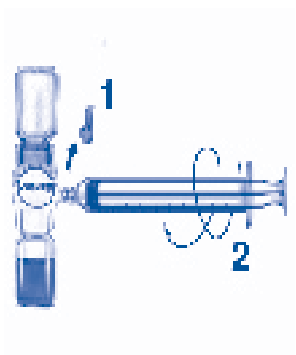
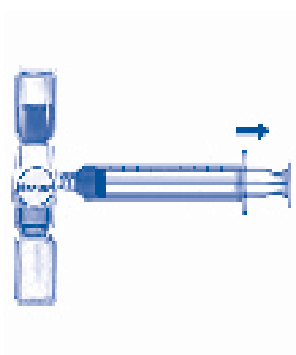


Fig. e



Remember
- Do not use after the expiry date stated on the labels and carton.
- Do not use ADVATE if the solution is turbid or not completely dissolved.
- Do not refrigerate the solution after preparation.
- Discard any unused solution appropriately.
- 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: .

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