Package leaflet: Information for the user

Aafact 500 IU powder for solution for injection
Aafact 1000 IU powder for solution for injection

Active substance: 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 or pharmacist
- 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.
- Do you suffer from a side effect or do you get a side effect not listed in this leaflet? Please contact your doctor or pharmacist.

What is in this leaflet:

1. WHAT IS AAFACT EN WHAT IS IT USED FOR

Aafact is delivered as powder for solution for injection. A vial of 5 or 10 ml of water for injections is supplied with the powder.
The active substance is human coagulation factor VIII. Factor VIII is an ingredient that is normally present in human blood and is a factor in the blood coagulation process. With a shortage of factor VIII a disorder in the blood coagulation occurs. Haemorrhages may occur as a result of this. This shortage is supplemented by administration of Aafact, so that haemorrhages are prevented or suppressed.

Aafact may be used with:
In patients with a congenital shortage of factor VIII (haemophilia A) or an acquired shortage of factor VIII:
* with acute haemorrhages;
* before, during and after operations;
* to prevent haemorrhages

2. WHAT YOU NEED TO KNOW BEFORE YOU USE AAFACT

Do not use Aafact

If you are hypersensitive (allergic) for the active substance or for any of the other excipients of Aafact (see section 6).

Special warnings and precautions for use

Immediately consult with your physician if, during treatment with Aafact, bleeding does not stop as expected.

The product must be clear and may not contain any particles or lumps after reconstitution in the provided water for injections. Check this prior to administration. The product must not be administered if any turbidity, particles or lumps are visible.

Aafact is not effective in patients with other coagulation disorders, such as a congenital factor IX shortage (haemophilia B), acquired factor IX shortage, and an inherited coagulation illness called Von Willebrand's Disease.

Some people with haemophilia A may produce antibodies against factor VIII. These antibodies may counteract totally or partially the efficacy of administered factor VIII. Therefore, the amount of factor VIII and/or antibodies against factor VIII in your blood will be regularly assessed during your Aafact use.

Aafact may induce a severe allergic reaction (anaphylactic shock). If an earlier use of blood or a blood product has shown that you are sensitive, this product should only be administered if there is no alternative (as in life-threatening situations). Administration of Aafact to patients who are hypersensitive to blood or blood products must occur in a hospital under the careful supervision of a physician.

Aafact may also induce other side effects of an allergic nature (see under Side effects, section 4). You are advised to discuss the following with the treating physician:
- How do you recognise the side effects and what are the symptoms?
- What should you do if side effects occur?
- Is it necessary to have certain medicinal products on hand in order to suppress or prevent the side effects?

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded.
- the testing of each donation and pools of plasma for signs of virus/infections
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infection.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus. The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products.

It is strongly recommended that every time you receive a dose of Aafact the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Other medicines and Aafact

Tell your doctor or pharmacist if you are using or have recently used any other medicinal products. This also applies to medicinal products obtained without prescription.

No information is available concerning possible interactions between Aafact and other medicinal products.

Pregnancy and breast-feeding

Aafact is intended to prevent or treat haemorrhages in people with haemophilia A. Due the nature of the hereditary transmission, the illness occurs mainly in men. There has been little experience in treating the shortage of factor VIII in women. The use of Aafact during pregnancy or while breastfeeding has not been investigated. Research in animals is not possible because Aafact is prepared from human blood. You are advised to consult with your physician if you are pregnant, while breastfeeding or if you have a desire to become pregnant.

Driving and using machines

Aafact has no influence on the ability to drive and use machines.

Aafact contains

After reconstitution in the supplied water for injections Aafact contains 100 IU factor VIII per ml. The product also contains the following excipients: polyethylene glycol, sodium chloride, albumin, L-histidine and calcium chloride.

Important information on some excipients of Aafact

The 500 IU vial of this medicinal product contains 1.2 mmol (27.6 mg) sodium and the 1000 IU vial contains 2.4 mmol (55.2 mg) sodium per dose. To be taken in consideration by patients on a controlled sodium diet.

3. HOW TO USE AAFACT

The quantity of Aafact that you need will be determined by your physician. The exact dose will depend on the amount of factor VIII in your blood (your blood level), on the location and extent of the bleeding, on the severity of your clinical situation and on your body weight. Your physician will check your blood level regularly.

After the administration of 1 IU (International Unit) of factor VIII per kilogram of body weight, your factor VIII blood level will increase by 2 IU/dl.

The usual amount is:

- To prevent haemorrhages: 20 – 40 IU Aafact per kilogram of body weight, 2 – 3 times per week.
  More frequent administration or higher doses may be necessary in some cases.
- With haemorrhages and during operations: as much as is needed in order to achieve the desired blood level (consult the table below).

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
▪ Early haemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat every 12 to 24 hours. 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 infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved
▪ Life-threatening haemorrhages	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
▪ Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
▪ Major surgery	80 – 100 (pre- and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

In view of storage at low temperature the product should be brought to room temperature before use.

Instructions for home treatment

The information below describes how Aafact can be administered with an administration set. The only persons allowed to administer home treatment are patients, their parents/carers or partners that have been trained in this. This instruction for use is only to support information previously provided to you.
Follow the instructions of the physician or pharmacist. Inspect the vials; there must be no cracks in them. Check whether the date of expiry has not been exceeded. The powder may only be dissolved in water for injections.

Dissolving the powder
The powder should be dissolved in 5 ml (500 IU) or 10 ml (1000 IU) of water for injections. During actual administration, the solution should not be too cold. The powder also dissolves better if both vials are brought to room temperature (15°C - 25°C) in advance.

1. Allow the vial of Aafact and the vial of water for injections to reach room temperature (15°C – 25°C).
2. Remove the plastic cap from the vials.
3. Disinfect the surface of the stoppers of both vials with a gauze soaked in 70 % alcohol.

4. Remove the protective sheath from one end of a transfer needle and pierce the stopper of the vial containing water for injections. Remove the protective sheath from the other end of the transfer needle. Invert the solvent vial and pierce the stopper of the vial containing the powder.
5. Tilt the product vial when transferring the solvent to allow the solvent to flow down the side of the vial.
6. Remove the empty vial and the transfer needle.
7. Swirl the vial gently to completely dissolve the powder. Do not shake! The powder dissolves within 5 minutes to produce a clear, colorless to light-yellow solution.

Immediately before administration, the solution should be inspected by holding the vial up to the light: the solution should not be turbid and must be free of particles or lumps. Do not use if you do see any turbidity, particles or lumps.
From a microbiological point of view, the product should be used immediately after reconstitution.
After reconstitution in water for injections Aafact should be kept at room temperature (15°C - 25°C). If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The solution is intended to be used at one time. Any unused product or waste material should be returned to the pharmacy.

Aafact should never be mixed with other medicinal products.

Administration
1. Using a hypodermic needle and syringe, draw the dissolved product out of the vial.
2. Aafact should be injected into a vein (intravenous administration).
3. Infuse the product at a rate not exceeding 10 ml per minute.

If you use more Aafact than you should
No symptoms of overdose with human coagulation factor VIII have been reported.

If you forget to use Aafact
Immediately contact your doctor and follow his / her instructions. Do not take a double dose to make up for a forgotten dose.

If you stop using Aafact
If you have any further questions on the use of this medicine ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

- Patients with haemophilia A may develop so-called antibodies (inhibitors) against factor VIII. This manifests itself in a treatment effect that falls below expectations. The product will be progressively less effective. Therefore, the physician will regularly check your blood for the presence of these antibodies and/or check the amounts of factor VIII. Consult your physician immediately if you suspect that Aafact is less effective. Treatment of patients with inhibitors should be performed in a haemophilia centre.
- In rare cases (1 to 10 in 10,000 users) sensitivity or allergic reactions may occur. The first signs of an allergic reaction may include: Sudden collection of fluid in the skin and mucous membranes (eg, throat and tongue), breathing difficulties and/or itching and rash

(angioedema), burning and stinging at the infusion site, chills, flushing, rash with intense itching (hives) and urticaria, headache, low blood pressure, fatigue (lethargy), nausea, restlessness, increased heart rate (tachycardia), tightness of the chest, tingling, vomiting and wheezing. Mild hypersensitivity reactions, such as hives (urticaria), may be treated where necessary with antihistamines (medicinal products against allergies), and corticosteroids (medicinal products that inhibit inflammation).

- In some cases the hypersensitivity reaction can proceed in a serious, life-threatening allergic reaction (anaphylaxis) whereby shock can occur. In the event of a severe allergic reaction (anaphylactic shock), administration must be stopped immediately and a doctor should be consulted.

Do you suffer from a side effect, please contact your doctor or pharmacist. This also applies to any side effect not listed in this leaflet. You may also report side effects directly through Dutch Centre Lareb, website www.lareb.nl, By reporting side effects you can help us to obtain information about the safety of this drug.

5. HOW TO STORE AAFACT

The vial with powder should be stored in the box at 2°C - 8°C. The refrigerator is an appropriate place for this. Before its shelf life has expired, Aafact can be stored for 2 months at room temperature (15°C - 25°C).

The vial containing the water for injections does not have to be stored in a cool place (2°C - 8 °C). Because the solution must be at room temperature (15°C - 25°C) before use, it is convenient to store the vial containing the water for injections separately. This vial must be stored in the original box at a temperature between 2°C - 25°C (avoid freezing).

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and carton.

Do not use Aafact if, after reconstitution in water for injection, the solution is cloudy or if the solution contains particles or lumps.

Do not throw away any medicines via wastewater 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 Aafact contains

The active substance in Aafact is human coagulation factor VIII. After reconstitution in water for injection Aafact contains 100 IU factor VIII per ml.
Aafact also contains the following excipients: polyethylene glycol, sodium chloride, albumin, L-histidine and calcium chloride.

What Aafact looks like and contents of the pack

The commercial package comprises a vial of Aafact meant for 5 ml (500 IU) or 10 ml (1000 IU) of solution.

A vial of 5 or 10 ml of water for injections is supplied with the package.

After reconstitution of the Aafact powder in water for injections the solution is colorless or slightly yellow.

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The following information is intended for healthcare professionals only:

Posology and method of administration
Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

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 clinical condition and weight of the patient.

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

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

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

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

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

Degree of haemorrhage/ Type of surgical procedure	**Factor VIII level required (%) (IU/dl)**	**Frequency of doses (hours)/Duration of therapy (days)**
Haemorrhage		
▪ Early haemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat every 12 to 24 hours. 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 infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved
▪ Life-threatening haemorrhages	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved

Surgery		
▪ Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
▪ Major surgery	80 – 100 (pre- and post-operative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

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 infusions. 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. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries.

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.

The safety and efficacy of Aafact in children aged younger than 6 years have not yet been established. No data are available.

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.

Method of administration
Aafact must be dissolved in 5 ml (500 IU) or 10 ml (1000 IU) water for injections. After reconstitution Aafact needs to be administered intravenously. It is advisable to infuse the product at a rate not exceeding 10 ml per minute.

For instructions on administration, see section 3 of this package leaflet.

Contra-indications
Hypersensitivity to the active substance or to any of the excipients. Known allergic reactions to mouse protein.

Special warnings and precautions for use
Allergic type hypersensitivity reactions are possible with Aafact. The product can contain traces of mouse proteins. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If symptoms of hypersensitivity occur, patients should be advised to immediately discontinue use of the medicinal product and to contact their physician. In case of shock, standard medical treatment for shock should be implemented.

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 exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.
Patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

In patients who displayed an atypical reaction during a previous use of blood or blood products, an anaphylactic reaction can occur. Such patients should preferably not be treated with the product, nor, similarly, with other blood products. If for some urgent reason this rule must be departed from, the product must be administered under close clinical control.

Overdose
With respect to the occurrence and symptoms of possible overdose with factor VIII-concentrates no data are yet available.

For more information on warnings and precautions for use, see section 2 of this package leaflet.