SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 500 or 1000 International Units (IU) human coagulation factor VIII.

Aafact contains approximately 100 IU/ml of human coagulation factor VIII after reconstitution.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Aafact is approximately 25 IU/mg protein.

Aafact is produced from the plasma of human donors.

The 500 IU vial of this medicinal product contains 1.2 mmol (27.6 mg) sodium per dose 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Management of acquired factor VIII deficiency.

4.2 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.

On demand treatment
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).

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.

Continuous infusion
Prior to surgery, a pharmacokinetic analysis should be performed to obtain an estimate of clearance.

The initial infusion rate can be calculated as follows: Clearance x desired steady state level = infusion rate (IU/kg/hr).

After the initial 24 hours of continuous infusion, the clearance should be calculated again every day using the steady state equation with the measured level and the known rate of infusion.

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.

Previously untreated patients
The safety and efficacy of Aafact in previously untreated patients have not yet been established. No data are available.

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

Method of administration
Intravenous use.

It is advisable to infuse the product at a rate not exceeding 10 ml per minute.

For instructions on reconstitution of Aafact before administration, see section 6.

4.3 Contra-indications

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

Known allergic reactions to mouse protein.

4.4 Special warnings and precautions for use

Hypersensitivity
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.

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, generalised 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.

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 exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

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.

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.

Viral safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).
The measures taken may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

It is strongly recommended that every time that Aafact 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.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived factor VIII products.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII 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

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

4.8 Undesirable effects

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).

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. 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.

For safety information with respect to transmissible agents, see section 4.4.

Notification of possible side effects:
It is important to report side effects after admission of the medicinal product. This will allow a continuous follow-up of the relationship between the risks and benefits of the medicinal product. Professionals in the healthcare are requested to report all possible side effects through the Dutch Centre Lareb; website www.lareb.nl.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

The in vivo recovery corresponds to an increase of factor VIII plasma levels by 0.02 IU per ml on the administration of 1 IU of factor VIII per kilogram of body weight. Factor VIII is removed from the plasma biphasically.

In the first phase, it becomes distributed throughout the tissue fluids.
The literature gives values of 8 - 20 hours for the biological half-life of factor VIII (second phase).
The biological half-life of factor VIII present in Aafact is 9 - 12 hours, although this differs from patient to patient.
The presence of antibodies against factor VIII can substantially reduce the half-life (see section 4.8, Undesirable effects).

5.3 Preclinical safety data

The active constituent of Aafact, factor VIII, is a normal constituent of the human body and has the same properties as endogenous factor VIII. Research into acute toxicity in animals is not imperative, since higher doses result in an overload of the circulation. Research into toxicity for the embryo or foetus is not feasible due to induction of and disturbance by antibodies.
Given that clinical trials have not shown any evidence of oncogenic and mutagenic effects of factor VIII concentrates prepared from human plasma, experimental research, especially into heterologous species, is considered unnecessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
sodium chloride
human albumin
L-histidine
polyethylene glycol
calcium chloride

Solvent: water for injections.

6.2 Incompatibilities

No medication should be added to Aafact.

This medicinal product should only be reconstituted in water for injections.

6.3 Shelf life

3 years

Before its shelf life has expired, Aafact can be stored for 2 months at room temperature (15°C - 25°C).

After reconstitution in water for injections Aafact needs to be kept at room temperature (15°C - 25°C). After reconstitution physical-chemical in-use stability has been demonstrated for 3 hours at room temperature (15°C - 25°C).

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Aafact should be stored at 2 - 8 °C, protected from light.

For the stability of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

Aafact (500 IU):	- vial: 8 ml-vial, glass type I - stopper: bromobutyl rubber - cap : combicapsule
Aafact (1000 IU):	- vial: 20 ml-vial, glass type I - stopper: bromobutyl rubber - cap : combicapsule
WFI (5 ml)	- vial: 6 of 11 ml-vial, glass type I - stopper: bromobutyl rubber - cap : aluminium seal
WFI (10 ml)	- vial: 10- of 20 ml-vial, glass type I - stopper: bromobutyl rubber - cap : aluminium seal

The solvent (10 ml WFI for Aafact 1000 IU and 5 ml WFI for Aafact 500 IU) is delivered together with Aafact, in a separate package.

6.6 Special precautions for use, handling and disposal

Reconstitution
The lyophilised powder must be dissolved in the prescribed volume of water for injections. Before the product is reconstituted the vials of Aafact, respectively water for injections stored at 2°C - 8 °C, should be warmed to room temperature (15°C - 25 °C).

Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution may vary in appearance from clear to slightly opalescent, and from colourless to light yellow. Do not use solutions that are cloudy or have deposits.

Instructions on how to use a transfer needle

1. Remove the plastic protective cap from both the vials containing the water for injections and the vial containing product
2. Disinfect the rubber stoppers of both vials with a piece of gauze soaked in alcohol (70%).
3. Remove the protective sheath from one end of the transfer needle and insert the needle into the vial containing the water for injections. Then remove the protective sheath from the other end of the transfer needle, turn the vial containing the transfer needle upside down and immediately insert the needle that is still free into the vial containing product.
4. The underpressure in the vial containing product will cause the water for injections to be sucked into the vial. It is recommended that while the water for injections is flowing across, the vial containing product be kept tilted and the water allowed to flow along the wall of the vial. This helps the product to dissolve more quickly. As soon as all the water has flowed across, the emptied vial and the transfer needle should be removed in a single action

   Generally the dried substance will dissolve completely within 5 minutes.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanquin Plasma Products B.V.
Plesmanlaan 125
NL-1066 CX Amsterdam

8. MARKETING AUTHORISATION NUMBER(S)

RVG 17121

9. DATE OF FIRST AUTHORISATION

07 June 1995

10. DATE OF REVISION OF TEXT

Latest complete revision: 11 November 2013.
Latest partial revision in paragraph 7: 8 December 2015.