Aafact®
Human coagulation factor VIII

Aafact 100 IU/ml Powder and solvent for solution for infusion
Human coagulation factor VIII.

TRADE NAME OF THE MEDICINAL PRODUCT
The trade name of the product is Aafact®

QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Ingredient
Aafact® consists of a protein fraction prepared from fresh-frozen, human plasma. The product is supplied as a sterile and pyrogen-free powder. A vial contains respectively 0.1 or 0.2 g of freeze-dried powder corresponding with respectively 500 and 1000 International Units (IU) of factor VIII. When reconstituted in the prescribed volume of water of injections (5 and 10 ml respectively) the product contains 100 IU for factor VIII per ml. The total measured quantity factor VIII is indicated on the label.

Viral Safety
The plasma originates from voluntary, nonremunerated donors who satisfy the requirements of the Blood Transfusion Council of The Netherlands Red Cross. This means, among other things, that each individual donation has been tested and found negative for hepatitis B surface antigen (HBsAg), for antibodies against human immunodeficiency virus 1 and 2 (HIV-1 and HIV-2, the inducers of AIDS), for antibodies against the hepatitis C virus and for antibodies against Treponema pallidum (the pathogen that causes syphilis).
The purification of factor VIII using immuno-affinity chromatography and a treatment with low concentrations of an organic solvent (tri(n-butyl)phosphate, TNBP) and a detergent (Triton X-100) ('SD method' or 'chemical viral inactivation') ensure that the risk of transmission of viral diseases, in particular AIDS, hepatitis B and hepatitis non-A, non-B (including hepatitis C), is extremely small.

PHARMACEUTICAL FORM
Aafact® is supplied as a powder and solvent for infusion for intravenous administration.

CLINICAL PARTICULARS
Therapeutic Indications
Aafact® is intended for use in cases of acute haemorrhage, pre-operative and post-operative treatment and prophylaxis in haemophilia A patients (congenital factor VIII deficiency) and in patients with an acquired reduction in factor VIII activity.

Posology and method of administration
The dosage in treatment and prophylaxis of haemorrhages depends on the severity of the disease, as well as the clinical condition and the weight of the patient. At the same time account should be taken of the half life of the factor VIII being administered. This is 9 -12 hours, although it differs from patient to patient.
Optimum monitoring requires that the factor VIII levels in patient's blood be measured at regular intervals. The administration of 1 IU of factor VIII per kilogram of body weight may be expected to increase factor VIII levels in the blood by 0.02 IU/ml.
For the long-term prevention of haemorrhages in individuals with severe haemophilia A, it is recommended that doses of 10 IU to 50 IU of factor VIII per kilogram of body weight be given 2 – 3 times per week. A higher frequency of administration or higher dosage may be required in some cases.

For the treatment of mild haemorrhage the factor VIII concentration needs to be brought up to at least 0.3 IU/ml (30 % of the normal level).
In the case of existing haemorrhages in muscles and joints, as well as minor surgical procedures such as tooth extractions, a concentration of at least 0.5 IU/ml (50 % of the normal level) should be achieved.
For surgical operations and the treatment of severe wounds or life-threatening situations the concentration needs to be increased to about 1.0 IU/ml (100 % of the normal level). This level should be kept at least to 0.6 IU/ml (60 % of the normal level) for a considerable time during and after the operation. This requires regular supervision of the factor VIII concentration in the patient's blood.
Aafact® should be dissolved in 5 ml (500 IU) or 10 ml (1000 IU) of water for injections. After dissolving Aafact should be administrated intravenously. It is advisable to infuse the product at a rate not exceeding 10 ml per minute.

Contra-indications
No contra-indications for the use of Aafact® are known.

Special warnings and special precaution for use
■ Aafact® has no effect whatsoever on haemophilia B patients (congenital factor IX deficiency) and in patients with an acquired reduction in factor IX activity.
Since Aafact® lacks any Von Willebrand factor activity this product is not indicated for haemorrhages in patients with Von Willebrand's disease.

■ Patients using Aafact® should have the factor VIII levels in their blood checked regularly in order to prevent the formation of antibodies against factor VIII, which can counteract the intended haemostatic effect.

■ 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.

■ Immediately before administration, the solution should be visually inspected to see whether it contains any particulate matter. If Aafact® is not fully dissolved, or if the solution is not entirely clear, then it should not be administered.
■ Because it has to be stored at low temperature, the product first must be allowed to reach room temperature before use.

Interactions with other medicinal products and other forms of interaction
No clinically relevant adverse interactions of Aafact® with other medicinal products are known.

Pregnancy and lactation
The safety of using human plasma coagulation factor VIII concentrate during pregnancy has not been established in controlled clinical trials. Animal experiments are not suitable to determine safety as regards reproduction, development of the embryo or foetus, the course of pregnancy, as well as perinatal and post-natal development. Accordingly, human plasma coagulation factor VIII concentrate should only be administered during pregnancy and lactation when absolutely necessary.

Effects on ability to drive and use machines
There are no indications that Aafact® may impair the ability to drive or use machines.

Undesirable effects
■ Some patients may experience reactions of an allergic nature. Mild reaction such as urticaria may be treated with antihistamines and corticosteroids. In the case of more severe reactions (e.g. anaphylactic shock) administration of the product should be stopped immediately, after which the reaction should first be treated with a high dose of corticosteroids and then with adrenaline, slowly administered intravenously (not by the intramuscular route).

■ Patients treated with factor VIII products can develop antibodies against factor VIII. In practice, this is seen in about 25 % of patients. In 5 - 10 % of patients, antibody production is so pronounced as to affect the treatment, by neutralising the administered factor VIII. This is expressed in a lack of clinically favourable result, and may represent a hazard to the patient. In such cases it is advisable to consult a centre which is specialised in the treatment of such patients.

■ Although precautions have been taken to eliminate blood-borne infectious agents both from the starting material (plasma) and the final product, the risk of infection by blood-borne infectious agents cannot be completely ruled out.

■ The generation of antibodies to product-specific mouse proteins cannot be ruled out.

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Factor VIII is a human plasma protein, which has an important role in intrinsic blood coagulation. In vivo, circulating factor VIII is bound to Von Willebrand factor. As a co-factor, factor VIII accelerates the conversion of factor X to activated factor X (factor Xa) by activated factor IX. The factor Xa produced converts prothrombin to thrombin. This thrombin converts fibrinogen into fibrin and eventually a clot starts to form. Factor VIII is used in factor VIII substitution therapy in cases of factor VIII deficiency.

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 Undesirable effects).

Preclinical safety data
The active constituents 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 mutagenis effects of factor VIII concentrates prepared from human plasma, experimental research, especially into heterologous species, is considered unnecessary.

PHARMACEUTICAL PARTICULARS

List of excipients

Aafact® consists of a protein fraction prepared from human fresh-frozen plasma. The preparation is supplied as a sterile and pyrogen-free powder. A vial consists respectively 0.1 or 0.2 g freeze-dried powder. After solution in the described volume of water for injections the product consists 100 IU factor VIII per ml and as well as 14 mg sodium chloride, 4 mg human albumin, 3.2 mg L-histidine, 0.4 mg polyethylene glycol and 0.2 mg calcium chloride per ml.

Incompatibilities

No medication should be added to Aafact®

Shelf life

Aafact® stored according to the instruction has a shelf life of three years. Before its shelf life has expired, Aafact® can be stored for 2 months at room temperature (15 - 25°C). Once it has been dissolved Aafact® can be kept for three hours at room temperature (15 - 25°C) awaiting for use. If the contents of the vial are only partially used, the remainder should be destroyed.

Special precaution for storage

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

Nature and contents of container

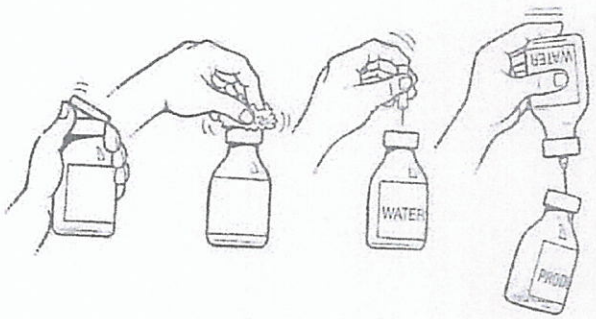
Aafact® (500 IU) :	- vial	: 8 ml-vial, glass type I
	- vial WFI	: 5 ml-vial, glass type I of solvent
	- stopper	: bromobutyl rubber
	- cap	: aluminium flip-off seal
Aafact® (1000 IU) :	- vial	: 20 ml-vial, glass type I
	- vial WFI	: 10 ml-vial, glass type I of solvent
	- stopper	: bromobutyl rubber
	- cap	: aluminium flip-off seal

Instruction for use/handling

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 2-8°C, should be warmed to room temperature (15 - 25°C).

Instruction 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. The solution may vary in appearance from clear to slightly opalescent, and from colourless to light yellow.



1 2 3 4

Date on which this patient information leaflet was last approved
mm-yyyy

Manufactured by
Sanquin, Plesmanlaan 125, NL-1066 CX Amsterdam, The Netherlands, tel +31 20 512 3355

Imported by
PT Graha Farma
Solo, Indonesia

GRAHA FARMA
SOLO - INDONESIA

HARUS DENGAN RESEP DOKTER

Reg. No. : DKI

Sanquin

PT. GRAHA FARMA
Jl. Dr. Supomo No. 246 Solo - 57141
- INDONESIA -