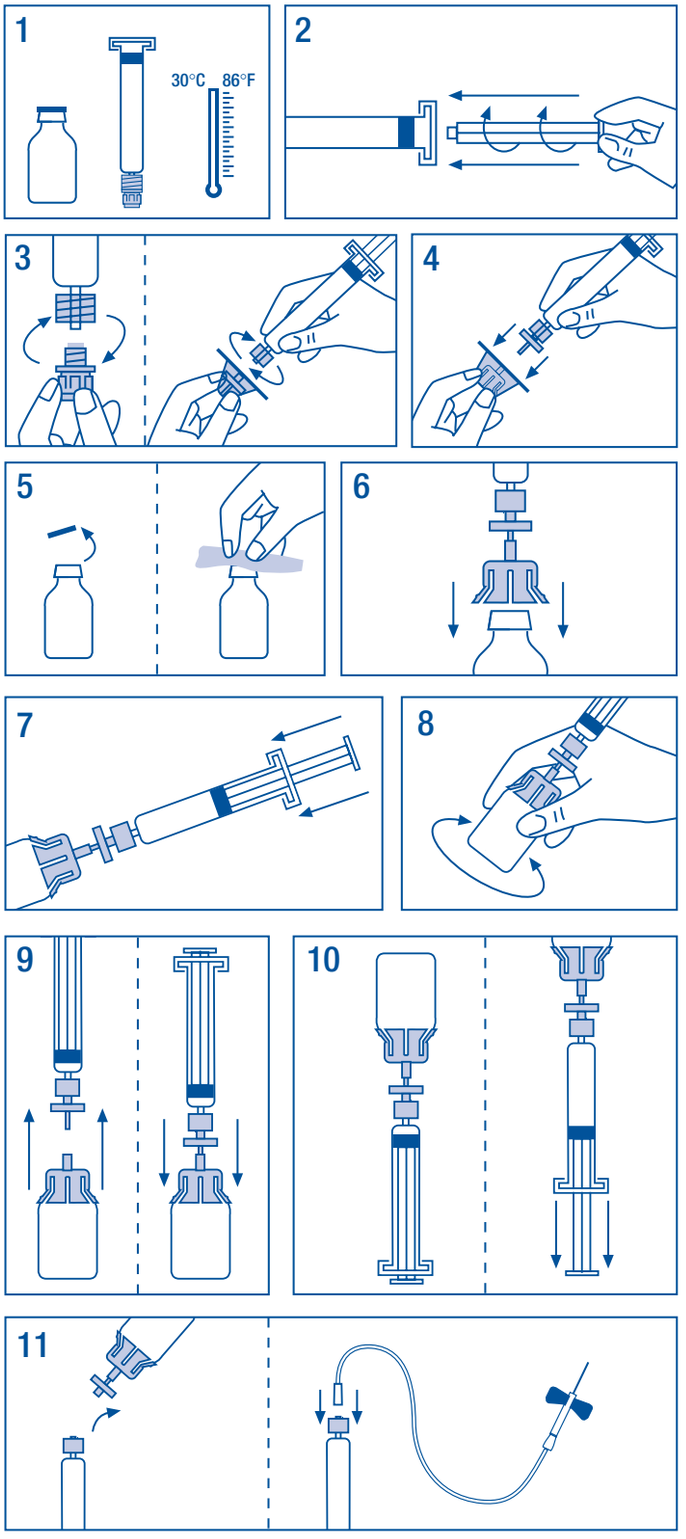

GRIFOLS

Fanhdi
250, 500 and 1000 I.U.

FACTOR VIII

Powder and solvent for solution for injection

Composition

Fanhdi is presented as a lyophilised powder for solution for injection containing nominally 250 I.U., 500 I.U. or 1000 I.U. of human coagulation factor VIII per vial.

The product contains approximately 25, 50 or 100 I.U./ml of human coagulation factor VIII when reconstituted with 10 ml of water for injection.

The potency (I.U.) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Fanhdi is at least of 2.5 to 10 I.U./mg protein depending on its strength (250, 500 or 1000 I.U.).

Excipients: histidine, human albumin, arginine and water for injections (solvent).

Pharmaceutical form and content

Powder and solvent for solution for injection, containing 250, 500 or 1000 I.U. of factor VIII.

Activity

Fanhdi is a high purity and stable FVIII lyophilised concentrate obtained from human plasma by means of a continuous purification process consisting of a polyethylene glycol (PEG) precipitation followed by an affinity chromatography and sodium chloride and glycine precipitations.

The process to manufacture Fanhdi has been validated for viral inactivation/removal, using HIV and model viruses for enveloped and non-enveloped viruses. Two specific steps designed to inactivate any contaminating viruses, consisting of a treatment with tri-n-butyl phosphate (TNBP) and polysorbate 80 and a heat treatment for 72 - 74 h at 81 ± 1 ºC, as well as two steps of the process related to inactivation/removal (polyethylene glycol precipitation and affinity chromatography) were studied, resulting altogether in a good viral inactivation/removal level.

Holder of the marketing authorisation

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Therapeutic indications

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

This product may be used in the management of acquired factor VIII deficiency.

No data is available to recommend the use of Fanhdi in von Willebrand disease.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Precautions

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of human proteins other than factor VIII. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.

In case of shock, the current medical standards for shock-treatment should be observed.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV
- testing of plasma pools for HCV genomic material
- inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, HAV and HBV.

The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as parvovirus B19 and other transmissible infective agents.

Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma-derived factor VIII concentrates is recommended.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. in haemolytic anaemia).

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 Nijmegen's modified assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic 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 human coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory test.

See also Undesirable effects.

In the interest of patients, it is recommended that, whenever possible, every time that Fanhdi is administered to them, the name and batch number of the product is registered.

Interactions and incompatibilities

Interactions

No interactions of human coagulation factor VIII products with other medicinal products are known.

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Only the provided infusion sets should be used because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

Warnings

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.

Effects on ability to drive

No effects on ability to drive and use machines have been observed.

Posology

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

The dosage 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 patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (I.U.), 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 (I.U.) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 International Unit (I.U.) factor VIII per kg body weight raises the plasma factor VIII activity by 2.1 ± 0.4% of normal activity. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (I.U./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 or I.U./dl) 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 (%) (I.U./dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 12 - 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 - 24 hours until threat is resolved.
Surgery		
Minor including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	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% (I.U./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, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 I.U. 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.

There are insufficient data from clinical trials to recommend the use of Fanhdi in children less than 6 years of age.

Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. 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 patients with haemophilia.

See also Precautions.

Method and route of administration

Do not use after the expiry date shown on the label. Left-over product must never be kept for later use, nor stored in a refrigerator.

To prepare the solution:

1. Warm the vial and syringe but not above 30 ºC.
2. Attach plunger to syringe containing diluent.
3. Remove filter from packaging. Remove cap from syringe tip and attach syringe to filter.
4. Remove vial adaptor from packaging and attach to syringe and filter.
5. Remove cap from vial and wipe stopper with antiseptic wipe provided.
6. Pierce vial stopper with adaptor needle.
7. Transfer all diluent from syringe to vial.
8. Gently shake vial until all product is dissolved. As with other parenteral solutions, do not use if product is not properly dissolved or particles are visible.
9. Briefly separate the syringe/filter from vial/adaptor, to release the vacuum.
10. Invert vial and aspirate solution into syringe.
11. Prepare injection site, separate syringe and inject product using the set with butterfly needle provided or a sterile needle. Injection rate should be 3 ml/min into a vein and never more than 10 ml/min to avoid vasomotor reactions.

Do not re-use administration sets.

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

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Reconstituted products should be inspected visually for particulate matter and discoloration prior administration.

Overdose

No symptoms of overdose with human coagulation factor VIII have been reported.

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 infrequently, and may in some cases progress to severe anaphylaxis (including shock).

On rare occasions, fever has been observed.

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 information on viral safety see Precautions.

Storage

Do not store above 30 ºC.

Do not freeze.

Do not use after expiry date.

Shelf-life

Shelf-life of Fanhdi is of 3 years when stored not above 30 ºC.

Chemical and physical in-use stability has been demostrated for 12 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Sizes

Fanhdi 250 I.U.

Fanhdi 500 I.U.

Fanhdi 1000 I.U.

Keep out of the reach and sight of children.

Revision of the text 17.12.2007