Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fanhdi 1000 IU powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human coagulation factor VIII.

Fanhdi is presented as a lyophilised powder for solution for injection containing nominally 1000 IU human coagulation FVIII per vial.

The product contains approximately 100 IU/ml of human coagulation factor VIII when reconstituted with 10 ml of water for injections.

The FVIII:C potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Fanhdi is at least of 10 IU FVIII:C/mg protein.

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Vial containing white or pale yellow powder and syringe with Water for Injections (solvent).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fanhdi is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

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

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

4.2 Posology and method of administration

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

Posology
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 (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 dosage 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 2.1 ± 0.4% of normal activity. The required dosage is determined using the following formula:

Required units = body weight (kg) · desired factor VIII rise (%) (IU/dl) · 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 IU/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 (%) (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 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% (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, 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 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.

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

Method of administration
The product should be administered via the intravenous route. Fanhdi should be administered at a flow rate of no more than 10 ml/min.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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, which may lead to 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.

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), and for the non-enveloped virus hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as 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).

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 severity of the disease as well as 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.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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.

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

It is strongly recommended that every time that Fanhdi 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 product.

Sodium content
The residual content of sodium in Fanhdi, arising from the manufacturing process, does not exceed 23 mg per vial. This is equivalent to 1.15% of the recommended maximum daily intake of sodium for an adult. However, depending on the body weight of the patient and the posology, the patient may receive more than one vial.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Fanhdi has no or negligible 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 infrequently, and may in some cases progress to severe anaphylaxis (including shock).

On rare occasions, fever has been observed.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Fanhdi (see section 5.1). 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.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA Standard System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	FVIII inhibitor	Uncommon (PTPs)* Very common (PUPs)*

* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

No case of overdose with human coagulation factor VIII has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antihaemorrhagics: blood coagulation factor VIII. ATC code: B02BD02.

In Fanhdi, factor VIII is presented as a complex with von Willebrand factor.

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 FVIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Paediatric population

There are insufficient data from clinical trials in children less than 6 years of age.

Data on Immune Tolerance Induction (ITI) have been collected in pediatric and adult patients with haemophilia A who have developed inhibitors to FVIII. The 57 patients from retrospective studies and 14 patients from prospective studies included a broad spectrum of primary and rescue ITI patients with varying prognoses for achieving immune tolerance. Data show that Fanhdi has been used to induce immune tolerance. In patients where tolerance was achieved, bleeding could be prevented or controlled on either prophylactic or on-demand therapy with a FVIII concentrate.

5.2 Pharmacokinetic properties

Plasma factor VIII activity decreases by a two-phase exponential decay.

The half-life of human factor VIII obtained in the clinical trial carried out with Fanhdi is 14.18 ± 2.55 hours and the "in vivo" recovery is 105.5 ± 18.5%, which is equivalent to approximately 2.1 ± 0.4 IU/dl per IU/kg administered (determinations performed following chromogenic method). Next are detailed the values for MRT 20.6 ± 4.8 h, AUC 19.3 ± 3.7 IU h/ml and clearance 2.6 ± 0.5 ml/h/kg.

5.3 Preclinical safety data

Human plasma coagulation factor VIII (active ingredient for Fanhdi) is a normal constituent of the human plasma and acts like the endogenous factor VIII. Single dose toxicity testing is of no relevance since higher doses result in overloading.

Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Albumin (human)
Arginine
Water for injections (solvent)

6.2 Incompatibilities

Fanhdi 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.

6.3 Shelf life

Unopened: 3 years.

Reconstituted:

Chemical and physical in-use stability has been demonstrated 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 the 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.

6.4 Special precautions for storage

Do not store above 30 ºC. Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Fanhdi is supplied in Type II glass vials containing 1000 I.U. of factor VIII (lyophilisate) and Type I glass pre-filled syringes containing 10ml of water for injection (solvent).

The accessories supplied with Fanhdi for reconstitution and administration of the product are: vial adaptor, filter, two alcohol swabs and butterfly needle.

Not all pack sizes may be marketed.

Pack size: 1 lyophilised vial, 1 pre-filled syringe with solvent and accessories.

6.6 Special precautions for disposal and other handling

Do not use after the expiry date shown on the vial label.

Left-over product must never be stored for later use, nor stored in a refrigerator.

To prepare the solution:

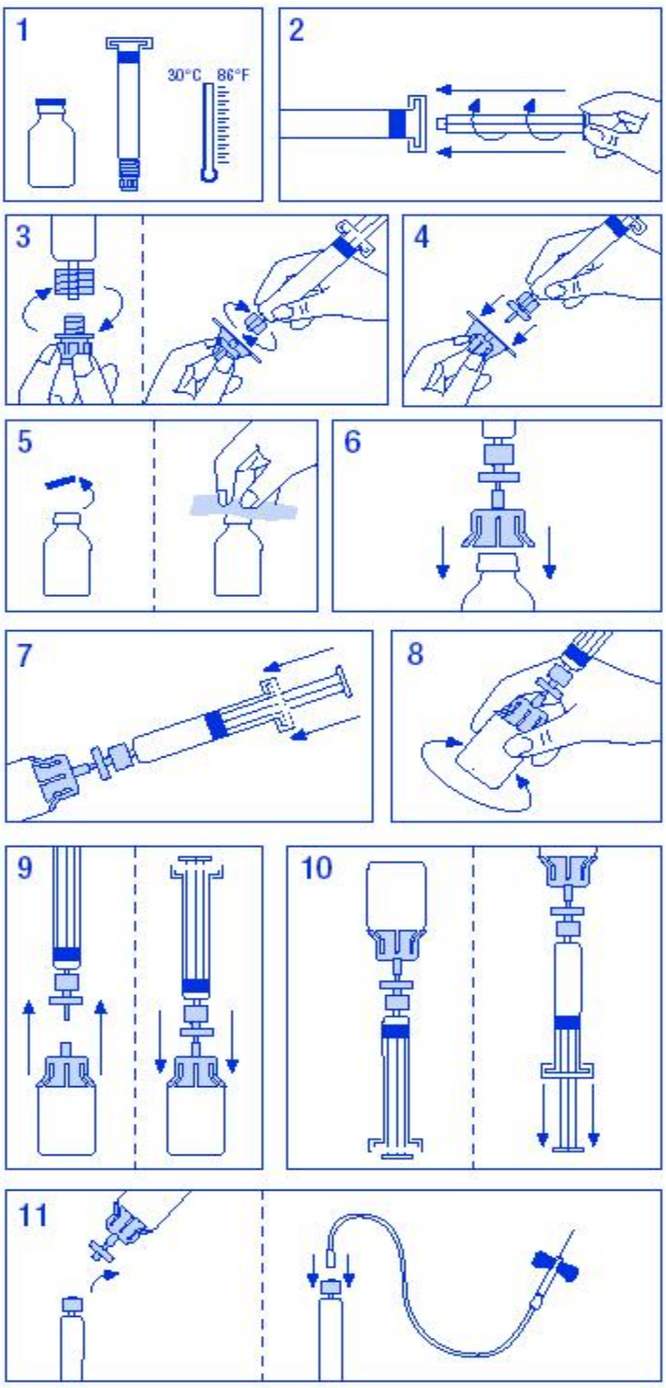
1. Warm the vial and syringe but not above 30ºC.
2. Attach plunger to syringe containing diluent.
3. Remove filter from packaging. Remove cap from syringe tip and attach syringe to filter.
4. Remove the vial adaptor from packaging and attach to syringe and filter.
5. Remove cap from vial and wipe stopper with swabs 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 butterfly needle provided. Injection rate should be 3 ml/minute into a vein and never more than 10 ml/minute to avoid vasomotor reactions.

Do not re-use the 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 to administration.



7 MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
c/Can Guasc, 2 - Parets del Vallès
08150 Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER

PA0849/001/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 July 2000

Date of last renewal: 07 July 2010

10 DATE OF REVISION OF THE TEXT

March 2018