

1. NAME OF THE MEDICINAL PRODUCT

FANHDI® 25 IU/ML (FACTOR VIII)
FANHDI® 50 IU/ML (FACTOR VIII)
FANHDI® 100 IU/ML 1000 IU/10 ML (FACTOR VIII)
FANHDI® 100 IU/ML, 1500 IU/15 ML (FACTOR VIII)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human coagulation factor VIII, Ph. Eur.

Fanhdi® is presented as a lyophilised powder for solution for injection containing nominally 250, 500, 1000 or 1500 IU human coagulation factor VIII per vial.

The product contains approximately 25, 50 or 100 IU/ml of human coagulation factor VIII when reconstituted with 10 ml of Water for Injections for the presentations of 250, 500 and 1000 IU. The presentation of 1500 IU is reconstituted with 15 ml of Water for Injections and contains approximately 100 IU/ml.

The factor VIII:C potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Fanhdi® is at least 2.5 to 10 IU factor VIII:C/mg protein depending on its strength (250, 500, 1000 or 1500 IU).

For a 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 prevention and control of bleeding in patients with moderate or severe factor VIII deficiency due to classical hemophilia A.

Fanhdi® is not effective in controlling the bleeding of patients with von Willebrand's disease.

4.2 Posology and method of administration

Posology

The dose and duration of Fanhdi® treatment must be adjusted according to each patient's needs.

The required dosage may be estimated using the following formula:

$$\text{Number of factor VIII} = \text{Body weight} \times \text{Desired factor VIII} \times 0.5 \\ \text{units required (I.U.)} \quad (\text{kg}) \quad \text{rise (\%)}$$

This calculation is based on the empirical finding that 1 I.U. of factor VIII per kg body weight raises the plasma factor VIII activity approximately 2% (i.e. 0.5 I.U./kg are required for 1% increase in plasma factor VIII level).

The patient's plasma factor VIII levels should be determined and monitored during treatment with Fanhdi®. This is particularly important in the case of surgical procedures.

Hemorrhagic event	Therapeutically necessary plasma level of FVIII activity	Period during which it is necessary to maintain the therapeutic plasma level of factor VIII activity
<ul style="list-style-type: none"> - Minor hemorrhages: - H. into joints 	30%	At least 1 day, depending on the severity of the hemorrhage
<ul style="list-style-type: none"> - Major hemorrhages: - H. into muscles - Teeth extraction - Mild trauma capitis - Minor operations - H. into the oral cavity 	40 - 50%	3 - 4 days or until adequate wound healing
<ul style="list-style-type: none"> - Life-threatening hemorrhages: - Major operations - Gastro-intestinal bleeding - Intracranial, intra-abdominal or intrathoracic hemorrhages - Fractures 	60 - 100%	During 7 days, then therapy for at least another 7 days

Patients with inhibitors:

If plasma factor VIII does not reach the expected levels or if the bleeding cannot be controlled after the administration of the adequate dose, the presence of inhibitors should be suspected.

Hemophilic patients having antibodies against factor VIII (inhibitors) need a specific therapy.

Immunotolerance may occur after treatment with human plasma coagulation factor VIII concentrate.

Prophylaxis:

For long-term prophylaxis against bleeding in patients with severe hemophilia A, Fanhdi® should be administered at doses of 10 to 50 I.U./kg given at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Method of administration

USE THE PRODUCT IN ROOM TEMPERATURE NOT ABOVE 30 °C

Fanhdi® is intended for intravenous administration only. Fanhdi® may be administered at a rate of no more than 10 ml/minute. (For full details of reconstitution and use refer to instructions for use/handling).

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, 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 HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal 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 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 in the 250, 500 and 1000 IU presentations, and 34.5 mg per vial in the 1500 IU presentation. This is equivalent to 1.15% and 1.72% respectively 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.

The adverse drug reactions reported are summarised and categorised according to the MedDRA system organ class in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing of seriousness. Frequency has been determined using the following criteria:

- very common: $\geq 1/10$ infusions
- common: $\geq 1/100$ to $< 1/10$ infusions
- uncommon: $\geq 1/1,000$ to $< 1/100$ infusions
- rare: $\geq 1/10,000$ to $< 1/1,000$ infusions
- very rare: $< 1/10,000$, not known (cannot be estimated from the available data.)

System Organ Class	Body System Preferred Term	ADR frequency evaluation
Blood and lymphatic system disorders	FVIII inhibitors	Uncommon (PTPs)* Very common (PUPs)*
General disorders and administration site conditions	Pyrexia	Rare

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

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 information on transmissible agents' safety, see section 4.4.

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.

Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

4.9 Overdose

No case of overdose 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 factor VIII 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 factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

In addition to its role as a factor VIII protecting protein, von Willebrand mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

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 paediatric and adult patients with haemophilia A who have developed inhibitors to FVIII. The 57 patients from a retrospective study 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 Fanhdi® obtained in the clinical trial carried out with this product is 14.18 ± 2.55 hours and the "in vivo" recovery is $105.5 \pm 18.5\%$, which is equivalent to approximately 0.021 ± 0.004 I.U./ml per I.U./kg administered (determinations performed following chromogenic method).

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® should not be mixed with other medicinal products.

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

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

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 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 °C.

Do not freeze.

Do not use after expiry date.

6.5 Nature and contents of container

Fanhdi® is supplied in type II glass vials containing 250, 500, 1000 or 1500 I.U. of FVIII (lyophilised) and type I glass pre-filled syringes containing 10 ml for the presentations of 250, 500 and 1000 I.U. or 15 ml for the presentation of 1500 I.U. of water for injections (solvent).

6.6 Special precautions for disposal and other handling

Do not use after 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 °C.
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 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/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 discolouration prior to administration.

7. MANUFACTURER:

Instituto Grifols, S.A.
08150 Barcelona - Spain

8. LICENSE HOLDER:

Medici Medical Ltd.,
3 Hamachshev St.
Netanya 4250713 - Israel

9. MARKETING AUTHORISATION NUMBERS:

FANHDI® 25 IU/ML (FACTOR VIII): 121 01 29838 00

FANHDI® 50 IU/ML (FACTOR VIII): 121 02 29839 00

FANHDI® 100 IU/ML, 1000 IU/10 ML (FACTOR VIII): 121 03 29840 00

FANHDI® 100 IU/ML, 1500 IU/15 ML (FACTOR VIII): 137 45 31605 00

Approved in: March 2008

Revised in: October 2020