Unit: Technical Assessment Unit

Public assessment report for biological products

(Fanhdi 100/120 IU/ml)

Administrative information:

Trade name of the medicinal product:	Fanhdi 100 IU FVIII/120 IU VWF per ml
INN (or common name) of the active substance(s):	Human Coagulation Factor VIII and Von Willebrand Factor (VWF)
Manufacturer of the finished product	Instituto Grifols, S.A., Can Guasch, 2. Pol. Ind. levante, 08150 Parets del Vallès, Barcelona Spain - SPAIN
Marketing Authorization holder	Instituto Grifols, S.A., Can Guasch, 2. Pol. Ind. levante, 08150 Parets del Vallès, Barcelona Spain - SPAIN
Applied Indication(s):	Haemophilia A (congenital factor FVIII deficiency) Von Willebrand disease
Pharmaceutical form(s) and strength(s):	Powder and Solvent for Solution for injection 100 IU/120 IU per ml
Route of administration	I.V injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

ADME: Absorption, distribution, metabolism, excretion
IU: International unit
IV: Intravenous
LD: Lethal dose
PK: Pharmacokinetic
TnBP: tri-n-butyl phosphate
VWD: Von Willebrand disease
VWF: Von Willebrand Factor

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

Fanhdi is an anti-haemorrhagic consisting of Human von Willebrand factor and Coagulation Factor VIII in combination. It is obtained from human plasma by means of a continuous purification process followed by affinity chromatography and precipitation with sodium chloride and glycine, steps designed to obtain a conventional high-purity product, as well as an acceptable factor VIII yield. Furthermore, Fanhdi is subjected to two specific viral inactivation steps to reduce the possibility of transmission of viral infections as much as possible.

It is indicated for the treatment and prophylaxis of bleeding in patients with Hemophilia A (congenital factor FVIII deficiency), and the treatment of bleeding and prophylaxis of surgical bleeding in patients with Von Willebrand disease when desmopressin treatment alone is ineffective or contra-indicated.

2. **<u>Quality aspects:</u>**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

- Recommended International Nonproprietary Name (INN): Human coagulation factor VIII and von Willebrand factor complex.
- Factor VIII:C is synthesized as a single-chain polypeptide which undergoes a quick proteolysis before or shortly after having been secreted into plasma. Plasma von Willebrand factor (VWF) is a glycoprotein that mediates platelet adhesion to sites of vascular injury and is a carrier protein for blood clotting factor VIII (FVIII).
- The active ingredient of the product is the natural complex formed by human coagulation factor VIII and von Willebrand factor. VWF is important in the hemostasis process and it is required to support platelet aggregation which promotes thrombus growth and consolidation. FVIII:C is essential in the coagulation mechanism.

- **Manufacture, process controls and characterization:**

➢ **Manufacturer**

Instituto Grifols, S.A., Polígono Levante, c/Can Guasch, 2, 08150 Parets del Vallès, Barcelona, Spain

➢ **Description of Manufacturing Process and Process Controls**

The manufacturing process steps of FVIII/VWF complex include a continuous purification process followed by affinity chromatography and precipitation. Furthermore, FVIII/VWF complex is subjected to two specific viral inactivation steps and a final heat treatment step.

- **Control of Materials**

- The active ingredient of Fanhdi is human coagulation factor VIII and von Willebrand factor complex, obtained from human plasma or cryoprecipitate by purification process. All human plasma used in the manufacture of Fanhdi is in accordance with the national requirements of the country of origin of the plasma donations.
- According to the available scientific data no material used in the manufacturing of Fanhdi is of risk of Transmitting Animal Spongiform Encephalopathy.
- All ingredients meet Ph. Eur. Specifications. Imidazole is not described in any pharmacopoeia but meets the specifications established by Instituto Grifols, S.A.

- **Controls of Critical Steps and Intermediates**

Detailed data for the identification and control of critical steps involved in the manufacturing process were provided and found satisfactory.

- **Process Validation**

Validation studies for viral inactivation, freeze-drying, heat treatment, purification and aseptic filling were submitted and according to the results, the process fulfills its function correctly.

- **Manufacturing Process Development**

The following reports and studies are submitted:
Process development: - Factor VIII HP-HT: Purification process development and characteristics
- Factor VIII HP-HT concentrate: Development and characteristics of the process for heat treatment in final vial.
Characterization study: Characterization of the FVIII concentrate Fanhdi.
Neoantigenicity studies: Study for the determination of the presence or absence of neoantigens due to the heat treatment for viral inactivation.
Consistency studies: - Production process consistency.
- Consistency of the manufacturing procedure in relation to von Willebrand factor measured as Ristocetin cofactor in intermediate purification stages of the Fanhdi FVIII/VWF concentrate.
- Consistency of the activity of Ristocetin cofactor in Fanhdi FVIII/VWF concentrate.

- **Specification**

The specifications are as per the European Pharmacopoeia monograph of Human coagulation factor VIII “0275”, and ICH guideline Q6B.

- **Analytical Procedures**

Overview of the analytical procedures along with their validation reports were provided.

- **Batch analysis**

Certificates of final analysis of 3 lots are submitted.

- **Reference Standards or Materials**

The primary reference standards and the In-house working reference materials are mentioned in the MA file.

- **Container closure system**

- Fanhdi is filled into 20 ml nominal capacity, 20 mm ø neck finish, type II glass vials. Glass material meets European Pharmacopoeia. Vials are closed with a 20 mm ø chloro-butyl-rubber stopper for freeze-drying, which meets European Pharmacopoeia.
- Certificate of analysis for glass bottles 20 ml type II, stopper 20 mm ø and cap were submitted.

- **Stability of drug substance**

Based on available stability data:

Approved Shelf Life: 12 months

Approved Storage Conditions: (≤-20°C)

2.2.3 Drug product:

- **Description and Composition of the Drug Product**

- The active ingredient of Fanhdi is human coagulation factor VIII and human von Willebrand factor in combination. The excipients used are human albumin as a stabilizer and histidine and arginine as solubilizing agents. The solvent used to reconstitute the product is water for injection.
- The packaging material in contact with the product consists of vials and stoppers which comply with the European Pharmacopoeia specifications.

- **Pharmaceutical Development**

➢ **Components of drug product**

- Active Ingredient: human coagulation factor VIII and human von Willebrand factor
- Excipients: human albumin, histidine and arginine
- Solvent: water for injection

➢ **Container closure system and their compatibility**

Fanhdi is filled into 20 ml nominal capacity, 20 mm ø neck finish, type II glass vials. Glass material meets European Pharmacopoeia. Vials are closed with a 20 mm ø chloro-butyl-rubber stopper for freeze-drying, which meets European Pharmacopoeia.

➢ **Microbiological Attributes**

Control of microbial container is controlled as discussed in Justification of specifications section.

- **Compatibility**
  Compatibility with the diluent and dosage device was submitted by the manufacturer.

- **Manufacture of the drug product:**

  Description of manufacturing process and process controls along with manufacturers and responsibilities

- **Manufacturer(s):**
  Instituto Grifols, S.A., Polígono Levante, c/Can Guasch, 2, 08150 Parets del Vallès, Barcelona, Spain, is responsible for the whole manufacturing process, i.e. from plasma starting material to the labelling, packaging, quality control testing and batch release of the finished product.
  The alternate secondary packaging site for the finished product is located at:
  GRIFOLS WORLDWIDE OPERATIONS LTD. (GWWO)
  Grange Castle Business Park, Grange Castle, Clondalkin, Dublin 22, Ireland.

- **Control of critical steps and intermediates**
  Detailed data for the identification and control of critical steps involved in the manufacturing process were provided and found satisfactory.

- **Process validation and / or evaluation**
  Validation studies for viral inactivation, freeze-drying, heat treatment, purification and aseptic filling were submitted and according to the results, the process fulfills its function correctly.

- **Product specification:**
  - Excipients are compendial and comply with the corresponding European Pharmacopoeia monographs.
  - The human albumin used as stabilizer in the final product is Human Albumin Grifols 20% obtained from human plasma by a continuous purification process. It meets the European Pharmacopoeia in force.
  - Excipients are analyzed according to the methods established in the corresponding European Pharmacopoeia monographs.
  - No novel excipients are used.
  - The drug product is analyzed as per the European Pharmacopoeia monograph of Human coagulation factor VIII "0275", and ICH guideline Q6B.
  - Overview of the analytical procedures along with their validation reports were provided.
  - The specifications include general characteristics, biological & general safety tests, potency & identity tests.
  - Justification of the drug product specifications at the release and during stability studies are provided.

- **Reference Standards or Materials**

The primary reference standards and the In-house working reference materials are mentioned in the MA file.

- **Container closure system**

- Fanhdi is filled into 20 ml nominal capacity, 20 mm ø neck finish, type II glass vials. Glass material meets European Pharmacopoeia. Vials are closed with a 20 mm ø chloro-butyl-rubber stopper for freeze-drying, which meets European Pharmacopoeia.
- Certificate of analysis for glass bottles 20 ml type II, stopper 20 mm ø and cap were submitted.

- **Stability of the drug product**

Based on available stability data:
Approved shelf life:
Finished product: 3 years
Solvent: 48 months

Approved Storage Conditions:
Solvent: store at (2-30℃)
Finished product: Don't store above 30℃
-Don't freeze
-After reconstitution, the product's chemical and physical in-use stability has been demonstrated for 12 hours at 25 ºC.
-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 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.
- Gently swirl vial avoiding foam until all product is dissolved, do not shake, as with other parenteral solutions, do not use if product is not properly dissolved or particles are visible.

Adventitious agents
Non-viral agents: TSE elimination studies Instituto Grifols has carried out a study in order to estimate the capacity of Fanhdi production process to eliminate prion agents in the presence of a hypothetic contamination.
Viral agents: Viral removal/inactivation studies: The Fanhdi production process includes two specific steps for viral inactivation. Studies have been conducted on these steps in order to validate their virus elimination capacity.
- Full reports for the non-viral and viral agents studies are submitted.

3. **Non –clinical aspect:**

Factor VIII/VWF is a complex of glycoproteins with high molecular weight. One of its components is factor VIII, with a molecular weight of approximately 270,000. Factor VIII is essential in the

blood coagulation process and its action takes place through the intrinsic pathway, finally giving rise to the prothrombin activator or prothrombinase.
Mode of action: Activated factor VIII acts as a pro-coagulant cofactor in the intrinsic clotting pathway. Factor IXa has a key role in the activation of factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.
-In addition to its role as a FVIII protecting and natural stabilizer, VWF also has important functions in the process of hemostasis in which it mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation in response to injury acts as a bridge between platelets and collagen exposed by the damaged endothelium via specific receptors, glycoprotein Ib and glycoprotein IX. This ensures that bound factor VIII is available at the site of the incipient clot.

Pharmacology:

In vitro study to assess the effect of Fanhdi on the ability of VWF present in a plasma derived high purity factor VIII concentrate (≥ 100 IU FVIII/mg of protein) to promote deposition and platelet adhesion on the injured vessel wall, as an indicator of its functionality showed that VWF present in the product maintains a high degree of functionality, promoting platelet adhesion on subendothelium under flow conditions, after its incorporation into an albumin-platelet-red cell preparation and resulting in a significant increase in platelet adhesion when compared to the VWF-free basal control.

Pharmacokinetics: No dedicated PK or ADME studies for Fanhdi were performed. These studies are not considered necessary due to the human origin of human Coagulation FVIII/VWF Complex, which is anticipated to behave in the same manner as naturally circulating proteins. As a human glycoprotein, is immunogenic in animals, there are no relevant kinetics in animals. In short term studies, the essential distribution and elimination are likely to parallel that in humans.

Toxicology: No dedicated studies were conducted to assess the toxicity of Fahndi. This is acceptable regarding the nature of a product as a homologous protein that was obtained from human plasma by a continuous purification process and with no modifications during the manufacturing process.
The toxicity of the impurities in the product due to purification process, namely polysorbate 80 and TnBP was extensively evaluated in the literature. The LD_{50} of polysorbates is 1420 mg/kg in mouse which is about 1000 times its content in a single dose of fahndi. Regarding TnBP, a review of published literature on the testing of mice, rats, rabbits, cats, and chickens, provided evidence that this level of exposure is greater than 800 times less than the lowest LD_{50} quoted for TnBP treatment (lowest quoted is rat IV, 100mg/kg).

- **Overall conclusion:** Limited nonclinical programme was conducted for Fahndi. This is acceptable regarding the nature of the product and the extensive clinical experience (more than 30 years). The safety steps during production process, including viral inactivation steps (solvent-detergent

treatment and final heating), ensures Fanhdi's reliability in terms of viral safety. Thus, Fahndi is considered acceptable from the preclinical point of view.

4. **Clinical aspect:**

Gan & Lee Insulin Glargine Injection (hereafter referred to as GL Glargine Injection), developed by Gan & Lee Pharmaceuticals for the Marketing Authorization Holder (MAH), as a proposed biosimilar to Lantus® (insulin glargine injection for subcutaneous injection; hereafter referred to as Lantus). The active ingredient of GL Glargine Injection has the same amino acid sequence as the active ingredient of Lantus.

Gan & Lee has conducted 4 studies with GL Glargine Injection to compare PK, PD, immunogenicity, safety, and efficacy to Lantus. In addition to the clinical studies conducted by the Applicant, the Applicant relied on the established clinical efficacy and safety data of Lantus.

➢ **Clinical Pharmacology:**

-GL Glargine injection demonstrated both pharmacokinetic and pharmacodynamic similarities to US Lantus and EU Lantus.

- Based on the primary and secondary PK endpoints in Phase I pivotal PK/PD similarity study **(GL-GLA-CT1002)** of the insulin glargine metabolite M1, Gan & Lee Insulin Glargine was similar to Lantus® US RLD and to Lantus® EU RP, since the 90% CI of the respective geometric LS-mean treatment ratio lay within the limits of 80.00 to 125.00%.
- Based on the primary PD endpoints $AUC_{GIR.0-24h}$ and $GIR_{max,}$ Gan & Lee Insulin Glargine was similar to Lantus® US RLD or Lantus® EU RP, since the 90% CI of the respective LS-mean treatment ratio of untransformed data lay within the limits of 80.00 to 120.00%. The similarity was also supported by the 90% CI of the LS-mean treatment ratio of log-transformed data which lay within the limits of 80.00 to 125.00%.

➢ **Clinical Efficacy:**

- **Results of studies** (GL-GLAT1-3001) and (GL-GLAT2-3002) **demonstrated** therapeutic equivalence and noninferiority of GL Glargine Injection compared to EU Lantus with respect to efficacy.
- **According to WHO Guidelines on evaluation of biosimilars "**An adequately powered comparative efficacy and safety trial **will not be necessary** if sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise".
- **According to EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues** "There is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins".

➢ **Clinical Safety:**

- Based on Phase I Pivotal study **(GL-GLA-CT1002)**, Gan & Lee Insulin Glargine, Lantus® US RLD and Lantus® EU RP were **well-tolerated** and safe at single SC doses of 0.5 U/kg, when administered to male subjects with T1DM.
- There were no clinically relevant differences between the AE profiles of the 3 IMPs with the majority of AEs being moderate in intensity and equally distributed.
- While anti-insulin antibody status had an effect on PK results, there was no clear difference in PD results between subjects with and without positive anti-insulin antibodies.
- **For studies (GL-GLAT1-3001) and (GL-GLAT2-3002),** during the 26-week treatment period, Overall, the incidence of AEs was consistent with treatment expectations, and no new safety signals were identified. The overall percentage of subjects with any TEAE, the proportions of subjects experiencing TEAEs overall and the most common TEAEs were **similar** in the GL Glargine Injection and EU Lantus treatment groups. No clinically meaningful differences were found in the safety outcomes between the GL Glargine Injection and EU Lantus treatment groups.

➢ **Clinical Immunogenicity:**

- Based on the results of studies **(GL-GLAT1-3001) and (GL-GLAT2-3002) in which the primary objective** was to evaluate **equivalence of GL Glargine Injection and EU Lantus in terms of immunogenicity** there were no clinically meaningful differences between the GL Glargine Injection and EU Lantus treatment groups in terms of immunogenicity.
- **According to WHO Guidelines on evaluation of biosimilars "**for well-characterized biological substances (insulin), where an extensive literature and clinical experience indicate that immunogenicity **does not impact upon product safety and efficacy, immunogenicity studies may not be necessary** provided that the biosimilar is highly similar to the RP and the risk-based evaluation indicates a low risk**".**
- **According to EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues "**Safety studies should be performed with specific focus on immunogenicity and that the potential impact of anti-drug antibodies, if detected, on glycemic control, insulin requirements and safety, especially local and systemic hypersensitivity reactions, should be investigated**"**, the data submitted by the applicant was in agreement with this guideline.

➢ **Benefit/ Risk discussion:** In conclusion the overall benefit/risk of Basalin 100 unit/ml solution for injection is favorable in treatment of DM in adults, adolescents and children aged 2 years and above.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.