SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FACTANE 100 IU/ml, powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human coagulation factor VIII ..... 100 IU
per 1 ml of reconstituted solution

After reconstitution:

- One 2.5 ml vial contains 250 IU of human coagulation factor VIII.
- One 5 ml vial contains 500 IU of human coagulation factor VIII.
- One 10 ml vial contains 1000 IU of human coagulation factor VIII.

The specific activity is greater than 100 IU/mg of total protein.

FACTANE contains approximately 20 IU/ml of von Willebrand factor.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Human coagulation factor VIII is indicated for the treatment and prevention of bleeding episodes and during surgery in factor VIII deficiency (haemophilia A) both in patients who have or have not previously been treated and who do not present any inhibitors against factor VIII.

Treatment may be continued in patients who develop factor VIII inhibitors (neutralising antibodies) at levels less than 5 Bethesda Units (BU) if clinical response is still obtained and circulating factor VIII levels increase.

Human coagulation factor VIII is indicated for the treatment of inhibitors by immune tolerance induction.

FACTANE does not contain von Willebrand factor in effective quantities and is therefore not indicated in von Willebrand disease.

4.2. Posology and method of administration

Posology

- **Treatment and prevention of bleeding episodes and during surgery**

As a general rule, administration of one IU of factor VIII per kg of body weight increases plasma factor VIII levels by approximately 2%. The following formulae can be used to determine the dosage required to obtain a given response (I) or the expected response after a given dose (II):

$$\textbf{I. Required units (IU)} = \text{body weight (kg)} \times \text{desired increase in factor VIII levels (\% of normal)} \times 0.5$$

II. Expected increase in factor VIII levels (% of normal) =

$$\frac{2 \times \text{no. of IU administered}}{\text{body weight (kg)}}$$

The doses and the duration of replacement therapy should be adapted to individual patient needs (weight, severity of the haemostasis disorder, site and severity of the bleeding episode, desired factor VIII levels and the presence of inhibitors). The table below provides an indication of the minimum plasma factor VIII levels required. In the case of the various haemorrhagic situations described, factor VIII activity should not fall below the plasma activity levels shown (in % of normal) during the period indicated.

Human coagulation factor VIII may also be used in the prophylaxis of bleeding, at doses adapted for each patient. Doses ranging from 15 to 30 IU per kg of body weight, administered every 2 to 3 days, have successfully reduced the number of bleeding episodes.

The clinical efficacy and safety of LFB-BIOMEDICAMENTS human coagulation factor VIII (non nanofiltered version) were demonstrated for the treatment and prevention of bleeding episodes and during surgery in 6-year old children in a retrospective trial performed in 103 previously-untreated children and presenting with FVIII:C levels < 1%.

Bleeding episode or surgical procedure	Plasma level of factor VIII required *	Frequency of injections and period during which therapeutic plasma levels should be maintained
Minor bleeding episode: haematoma, haemarthrosis, epistaxis.	15 - 30%	At least one injection, depending on the severity of the bleeding episode.
Major bleeding episode: muscle haemorrhage, mild head injury, bleeding from the oral cavity. **Moderately serious surgical procedure** including tooth extraction.	30 - 50%	2 - 4 days or until healing is achieved.
Life-threatening haemorrhage: gastro-intestinal, abdominal, cerebral or thoracic haemorrhage, head injuries and skull fractures. **Major surgical procedure**	50 - 100%	For 7 days, then continue treatment for at least 4 to 7 additional days, to maintain factor VIII levels between 30 and 50%.

(*measured as activity and expressed as a percentage of normal levels)

Important

The dose and frequency of human coagulation factor VIII injections to be administered should always be adapted for each individual case and must be based on the observed clinical efficacy as well as the resulting circulating factor VIII levels.

Patients under replacement therapy for haemophilia A should be monitored regularly, especially for the development of factor VIII inhibitors. If the desired plasma factor VIII activity levels are not attained or if bleeding is not controlled with administration of a dose calculated using the formula above, an assay should be performed to determine if the patient has developed factor VIII inhibitors. The benefits of treatment with human coagulation factor VIII therapy should be reconsidered in such cases (therapeutic inefficacy, increase of inhibitor titre).

Patients with inhibitors

Human coagulation factor VIII may still be effective in patients who during treatment develop factor VIII inhibitors (neutralising antibody) at levels less than 5 Bethesda Units (BU). Plasma factor VIII

levels are an indication of the efficacy of replacement therapy. Inhibitor titre should be measured to ensure that no anamnestic response has developed.
High doses of human coagulation factor VIII may be necessary to control severe bleeding in patients with high titres of inhibitors (greater than 5 BU). The magnitude of the doses required to maintain adequate human coagulation factor VIII levels in some patients may make treatment difficult to manage. If haemostasis cannot be obtained with human coagulation factor VIII in the presence of high titres of inhibitors, an activated factor VII concentrate or activated prothrombin complex concentrate should be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia A.

- **Inhibitor treatment by immune tolerance induction**

Immune tolerance treatment should be initiated and conducted by a centre with experience in the treatment of patients with haemophilia A.

Immune tolerance induction (ITI)	**Doses***	**Administration procedures**
Initiation levels 0.6 to 5 BU	50 IU/kg/day 3 times per week to 100 IU/kg/day every day	ITI should be initiated as soon as possible
levels > 5 BU	50-100 IU/kg/day 3 times per week to 100-300 IU/kg/day every day	
After disappearance of the inhibitors, resumption of normal recovery and half-life	100 IU/kg/day, then 50 IU/kg/day, then 50 IU/kg every other day then prophylactic treatment	in monthly increments 3 times per week for at least 1 year

(* indicative treatment to be adapted based on biological controls)

Clinical data from retrospective studies of 6 patients illustrated that the inhibitors had completely disappeared under immune tolerance induction in 5 of the patients after several years of follow-up and that they had partially disappeared in the sixth.

Method of administration

FACTANE is presented in the form of a powder to be reconstituted at the time of use with water for injections, as described in paragraph 6.6. "Instructions for use, handling and disposal".

FACTANE should only be injected intravenously, as a single dose, immediately after reconstitution, at a maximum rate of 4 ml/minute.

The solution is clear or slightly opalescent. Do not use solution which is cloudy or has deposits.

4.3. Contraindications

Hypersensitivity to any of the components of the preparation.

4.4. Special warnings and special precautions for use

Replacement therapy with human coagulation factor VIII to treat haemophilia A in patients both without and, especially, with factor VIII inhibitors must be managed or supervised by a haemophilia specialist.

If allergic or anaphylactic reactions occur, the injection or infusion should be stopped immediately. In case of shock, the standard medical treatment for shock should be implemented.

The formulae for calculation of posology shown above provide an estimation of the dose required. It is, however, strongly recommended that appropriate laboratory tests be performed at regular intervals to confirm that the desired plasma levels of factor VIII have been achieved and are maintained. For major surgical interventions, the replacement therapy must be precisely monitored by means of coagulation tests.

If the expected plasma factor VIII levels are not attained or if bleeding is not controlled with appropriate doses of human coagulation factor VIII, an assay should be performed to determine if the patient has developed factor VIII inhibitors (antibodies which neutralise the factor VIII). The presence of plasma inhibitors should then be demonstrated and the inhibitor levels should be quantified in international units using appropriate laboratory tests, particularly in previously-untreated patients, referred to as "PUPs".

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

- selection of donors by a medical interview and screening of each donation for the three major pathogenic viruses HIV, HBV, HCV;
- testing of plasma pools for hepatitis C virus genomic material;
- removal/inactivation procedures included in the production process that have been validated using model viruses and are considered effective for HIV, HBV, HCV, parvovirus B19 and HAV.

The viral removal/inactivation procedures may be of limited value against certain particularly resistant viruses such as parvovirus B19.

Appropriate vaccination (hepatitis A and hepatitis B) for patients receiving FACTANE is recommended.

4.5. Interaction with other medicinal products and other forms of interaction

There are currently no known interactions between human coagulation factor VIII products and other medicinal products.

4.6. Pregnancy and lactation

Haemophilia A is a disease affecting almost exclusively men. Therefore, the safety of factor VIII concentrates has not been evaluated in controlled clinical trials in pregnant women. Animal experimentation data are not sufficient to establish its safety for reproduction, pregnancy, embryonic or foetal development or post-natal development.
Therefore, human coagulation factor VIII should only be prescribed during pregnancy and lactation if absolutely necessary.

4.7. Effects on ability to drive and use machines

No effects of human coagulation factor VIII on the ability to drive and use machines have been observed.

4.8. Undesirable effects

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. This can result in an insufficient clinical response.

During clinical trials with LFB-BIOMEDICAMENTS human coagulation factor VIII (non nanofiltered version) conducted in 104 previously-untreated patients presenting with FVIII:C levels < 1%, 15 patients developed inhibitors (14.4%), of which 5 at levels above 5 BU.

No inhibitors appeared in 32 severe haemophilia patients previously treated for at least 6 months during clinical trials with FACTANE.
No data is available on previously-untreated patients using FACTANE (nanofiltered factor VIII).

Patients treated with human coagulation factor VIII should be carefully monitored for the development of inhibitors using appropriate clinical observations and laboratory tests.

Allergic or anaphylactic reactions are rarely observed. Patients must be informed about the early signs of allergies, such as pruritus, generalised urticaria, chest tightness, wheezing and hypotension, and should be notified that administration must be stopped immediately if any of these symptoms occur. In case of shock, the standard medical treatment for shock should be implemented.

On rare occasions, fever has been observed.

4.9. Overdose

No adverse events caused by accidental overdose of FACTANE have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: blood and haematopoietic organs,
human coagulation factor VIII, ATC code: B02BD02.

FACTANE contains primarily factor VIII, which is responsible for its coagulant activity. It provides haemostasis in haemophilia A patients.

Haemophilia A is a hereditary, blood coagulation disorder caused by a deficiency of factor VIII which results in profuse bleeding episodes, either spontaneously or following surgical or accidental trauma.

Factor VIII:C is the coagulant component of the factor VIII complex which circulates in plasma. It binds non-covalently to von Willebrand factor.

These two proteins have different biological and immunological properties and are under different genetic control. Factor VIII:C acts as a cofactor to factor IX in the activation of factor X. Once activated, factor X converts prothrombin into thrombin, which in turn converts fibrinogen into fibrin, resulting in clot formation.

The residual amount of von Willebrand factor (antigen) in this preparation is approximately 20 IU/ml.

5.2. Pharmacokinetic properties

Peak plasma levels of FACTANE are usually obtained 15 minutes after injection.
In a study carried out in 12 patients receiving FACTANE, FVIII:C recovery was 2.6 ± 0.7 IU/dl/IU/kg and half-life was 12.1 ± 4.7 hours.

5.3. Preclinical safety data

The factor VIII contained in this preparation is a normal constituent of human plasma and reacts in the same manner as endogenous factor VIII.

Neither repeated dose toxicity studies nor reproduction studies have been performed in animals.

The preclinical safety data do not suggest that FACTANE has any mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder: sucrose, mannitol, glycine, lysine hydrochloride and calcium chloride.
Solvent: water for injections.

6.2. Incompatibilities

Human coagulation factor VIII must not be mixed with any other substance and/or medicinal products.

Only approved injection/infusion sets should be used because treatment failure can occur as a consequence of human coagulation factor adsorption to the internal surfaces of some injection/infusion materials.

6.3. Shelf life

3 years.
The product should be used immediately after reconstitution. The product has, however, been shown to be stable for 3 hours at 25°C.

6.4. Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Store in the original outer package in order to protect from light.

The product may be stored within its shelf life at temperatures no greater than 25°C for a maximum of 6 months, without being "re-refrigerated" during this period. It must be discarded if it is not used within this 6-month period.

Do not freeze.

6.5. Nature and contents of container

Powder in a vial (glass) + 2.5 ml of solvent in a vial (glass) with a transfer system and a filter needle – box of 1.
Powder in a vial (glass) + 5 ml of solvent in a vial (glass) with a transfer system and a filter needle – box of 1.
Powder in a vial (glass) + 10 ml of solvent in a vial (glass) with a transfer system and a filter needle – box of 1.

6.6. Instructions for use, handling and disposal

Reconstitution:

Use current guidelines for aseptic procedure.

- Never use vials immediately after removal from the refrigerator.
- Bring the two vials (powder and solvent) to room temperature.
- Remove the protective cap from the solvent vial (water for injections) and from the powder vial.
- Disinfect the surface of each stopper.
- Remove the translucent protective cap from the transfer system and completely insert the exposed needle through the centre of the stopper of the solvent vial while simultaneously twisting the needle.
- Remove the second protective cap from the other end of the transfer system.
- Keeping both vials horizontal (vented spike pointing upwards), quickly push the free end of the needle into the centre of the stopper of the powder vial. Ensure that the needle always remains immersed in the solvent to avoid releasing the vacuum prematurely.
- Immediately place the system upright in a vertical position, keeping the solvent vial directly above the powder vial, to allow the solvent to transfer into the powder.
- During transfer, direct the jet of solvent over the whole surface of the powder. Ensure that all of the solvent is transferred.
- The vacuum is automatically released at the end of the transfer procedure (sterile air).
- Remove the empty vial (solvent) with the transfer system.
- Gently swirl for a few minutes with a rotating movement to avoid the formation of foam until the powder has completely dissolved.

The powder generally dissolves instantly and should be completed dissolved in less than 10 minutes. The solution should be clear or slightly opalescent. Do not use solution which is cloudy or contains deposits.

Administration:

- Draw the product into a sterile syringe using the filter needle provided.
- Remove the needle from the syringe and replace it with an intravenous or epicranial needle.
- Expel the air from the syringe and insert into the vein after disinfecting the surface.
- Inject intravenously immediately after reconstitution as a single dose at a maximum rate of 4 ml/minute.

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

7. MARKETING AUTHORISATION HOLDER

LFB-BIOMEDICAMENTS
3, avenue des Tropiques - BP 305 - LES ULIS - 91958 Courtabœuf Cedex - FRANCE

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT