# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human von Willebrand factor ..... 100 IU*
per 1 ml of reconstituted solution

One vial contains 1000 IU human von Willebrand factor per 10 ml after reconstitution.

*The von Willebrand factor potency (IU) is measured according to ristocetin cofactor activity (VWF:RCo) compared to the international standard for factor Willebrand concentrate (WHO).

Before the addition of albumin, the specific activity of WILFACTIN is greater than or equal to 50 IU of VWF:RCo/mg of protein.

The residual human coagulation factor VIII present in WILFACTIN is usually less than or equal to 10 IU/100 IU VWF:RCo. The factor VIII potency has been determined using the European Pharmacopoeia chromogenic assay.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

WILFACTIN is indicated in the prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD) when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

WILFACTIN should not be used in the treatment of haemophilia A.

## 4.2. Posology and method of administration

Treatment of von Willebrand disease should be supervised by a physician experienced in the treatment of haemostatic disorders.

***Posology***

Generally, the administration of one IU/kg of von Willebrand factor raises the circulating level of VWF:RCo by 0.02 IU/ml (2%).

Levels of VWF:RCo of > 0.6 IU/ml (60%) and FVIII:C of > 0.4 IU/ml (40%) should be achieved.

Haemostasis cannot be ensured until FVIII coagulant activity (FVIII:C) has reached 0.4 IU/ml (40%). Injection of von Willebrand factor alone does not induce a maximum rise of FVIII:C for at least 6-12 hours. It cannot immediately correct the FVIII:C level. So, if the patient's baseline plasma FVIII:C level is below this critical level, in all situations where a rapid correction of haemostasis should be achieved, such as treatment of haemorrhage, severe trauma or emergency surgery, it is necessary to administer a factor VIII product with the first injection of von Willebrand factor, in order to achieve a haemostatic plasma level of FVIII:C.

However, if an immediate rise in FVIII:C is not necessary, for example if the baseline FVIII:C level is sufficient to ensure haemostasis or in the case of a planned surgery, the physician may decide to omit the co-administration of FVIII at the first injection of VWF.

- **Start of treatment:**

The first dose of WILFACTIN is 40 to 80 IU/kg for the treatment of haemorrhage or trauma, in conjunction with the required amount of factor VIII product, calculated according to the patient's baseline plasma level of FVIII:C, in order to achieve an appropriate plasma level of FVIII:C, immediately before the intervention or as soon as possible after the onset of the bleeding episode or severe trauma. In case of surgery, it should be given 1 hour before the procedure.

An initial dose of 80 IU/kg of WILFACTIN may be required, especially in patients with type 3 VWD where maintenance of adequate levels may require higher doses than other types of VWD.

For elective surgery, treatment with WILFACTIN should start 12 to 24 hours before surgery and should be repeated 1 hour before the procedure. In this case co-administration of a factor VIII product is not required, since endogenous FVIII:C has usually reached the critical level of 0.4 IU/ml (40%) before surgery. However, this should be confirmed in each patient.

- **Subsequent injections:**

If required, treatment should be continued with an appropriate dose of WILFACTIN, 40 to 80 IU/kg per day, in one or two injections daily over one to several days. The dose and duration of treatment depend on the clinical status of the patient, the type and severity of bleeding and both VWF:RCo and FVIII:C levels.

Home treatment may be initiated upon the advice of a physician, especially in cases of minor or moderate bleeding**.**

- **Prophylaxis**

WILFACTIN may be administered as long term prophylaxis, at doses adapted for each patient. Doses of WILFACTIN ranging from 40 to 60 IU/kg, administered 2 to 3 times per week, reduce the number of bleeding episodes.

There is no data from a clinical study to characterise the response to use of WILFACTIN in children less than 6 years of age and in patients who have never been treated.

***Method of administration***

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

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

## 4.3. Contraindications

Hypersensitivity to any of the constituents.

## 4.4. Special warnings and precautions for use

In actively bleeding patients, it is recommended to co-administer a FVIII product with a von Willebrand factor product with a low FVIII content as a first line treatment.

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness in the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented.

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 (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and hepatitis B) should be considered for patients regularly receiving human plasma-derived von Willebrand factor.

It is recommended that every time that WILFACTIN 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.

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations.

Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a VWF inhibitor is present. In patients with high levels of inhibitor, VWF 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 haemostatic disorders.

This medicinal product contains some sodium.
One vial (1000 IU) of WILFACTIN contains 0.3 mmol (6.9 mg) sodium. For more than 3300 IU injected (more than 1 mmol sodium), to be taken into consideration by patients on a controlled sodium diet.

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

No interactions of VWF products with other medicinal products are known.

## 4.6. Pregnancy and lactation

The safety of WILFACTIN has not been evaluated during pregnancy and lactation in controlled clinical trials. Animal studies are not sufficient to establish its safety with respect to reproduction, pregnancy, development of the embryo or foetus, or peri- and post-natal development.

Therefore, WILFACTIN should be administered to pregnant and lactating von Willebrand factor deficient women only if clearly indicated.

## 4.7. Effects on ability to drive and use machines

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

## 4.8. Undesirable effects

Hypersensitivity or allergic reactions (which may include angiodema, 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 with von Willebrand factor products, and may in some cases progress to severe anaphylaxis (including shock).

On rare occasions, fever has been observed.

Patients with VWD, especially type 3 patients, may very rarely develop neutralising antibodies (inhibitor) to VWF. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies may occur in close association with anaphylactic reactions. Therefore, patients experiencing anaphylactic reaction should be evaluated for the presence of an inhibitor.
In all such cases, it is recommended that a specialised haemophilia centre be contacted.

In clinical studies, carried out in 62 patients of which 23 were type 3, no inhibitors were detected after administration of WILFACTIN.

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors.

For safety with respect to transmissible agents, see section 4.4.

## 4.9. Overdose

No symptoms of overdose with von Willebrand factor have been reported.

Thromboembolic events may occur in case of major overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics: human von Willebrand factor
ATC Code: B02BD

WILFACTIN behaves in the same way as endogenous von Willebrand factor.
Administration of von Willebrand factor allows correction of the haemostatic abnormalities exhibited by patients who suffer from von Willebrand factor deficiency (von Willebrand's disease) at two levels:

- VWF re-establishes platelet adhesion to the vascular sub-endothelium at the site of the vascular damage (as it binds both to the vascular sub-endothelium and to the platelet membrane) providing primary haemostasis, as shown by the shortening in bleeding time. This effect occurs immediately and is known to depend to a large extent on the level of polymerisation of the active substance.
- VWF produces delayed correction of the associated factor VIII deficiency. Administered intravenously, VWF binds to endogenous FVIII (which is produced normally by the patient) and by stabilising this factor, avoids its rapid degradation. Because of this, administration of pure VWF (VWF product with a low FVIII level) restores the FVIII:C level to normal as a secondary effect after the first injection. This effect is sustained and persistent during subsequent injections. Administration of a FVIII:C containing VWF preparation restores the FVIII:C level to normal immediately after the first infusion.

### 5.2. Pharmacokinetic properties

A pharmacokinetic study with WILFACTIN was carried out in 8 patients with type 3 von Willebrand disease which demonstrated that for VWF:RCo:

- The plasma peak is obtained between 30 minutes and 1 hour after injection.
- The mean recovery is 2.1 IU/dl/IU/kg injected.
- The half-life is between 8 and 14 hours, with a mean of 12 hours.

The increase in FVIII levels is progressive and returns to normal within a variable delay of 6 to 12 hours. The FVIII levels increase by a mean of 6 % (IU/dl) per hour. Thus, even in patients with an initial FVIII:C level less than 5% (IU/dl), as of 6 hours post injection, the FVIII:C level increases to approximately 40% (IU/dl) and this level is maintained for 24 hours.

### 5.3. Preclinical safety data

Von Willebrand Factor is a normal constituent of human plasma and acts like physiological von Willebrand Factor. Based on data obtained from several pre-clinical studies using animal models, there is no evidence for other toxic effects of WILFACTIN than those related to the immunogenicity of human proteins in laboratory animals. Repeated dose toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Powder: human albumin, arginine hydrochloride, glycine, sodium citrate and calcium chloride.

Solvent: water for injections.

### 6.2. Incompatibilities

WILFACTIN must not be mixed with other medicinal products, except for FACTANE (plasma-derived coagulation factor VIII).

Only polypropylene injection/infusion sets should be used because treatment failure can occur as a consequence of human von Willebrand factor adsorption to the internal surfaces of some injection/infusion equipment.

### 6.3. Shelf life

3 years.

**From a microbiological point of view it is recommended to use the product immediately after reconstitution. Physical-chemical stability has however been demonstrated after 24 hours at 25°C.**

### 6.4. Special precautions for storage

Store in the original container. Do not store above 25°C. Protect from light. Do not freeze.

### 6.5. Nature and contents of container

Powder in a vial (type I glass) + 10 ml of solvent in a vial (type II glass) with a transfer system incorporating a sterilising air vent and a filter-needle - Pack size of 1.

## 6.6. Instructions for use, handling and disposal

***Reconstitution:***

**Use current guidelines for aseptic procedure.**

- If necessary, bring the two vials (powder and solvent) to ambient 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 sheath 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 sheath 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 the 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 instantaneously and should be completely dissolved in less than 10 minutes.

The reconstituted product should be inspected visually prior to administration. The solution should be clear or slightly opalescent, colourless or slightly yellow. Do not use solution which is cloudy or has 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 as a single dose, immediately after reconstitution, at a maximum rate of 4 ml/minute.

Any unused product or waste material 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 NUMBER

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

May 2009