SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Willfact 500 IU powder and solvent for solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Willfact is presented as powder and solvent for solution for injection containing nominally 500 IU human von Willebrand factor (VWF) per vial.

The product contains approximately 100 IU/mL human von Willebrand factor when reconstituted with 5 mL water for injection.

Before the addition of albumin, the specific activity of Willfact is greater than or equal to 60 IU VWF:RCo/mg of protein.

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

The quantity of human factor VIII (FVIII) in Willfact is ≤ 10 IU/100 IU VWF:RCo.

The FVIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay.

Excipient with known effect:

This medicinal product contains sodium:
One 5 mL vial (500 IU) contains 0.15 mmol (3.4 mg) sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: White or pale yellow lyophilised powder or friable solid.

Solvent: Clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

WILLFACT can be used for all age groups.

WILLFACT 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, 1 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 of FVIII:C of > 0.4 IU/mL (40 %) should be achieved.

Haemostasis cannot be ensured until factor VIII coagulant activity (FVIII:C) has reached 0.4 IU/mL (40 %). A single 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 in a planned surgery, or if the baseline FVIII:C level is sufficient to ensure haemostasis, the physician may decide to omit the co-administration of FVIII at the first injection of VWF.

- Start of treatment:

The first dose of Willfact 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 Willfact may be required, especially in patients with type 3 von Willebrand disease where maintenance of adequate levels may require higher doses than in other types of VWD.

For elective surgery, treatment with Willfact should start 12-24 hours before surgery and should be repeated 1 hour before the procedure. In this case, co-administration of 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 Willfact, 40 - 80 IU/kg per day in 1 or 2 injections daily over one to several days. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding and both VWF:RCo and FVIII:C levels.

- Long-term prophylaxis:

Willfact can be administered as long-term prophylaxis in a dose which is determined individually for each patient. Willfact doses between 40 and 60 IU/kg, administered two to three times per week, reduce the number of haemorrhagic episodes.

- Outpatient treatment:

Home treatment may be initiated, especially in cases of minor to moderate bleeding or during long term prophylaxis to prevent bleeding, with the treating physician's approval. The physician should ensure that appropriate training is provided and that the treatment is reviewed at predefined intervals.

Paediatric population

For each indication, dosing is based on bodyweight. The dose and duration of treatment should be adjusted to the clinical condition of the patient, and their VWF:RCo and FVIII:C plasma levels.

- Start of treatment:
  - For children below 6 years of age, the initial dose may be guided by the patient's incremental recovery (IR) or, if IR data are not available, an initial dose between 60 and 100 IU/kg may be required with the goal to raise patients VWF:RCo levels to 100 IU/dL.
  - For children above 6 years of age and adolescents, the posology is the same as adult patients.

- Subsequent injections:

For children and adolescents, subsequent doses should be individualised to the clinical condition and to the vWF:RCo levels and adjusted to the clinical response.

For elective surgery:

- In children below 6 years of age, following a first dose administered 12 to 24 hours prior to the procedure, the repeated dose may be administered 30 minutes before the procedure.
- For children above 6 years of age and adolescents the posology is the same as adult patients.

- Prophylaxis:

For children and adolescents, the dose and the re administration frequency should be individualised to the patient's incremental recovery and vWF:RCo levels and adjusted to the clinical response.

Method of administration

Dissolve the preparation as described under section 6.6.

Willfact should be administered via the intravenous route at a maximum rate of 4 mL/minute.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Hypersensitivity

As with any intravenous administration of a plasma-derived protein, hypersensitivity reactions are possible. Patients must be closely monitored and carefully observed for any symptoms throughout the injection period. 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, the administration should be discontinued immediately. In case of anaphylactic shock, standard medical treatment should be implemented.

Transmissible agents

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). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A 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).

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

It is strongly recommended that every time Willfact 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.

Thromboembolism

Willfact is a von Willebrand factor product with a low FVIII content. Nevertheless, there is a risk of occurrence of thromboembolic 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.

When usingWillfact, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. Therefore, in patients requiring frequent dosing of WILLFACT, especially if in combination with a factor VIII product, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels, which may increase the risk of thromboembolic events.

Immunogenicity

Patients with von Willebrand disease, especially type 3 patients, may develop neutralising antibodies (inhibitors) to von Willebrand factor. 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 von Willebrand factor inhibitor is present. In patients with high levels of inhibitor, von Willebrand factor therapy may not be effective and other therapeutic options should be considered.

Excipient related considerations (sodium content)

This medicinal product contains sodium.

If more than 3300 IU is injected (more than 1 mmol sodium), this should be taken into consideration by patients on a controlled sodium diet (see section 2 for quantity per vial).

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human von Willebrand factor products with other medicinal products are known.

4.6 Fertility, pregnancy and lactation

Animal studies are insufficient to assess Willfact safety with respect to fertility, reproduction, pregnancy, embryonic/fœtal development or peri- and postnatal development.
The safety of Willfact during pregnancy and lactation has not been investigated in clinical studies.

Willfact 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 the ability to drive or use machines have been observed.

4.8 Undesirable effects

Summary of the safety profile

During treatment with WILLFACT the following adverse reactions may occur:
Allergic reactions and anaphylactic reactions (including shock in rare cases), thromboembolic events (mostly in patients with risk factors), inhibitor formation against VWF and administration site reactions.

Tabulated list of adverse reactions
The table below provides an overview of adverse drug reactions observed in 6 clinical trials and one non-interventional post-marketing study, and from other post marketing sources. During the studies, 226 patients were exposed to WILLFACT for a total of 16 640 exposure days.

The adverse drug reactions were categorized according to the MedDRA System Organ Class (SOC), Preferred Term Level (PT) and frequency.

Frequency of adverse event occurrence has been estimated 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).

For spontaneously reported post-marketing adverse reactions, the reporting frequency is categorised as not known.

MedDRA Standard System Organ Class	**Adverse Drug Reactions (Preferred Term)**	**Frequency by number of patients**
Blood and lymphatic system disorders	Von Willebrand's factor inhibition*	Not known
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactic shock*	Not known
Nervous system disorders	Dizziness	Uncommon
	Paraesthesia, Hypoaesthesia	Uncommon
Vascular disorders	Hot flush	Uncommon
	Thromboembolic events*	Not known
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
General disorders and administration site conditions	Administration site reactions** (including Infusion site reaction, infusion site inflammation and vessel puncture site inflammation)	Common
	Sense of oppression	Uncommon
	Chills, Feeling cold	Uncommon
	Pyrexia*	Not known

* Reported during the post-marketing experience/surveillance with a frequency "not known", per convention.
** MedDRA High Level Group Terms.

Description of selected adverse reactions
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the
infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lipothymia/malaise, 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).

Patients with von Willebrand disease, especially type 3 patients, may very rarely develop neutralising antibodies (inhibitors) to von Willebrand factor. 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.

Willfact is a von Willebrand factor product with a low FVIII content. Nevertheless, there is a risk of occurrence of thromboembolic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored.For safety information with respect to transmissible agents, see section 4.4.

Paediatric population
WILLFACT was assessed in 56 patients under 18 years of age, among them, 23 were below 6 years old, 21 were aged between 6 to 11 years old and 12 over 11 years old.

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: "Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store ".

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:

Anti-haemorrhagics: blood coagulation factors, human von Willebrand factor
ATC code: B02BD10

Mechanism of action

Willfact 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:

- Von Willebrand factor re-establishes platelet adhesion to the vascular subendothelium at the site of vascular damage (as it binds both to the vascular subendothelium and to the platelet membrane) providing primary haemostasis as shown by the shortening of the bleeding time. This effect occurs immediately and is known to depend to a large extent on the level of multimerisation of the active substance.

- Von Willebrand factor produces delayed correction of the associated factor VIII deficiency. Administered intravenously, von Willebrand factor binds to endogenous factor VIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation. Because of this, administration of pure von Willebrand factor (VWF product with a low FVIII level) restores the FVIII:C level to normal as a secondary effect after the first infusion. 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 Willfact was carried out on 8 adult patients with type 3 von Willebrand disease. It demonstrated that for VWF:RCo:

- The mean AUC0-∞ is 3444 IU.h/dL after single dose of 100 IU/kg Willfact,
- The mean recovery is 2.1 [IU/dL]/[IU/kg] of the injected preparation,
- The half-life is between 8 and 14 hours, with a mean value of 12 hours,
- The mean clearance is 3.0 mL/h/kg.

Peak plasma levels of von Willebrand factor usually occur within 30 minutes and 1 hour after injection.

Normalisation of FVIII level is progressive, varies and usually requires between 6 and 12 hours. This effect is sustained for 2 to 3 days.

The increase in FVIII level is progressive and returns to normal after 6 to 12 hours. The FVIII level increases by a mean of 6 % (IU/dL) per hour. Thus, even in patients with an initial FVIII:C level less than 5 % (IU/dL), the FVIII:C level increases to around 40 % (IU/dL) 6 hours after the injection, and this level is maintained over 24 hours.

<u>Paediatric data</u>
Full pharmacokinetic profile (Cmax, Tmax, AUC, clearance, half-life and mean residence time), after Willfact injection, is not characterized in the paediatric population <18 years old.

In 7 children under 6 years of age (2 between 28 days to 23 months and 5 between 24 months to 6 years) with severe von Willebrand disease (5 type 3, 1 type 1 and 1 type 2), after a mean infusion of 101.1 ± 5.0 IU/kg, a mean VWF:RCo incremental recovery of 1.75 ± 0.35 (IU/dL)/(IU/kg), was observed at 15 minutes post-infusion with a large inter-individual variability (range from 1.14 to 2.03). Only four of these children had both evaluable initial and 6-month control recovery tests after exposure

of 3 to 9 treatment days. The observed mean recovery ratio was 0.87 ± 0.12 (IU/dL)/(IU/kg), (range from 0.7 to 1.0).

5.3 Preclinical safety data

Based on data obtained from several preclinical studies using animal models, there is no evidence for other toxic effect of WILLFACT 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 WILLFACT has any mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Solvent:
water for injections.

6.2 Incompatibilities

Willfact must not be mixed with other medicinal products in the same syringe except for “plasma-derived coagulation factor VIII produced by LFB-BIOMEDICAMENTS”, with which a compatibility study was carried out. This FVIII coagulation factor is however not marketed in all countries.

Only licensed polypropylene injection 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 equipment.

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Do not freeze.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

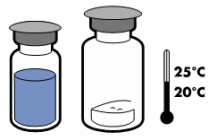
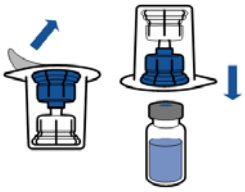
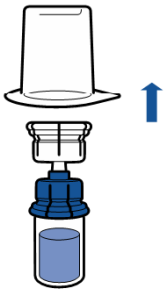
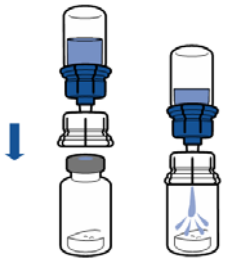
6.5 Nature and contents of container

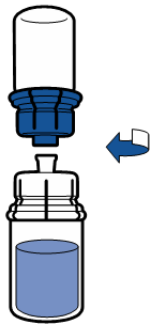
1 pack contains: powder in a vial (Type I glass) with a bromobutyl stopper, solvent in an injection vial (Type I glass) with a chlorobutyl (5 and 20 ml) / bromobutyl (10 ml) stopper, and a transfer system.

6.6 Special precautions for disposal

Reconstitution

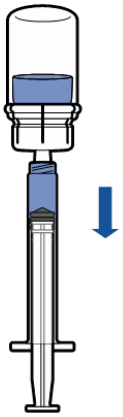
The currently applicable guidelines for aseptic procedures must be followed. The transfer system is only used to reconstitute the drug, as described below. It is not intended in administering the drug to the patient.

	• Bring the two vials (powder and solvent) to a temperature not above 25°C.
	• Remove the protective cap from the solvent vial (water for injections) and from the powder vial. • Disinfect the surface of each stopper.
	• Remove the cap from the Mix2Vial device. Without removing the device from its packaging, attach **the blue end of the Mix2Vial** to the stopper of the solvent vial.
	• Remove and discard the packaging. Take care not to touch the newly-exposed part of the device.
	• Turn the solvent vial-device assembly over and attach to the powder vial **using the transparent part of the device**. The solvent will automatically transfer to the powder vial. Hold the assembly and gently swirl to completely dissolve the product.
	• Now, holding the reconstituted product part in one hand and the solvent part in the other, unscrew the Mix2Vial device to separate the vials.

The powder generally dissolves instantaneously and should have dissolved in less than **5 minutes**.

Administration

	• Hold the vial of reconstituted product in vertical position while screwing a sterile syringe onto the Mix2Vial device. Then slowly draw the product up into the syringe. • Once the product has been transferred to the syringe, firmly hold the syringe (with the piston pointing downward), unscrew the Mix2Vial device and replace it with an intravenous or butterfly needle. • Expel the air from the syringe and insert into the vein after disinfecting the surface. • Inject slowly by intravenous route immediately after reconstitution as a single dose at a maximum rate of 4 mL/minute.

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

The reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent, colourless or slightly yellowish. Do not use solutions that are cloudy or have deposits.

7 MARKETING AUTHORISATION HOLDER

LFB-BIOMEDICAMENTS
3, Avenue des Tropiques
ZA de Courtaboeuf
91940 Les Ulis
FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 28315/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/12/2019

10 DATE OF REVISION OF THE TEXT

03/07/2024