Package leaflet: Information for the user

WILLFACT 500 IU
powder and solvent for solution for injection

WILLFACT 1000 IU
powder and solvent for solution for injection

WILLFACT 2000 IU
powder and solvent for solution for injection

human von Willebrand factor

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effect not listed in this leaflet. See section 4.

What is in this leaflet

1. What WILLFACT is and what it is used for

Willfact is made from human plasma (the liquid part of the blood) and contains the active substance called human von Willebrand factor (VWF).

VWF is involved in blood clotting. Lack of this factor, such as in von Willebrand disease, means that blood does not clot as quickly as it should, so there is an increased tendency to bleed. The replacement of VWF by Willfact will temporarily repair blood clotting mechanisms.

Willfact is indicated in the prevention and treatment of surgical or other bleeding in patients with von Willebrand disease 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.

2. What you need to know before you use WILLFACT

Do not use Willfact
- If you are allergic to human von Willebrand factor or to any of the other ingredients of this medicine (listed in section 6).
- If you suffer from **Haemophilia A.**

Warnings and precautions
Your treatment with Willfact should always be **supervised by a doctor** experienced in the treatment of haemostatic disorders.

If you experience heavy bleeding and a blood examination shows that your factor VIII blood value is reduced, you will receive the VWF preparation in addition to a factor VIII preparation within the first twelve hours.

Allergic reactions
As with every protein medicine for intravenous use derived from human blood or plasma, **hypersensitivity reactions in the form of an allergy** may occur.

During the injection you will be monitored to detect any early sign of hypersensitivity. These include rash (hives or generalised urticaria), tightness of the chest, wheezing, drop in blood pressure (hypotension) and severe allergic reactions (anaphylaxis).

Your doctor will inform you of the warning signs of an allergic reaction.

Should signs or symptoms of hypersensitivity occur, treatment should be discontinued and you should seek immediate medical attention.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- Careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- The testing of each donation and pools of plasma for signs of virus/infections,
- The inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV-AIDS), hepatitis B virus and hepatitis C virus.

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (as there is a risk of infection of the unborn child) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

Vaccinations
Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived von Willebrand factor.

Recording of batch number
It is strongly recommended that every time you receive a dose of Willfact, the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Risk of thrombosis
Blood vessels may also become blocked by blood clots (thromboses).
This risk exists particularly if your previous medical history or laboratory results indicate that you present certain risk factors.
In this case you will be monitored very carefully for the early signs of thrombosis, and a preventive treatment (prophylaxis) against vein blockages by blood clots should be introduced.

When using a factor VIII-containing von Willebrand factor product, your doctor should be aware that the continued treatment may cause an excessive rise in FVIII. If you receive such FVIII-containing VWF product, your doctor should monitor your FVIII plasma level regularly. This ensures that your FVIII plasma level is not sustained excessively, which may otherwise increase the risk of thrombotic events.

Limited effectiveness
It is possible that, in patients with von Willebrand disease, especially type 3 patients, proteins may be formed that neutralise the effect of VWF. These proteins are called neutralising antibodies or inhibitors. If the laboratory results show that your VWF levels are not being replenished, or if the bleeding does not stop despite a sufficient dose of Willfact, your doctor will check whether VWF inhibitors are being formed in your body. If these inhibitors are present in high concentration, treatment with VWF may not be effective, and other treatment options should be considered. The new treatment will be provided by a doctor who has experience in the treatment of haemostatic disorders.

Other medicines and Willfact
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
Willfact should be used during pregnancy and breastfeeding only if it is clearly indicated.

The safety of Willfact during pregnancy and breastfeeding has not been evaluated in clinical studies. Animal studies are not sufficient to establish its safety with respect to fertility, pregnancy and development of the child during pregnancy and after birth.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

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

Willfact contains sodium
One 5 mL vial (500 IU) of Willfact contains 0.15 mmol (3.4 mg) sodium.
This is equivalent to 0.17 % of the recommended maximum daily dietary intake of sodium for an adult.

One 10 mL vial (1000 IU) of Willfact contains 0.3 mmol (6.9 mg) sodium.
This is equivalent to 0.35 % of the recommended maximum daily dietary intake of sodium for an adult.

One 20 mL vial (2000 IU) of Willfact contains 0.6 mmol (13.8 mg) sodium.
This is equivalent to 0.69 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use WILLFACT

Your treatment should be initiated and monitored by a doctor who is experienced in the treatment of bleeding disorders.

If your doctor thinks that administration could be performed at your home, appropriate instructions will be provided to you by your doctor.

Dose
Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
Preferably, Willfact should be administrated by your doctor or nurse. However, if you have been prescribed Willfact to use at home, your doctor will make sure that you are shown how to inject it and how much to use. Follow the directions given to you by your doctor and ask for help if you have problems handling the syringe, the syringe should always be used by someone trained to use it.

Your doctor will calculate your dose of Willfact (in international units or IU).
The dose depends on:

- Body weight,
- The site of the bleeding,
- Intensity of the bleeding,
- Your clinical condition,
- The required surgery,
- The VWF activity levels in your blood after surgery,
- The severity of your disease.

This dose varies between 40 and 80 IU/kg.

Your doctor will recommend that you undergo blood tests during treatment to control:
- factor VIII levels (FVIII:C),
- von Willebrand factor levels (VWF:RCo),
- the presence of inhibitors,
- preliminary signs of formation of clots if you are at risk for such complications.

Based on the results of these tests, your doctor may decide to adapt the dose and frequency of your injections.

In certain cases, use of a factor VIII preparation (another coagulation protein) in addition to Willfact may be necessary to more rapidly treat or prevent bleeding (in emergency situations or acute bleeding).
Willfact can also be administered as long-term prophylaxis; the dose level is also determined individually in this case. Willfact doses between 40 and 60 IU/kg administered two to three times per week reduce the number of bleeding episodes.

Use in children and adolescents
Dosing in children and adolescents is based on bodyweight. In some cases, especially in younger patients (below 6 years), higher doses (up to 100 IU/kg) may be needed.

Please talk to your doctor if you feel that the effect of Willfact is too strong or too weak.

Method of administration
Detailed instructions for reconstitution and administration of the medicinal product are given at the end of the Package Leaflet.

If you use more Willfact than you should
No symptoms of overdose with Willfact have been reported.
However, the risk of thrombosis cannot be excluded in case of major overdose.

If you forget to use Willfact
If you forget to use Willfact, talk to your doctor.
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Willfact can cause side effects, although not everybody gets them.

Please contact your doctor immediately if:

- You notice symptoms of hypersensitivity or allergic reactions (observed uncommonly: may affect up to 1 in 100 people).
  In some cases, these reactions can progress to a severe allergic reaction (anaphylaxis) including anaphylactic shock (observed with an unknown frequency).

The warning signs of allergic reactions are:
- Difficulty breathing and swallowing
- Wheezing
- Tightness of the chest
- Increased heart rate
- Decrease or drop in blood pressure
- Fainting
- Extreme fatigue
- Restlessness, nervousness
- Headache
- Chills, feeling cold
- Flushing, hot flashes
- Swelling in different parts of the body
- Skin rash, generalised urticaria
- Burning and stinging at the infusion site
- Tingling
- Vomiting
- Nausea

If one of these effects occurs, **immediately stop the treatment and alert a doctor** to start appropriate treatment depending on the type and severity of the reaction.

- You notice that the medicine stops working properly (bleeding is not controlled). This can be due to von Willebrand's factor inhibition (observed with an unknown frequency).

Proteins may be formed in patients with von Willebrand disease, especially type 3 patients, which neutralise the effect of VWF. These proteins are called neutralising antibodies or inhibitors. Patients treated with VWF should be carefully monitored by their doctors for the development of inhibitors by appropriate clinical observations and laboratory tests. If such inhibitors occur, the condition can manifest itself as an inadequate clinical response.or occur concomitantly to severe allergic reactions.

- You notice any symptoms of an impaired perfusion in your extremities (e.g. cold and pale extremities) or vital organs (e.g. severe chest pain). This can be due to the formation of blood clots in the blood vessels (observed with an unknown frequency).

There is a risk of formation of blood clots (thrombosis), particularly in patients with known risk factors. After correction of the von Willebrand factor deficiency, you must be monitored for early signs of thrombosis or disseminated intravascular coagulation and receive treatment to prevent thrombosis in situations involving an increased risk of thrombosis (after operations, during confinement to bed, in cases of deficiency in a coagulation inhibitor or fibrinolytic enzyme).

If you receive FVIII-containing VWF preparations, the risk of thrombosis may also be increased due to persistently elevated FVIII plasma levels.

The following side effect has been observed commonly (may affect up to 1 in 10 people):
- Infusion site reactions

The following side effects have been observed uncommonly (may affect up to 1 in 100 people):
- Dizziness
- Paraesthesia, Hypoaesthesia
- Hot flush
- Itching
- Sense of oppression
- Chills, feeling cold

The other following side effect has been observed with an unknown frequency:
- Fever

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store WILLFACT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the vial label and carton.
Do not store above +25°C. Store in the original container in order to protect from light.
Do not freeze.

For sterility reasons, the product should be used immediately after reconstitution. Chemical and physical in-use stability has, however, been demonstrated for 24 hours at +25°C.

Do not use this medicine if you notice that the solution is cloudy or that it contains any deposit.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist or your nurse how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Willfact contains
The *active substance* is: human von Willebrand factor (500 IU, 1000 IU or 2000 IU), expressed in International Units (IU) of Ristocetin Cofactor activity (VWF:RCo).

After reconstitution with 5 mL (500 IU), 10 mL (1000 IU) or 20 mL (2000 IU) of water for injections, one vial contains approximately 100 IU/mL of human von Willebrand factor.

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

The *other* ingredients are:
Powder: human albumin, arginine hydrochloride, glycine, sodium citrate and calcium chloride dihydrate.
Solvent: water for injections.

What Willfact looks like and contents of the pack
Willfact is presented as a white or pale yellow powder or friable solid and a clear or colourless solvent for solution for injection after reconstitution with a transfer system.
Willfact is available in pack sizes of 500 IU/5 mL, 1000 IU/10 mL and 2000 IU/20 mL.

The reconstituted solution should be clear or slightly opalescent, colourless or slightly yellow.

Marketing Authorisation Holder and Manufacturer

LFB-BIOMEDICAMENTS
3, avenue des Tropiques,
ZA de Courtabœuf,
91940 Les Ulis,
FRANCE

To report a suspected side effect that has not been reported via the Yellow Card Scheme (above), please contact: Medical Information, PharmaLex UK Services Ltd, Tel: 01628 531171 – medinfo.uk@pharmalex.com

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Austria	Willfact
Czech Republic	WILLFACT
Denmark	Willfact
Germany	WILLFACT
Hungary	Willfact
Norway	Willfact
Poland	Willfact
Slovak Republic	Willfact
Spain	Willfact
Sweden	Willfact
United Kingdom (Northern Ireland)	Willfact

This leaflet was last approved in 07/2024.

INSTRUCTIONS FOR USE:

Posology
Generally, the administration of one IU/kg of von Willebrand factor raises the circulating level of VWF:RCo levels by approximately 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 factor VIII 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 to 12 hours. It cannot immediately correct the FVIII:C level. Therefore, if the patient's baseline FVIII:C levels are below this critical level, in all situations where rapid correction of haemostasis is required, such as treatment of a haemorrhage, severe trauma or emergency surgery, factor VIII must be administered 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, such as in the case of a planned surgery, or if baseline FVIII:C levels are sufficient to ensure haemostasis, the doctor may decide to do without the co-administration of FVIII for the first injection of von Willebrand factor.

- 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 patients'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, the first injection should be administered 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, the first injection of Willfact should be given 12 to 24 hours before surgery and the second should be given before the procedure. In such cases, 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 the intervention. However, this should be confirmed in each patient.

- Subsequent injections:

If required, treatment should be continued with 40 to 80 IU/kg of Willfact alone per day, in one or two daily injections over one to several days. The dose and frequency of the injections should always be adapted to fit the type of surgery, the clinical and biological status of the patient (VWF:RCo and FVIII:C) and the type and severity of the bleeding episode.

- Long-term prophylaxis:

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

- Outpatient treatment:

Home treatment may be initiated with the doctor's approval, especially in cases of minor to moderate bleeding or during long term prophylaxis to prevent bleeding.

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:

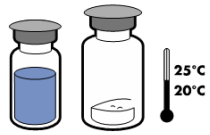
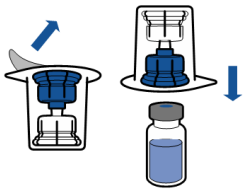
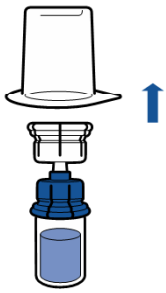
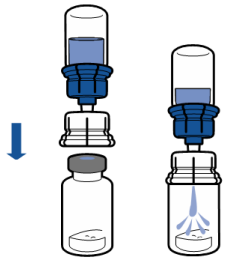
For children and adolescents, the dose and the re administration frequency should be individualised to the patient's incremental recovery and vWF:RCo levels and adjusted to the clinical response.

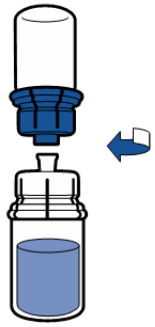
Mode and route of administration

Intravenous administration.

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.

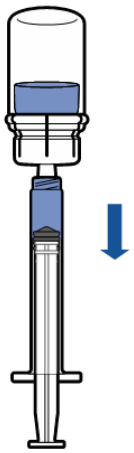
	• Bring the two vials (powder and solvent) to a temperature not above 25°C.
	• Remove the protective cap from the solvent vial (water for injections) and from the powder vial. • Disinfect the surface of each stopper.
	• Remove the cap from the Mix2Vial device. Without removing the device from its packaging, 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.

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

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.

Storage after reconstitution
For sterility reasons, the product should be used immediately after reconstitution. Chemical and physical in-use stability has, however, been demonstrated for 24 hours at +25°C.
Any unused product or waste material should be disposed of in accordance with local requirements.