

DATA SHEET

WILATE

NAME OF THE MEDICINE

WILATE Human coagulation factor VIII (FVIII) and von Willebrand factor (VWF) powder and solvent for solution for injection.

DESCRIPTION

WILATE contains 450 IU/900 IU human coagulation factor VIII (FVIII) and 400 IU/800 IU human von Willebrand factor (VWF) prepared from human plasma for fractionation. WILATE is presented as a powder and solvent for solution for injection. WILATE is available in the following presentations:

- WILATE 450 in 5 mL containing 450 IU human coagulation FVIII and 400 IU human VWF per vial. The product contains 90 IU/mL FVIII and 80 IU/mL VWF when reconstituted with the solvent (5 mL Water for Injections with 0.1% Polysorbate 80).
- WILATE 900 in 10 mL containing 900 IU human coagulation FVIII and 800 IU human VWF per vial. The product contains 90 IU/mL FVIII and 80 IU/mL VWF when reconstituted with the solvent (10 mL Water for Injections with 0.1% Polysorbate 80).

The potency of FVIII (FVIII:C) is determined by using the current “International Standard for Human Coagulation Factor VIII Concentrate”. The determination of the VWF potency is carried out by determination of the Ristocetin Cofactor potency (VWF:RCo) by using the current “International standard for von Willebrand Factor Concentrate”. The potencies (IU) of human coagulation factor VIII (FVIII:C) and human von Willebrand factor (VWF) are determined according to the European Pharmacopoeia assays. The specific activity of WILATE is ≥ 60 IU FVIII:C/mg and ≥ 53 IU VWF:RCo/mg of total protein.

Vial of Wilate		
Factor VIII	450 IU	900 IU
Von Willebrand Factor	400 IU	800 IU
Total Protein	≤ 7.5 mg	≤ 15.0 mg
<i>Excipients</i>		
Sodium Citrate	14.7 mg	29.4 mg
Sodium Chloride	117 mg	234 mg
Glycine	50 mg	100 mg
Calcium Chloride	0.8 mg	1.5 mg
Sucrose	50 mg	100 mg
Vial of Solvent		
Water for injections with 0.1% Polysorbate 80	5 mL	10 mL
Polysorbate 80	1 mg/mL	1 mg/mL

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Von Willebrand factor & coagulation factor VIII in combination

ATC Code: B02BD06

Von Willebrand disease (VWD)

The VWF (from the concentrate) is a normal constituent of the human plasma and behaves in the same way as endogenous VWF.

Administration of VWF allows correction of the haemostatic abnormalities exhibited in patients who suffer from VWF deficiency (VWD) at two levels:

- VWF re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium 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 polymerisation of the protein;
- VWF produces delayed correction of the associated FVIII deficiency. Administered intravenously, VWF binds 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. Administration of a FVIII-containing VWF preparation (e.g. WILATE) restores the FVIII:C level to normal immediately.

Pharmacokinetic properties

Von Willebrand disease (VWD)

VWF (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous VWF.

In VWD type 3 patients, for VWF:RCo and VWF:Ag median recovery values of 68 and 99% were calculated, respectively. These values correspond to median increments in plasma of 1.5 and 2.1% per substituted IU/kg BW. The following results were observed in one clinical study involving 8 patients with VWD type 3:

Parameter	Mean	Median	Range
Recovery (%/IU/kg)	VWF:RCo: 1.5	1.5	1.2 - 2.2
AUC* _{0-∞} (IU/mL x h)	VWF:RCo: 13.6	15.3	5.9 – 19.1
Half-life (h)	VWF:RCo: 17.5	16.6	7.4 – 30.6
MRT* (h)	VWF:RCo: 23.2	23.3	10.2 – 37.1
Clearance (mL/h/kg)	VWF:RCo: 3.9	3.4	2.5 – 7.4

* AUC = area under the curve; MRT = mean residence time

INDICATIONS

Von Willebrand disease (VWD)

Treatment and prophylaxis of bleeding in patients with VWD due to a quantitative and/or qualitative deficiency in VWF, when DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contra-indicated. The major indications are:

- the prevention and treatment of bleeding episodes, and
- the prevention and treatment of bleeding in minor surgeries.

CONTRAINDICATIONS

WILATE is contraindicated in any patient who has a history of an allergic reaction to human coagulation FVIII, human VWF or to any constituent of WILATE.

PRECAUTIONS

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 pathogens of unknown nature and theoretically to Creutzfeld-Jacob Disease (CJD) agents.. The risk of transmission of infective agents is however reduced by:

- i. selection of donors by a medical interview and screening of individual donations and plasma pool for HBsAg and antibodies to HIV and HCV
- ii. testing of plasma pools for HCV genomic material
- iii. inactivation/ removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, HAV, and HBV.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 may cause serious reactions in pregnant women who are sero-negative (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. in haemolytic anaemia).

The manufacturing process was investigated for the capacity to decrease the amount of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents. The manufacturing process of Wilate has been shown to significantly decrease the amount of this experimental model agent. The TSE reduction steps are S/D treatment, different chromatography purification steps and precipitation with aluminium hydroxide.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular or repeated receipt of human plasma-derived FVIII/VWF concentrates.

In the interest of patients, it is strongly recommended that, whenever possible, every time that WILATE is administered, the name and batch number of the product is recorded.

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 of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician.

In case of shock, the current medical standards for treatment of shock are to be observed.

Von Willebrand disease (VWD)

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving FVIII-

containing VWF products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events.

There is a risk of occurrence of thrombotic events when using FVIII-containing VWF products, 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.

Use in Pregnancy and lactation

Animal reproduction studies have not been conducted with FVIII/VWF.

Von Willebrand disease (VWD)

Experience in the treatment of pregnant or lactating women is not available. WILATE should be administered to pregnant or lactating VWF deficient women only if clearly indicated, taking into consideration that delivery confers an increased risk of haemorrhagic events in these patients.

Interactions with other medicines

No interactions of human coagulation FVIII and VWF products with other medicinal products are known.

Effects on ability to drive and use machines

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

ADVERSE EFFECTS

Hypersensitivity or allergic reactions (which may include angioedema, 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, and may in some cases progress to severe anaphylaxis (including shock). In rare occasions, fever has been observed.

Von Willebrand disease (VWD)

Patients with VWD, especially type 3 patients, may very rarely develop neutralising antibodies to VWF. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies may precipitate and may occur concomitantly to 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.

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.

In patients receiving FVIII-containing VWF products, sustained excessive FVIII:C plasma levels may increase the risk of thrombotic events.

For information on viral safety see **WARNINGS**.

DOSAGE AND ADMINISTRATION

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

Von Willebrand disease (VWD)

The ratio between FVIII:C and VWF:RCo is roughly 1:1. Generally, 1 IU/kg body weight (BW) FVIII:C and VWF:RCo raises the plasma level by 1.5-2% of normal activity for the respective protein. Usually, about 20 to 50 IU WILATE/kg BW are necessary to achieve adequate haemostasis. This will raise the FVIII:C and VWF:RCo in the patients by approximately 30 to 100%.

An initial dose of 50 to 80 IU WILATE/kg BW may be required, especially in patients with VWD type 3, where the maintenance of adequate plasma levels may require higher doses than in other types of VWD. In addition, patients with gastro-intestinal bleedings usually need higher initial and maintenance dosages.

Prevention of haemorrhage in case of surgery or severe trauma:

For prevention of bleeding in case of surgery the injection of WILATE should start 30 minutes before the surgical procedure. In case of elective surgery, treatment should start 12-24 hours before surgery and should be repeated one hour before the procedure. Levels of VWF:RCo of ≥ 60 IU/100 mL ($\geq 60\%$) and FVIII:C levels of ≥ 50 IU/100 mL ($\geq 50\%$) should be achieved.

An appropriate dose should be re-administered every 12-24 hours of treatment. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding, and both FVIII:C and VWF:RCo levels.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C in patients with VWD. After 24-48 hours of treatment, in order to avoid an excessive rise in FVIII:C, reduced doses and/or prolongation of the dose interval should be considered.

There is insufficient data to recommend the use of WILATE in children less than 6 years of age.

Incompatibilities

WILATE must not be mixed with other medicinal products or administered simultaneously with other intravenous preparations in the same infusion set.

Only the provided injection/infusion sets can be used because treatment failure can occur as a consequence of human coagulation FVIII/VWF adsorption to the internal surfaces of some infusion equipment.

Administration:

For intravenous injection after reconstitution with the enclosed solvent.

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Wilate contains no antimicrobial agent. The powder should be reconstituted only directly before injection. To reduce microbiological hazard, use as soon as practicable after dilution. If storage of reconstituted solution is necessary, hold at 2°C to 8°C for not more than 12 hours.

The reconstituted solution should be used on one occasion only. Any solution remaining should be discarded appropriately.

Instructions for reconstitution:

1. Warm the Powder and Solvent in the closed vials up to room temperature. This temperature should be maintained during reconstitution. If a water bath is used for warming, care must be taken to avoid water coming into contact with the rubber stoppers (latex-free) or the caps of the vials. The temperature of the water bath should not exceed +37°C.
2. Remove the caps from the powder vial and the solvent vial and clean the rubber stoppers with an alcohol swab.
3. Remove the protective cover from the short end of the double-ended needle, making sure not to touch the exposed tip of the needle. Then perforate the centre of the solvent vial rubber stopper with the vertically held needle. In order to withdraw the fluid from the solvent vial completely, the needle must be introduced into the rubber stopper in such a way that it just penetrates the stopper and is visible in the vial.
4. Remove the protective cover from the other, long end of the double-ended needle, making sure not to touch the exposed tip of the needle. Hold the solvent vial upside-down above the upright powder vial and quickly perforate the centre of the concentrate vial rubber stopper with the needle. The vacuum inside the concentrate vial draws in the solvent.
5. Remove the double-ended needle with the empty solvent vial from the powder vial, then slowly rotate the vial until the concentrate is completely dissolved. WILATE dissolves quickly at room temperature to a clear solution.

The solution is clear to slightly opalescent. If the concentrate fails to dissolve completely or an aggregate is formed, the preparation must not be used.

Instructions for injection:

As a precautionary measure, the patients pulse rate should be measured before and during the FVIII injection. If a marked increase in the pulse rate occurs the injection speed must be reduced or the administration must be interrupted.

1. After the powder has been reconstituted in the manner described above, remove the protective cover from the filter needle and perforate the rubber stopper of the concentrate vial.
2. Remove the cap of the filter needle and attach the syringe.
3. Turn the vial with the attached syringe upside-down and draw the solution up into the syringe.
4. Clean the intended injection site with an alcohol swab.
5. Remove the filter needle from the syringe and attach the butterfly infusion needle to the syringe instead.
6. Inject the solution intravenously at a slow speed of 2-3 mL/minute.

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

OVERDOSAGE

No symptoms of overdose with human FVIII or VWF have been reported.

PRESENTATION

WILATE comes in two presentations (450IU or 900IU) as a combination package. Each package contains:

WILATE 450 in 5 mL

1 package contains:

- 1 vial with powder
- 1 vial with solvent (5 mL Water for Injections with 0.1% Polysorbate 80)
- 1 equipment pack with the medical devices (1 disposable syringe, 1 transfer set [1 double-ended needle and 1 filter needle], 1 infusion set)
- 2 alcohol swabs

WILATE 900 in 10 mL

1 package contains:

- 1 vial with powder
- 1 vial with solvent (10 mL Water for Injections with 0.1% Polysorbate 80)
- 1 equipment pack with the medical devices (1 disposable syringe, 1 transfer set [1 double-ended needle and 1 filter needle], 1 infusion set)
- 2 alcohol swabs

STORAGE CONDITIONS

Shelf life is 2 years.

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Protect from light.

Do not use after expiry date.

Once removed from refrigeration, store below 25°C and use within 1 month. In this case, the new date of expiry should be noted on the outer carton.

Medicine Classification

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

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