SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Wilate 450, 450 IU FVIII/400 IU VWF, powder and solvent for solution for injection

Wilate 900, 900 IU FVIII/800 IU VWF, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Wilate, is presented as a powder and solvent for solution for injection. Each vial contains nominally 450 IU/900 IU human coagulation factor VIII and 400 IU/800 IU human von Willebrand factor (VWF).

The product contains approximately 80 IU/ml human von Willebrand factor when reconstituted with 5 ml/10 ml Water for Injections with 0.1 % Polysorbate 80.

The specific activity of Wilate is approximately ≥ 53 IU VWF:RCo/mg 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 product contains approximately 90 IU/ml human coagulation factor VIII when reconstituted with 5 ml/10 ml Water for Injections with 0.1% Polysorbate 80.

The FVIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Wilate is approximately ≥ 60 IU FVIII:C/mg protein.

Produced from the plasma of human donors.

Excipient(s) with known effect:

Wilate 450: 11.7 mg sodium per ml reconstituted solution (58.7 mg sodium per vial).

Wilate 900: 11.7 mg sodium per ml reconstituted solution (117.3 mg sodium per vial).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Freeze-dried powder: white or pale yellow powder or crumbly solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Von Willebrand disease (VWD)

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

Haemophilia A

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of coagulation disorders. The product is of single use and the full content of the vial should be administered. In case any content remains, it should be disposed of in accordance with local requirements.

Von Willebrand disease (VWD)

The ratio between FVIII:C and VWF:RCo is roughly 1:1. Generally, 1 IU/kg FVIII:C and VWF:RCo raises the plasma level by 1.5-2% of normal activity for the respective protein.

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

Usually, about 20 to 50 IU Wilate/kg are necessary to achieve adequate haemostasis.

An initial dose of 50 to 80 IU Wilate/kg 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.

For prevention of bleeding in case of surgery, Wilate should be given 1-2 hours before start of the surgical procedure. Levels of VWF:RCo of ≥ 60 IU/dl (≥ 60%) and FVIII:C levels of ≥ 40 IU/dl (≥ 40%) 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.

In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to reveal sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events, particularly in patients with known clinical or laboratory risk factors. In case excessive FVIII:C plasma levels are observed, reduced doses and/or prolongation of the dose interval or the use of VWF product containing a low level of FVIII should be considered.

Prophylaxis:
For long term prophylaxis against bleeds in VWD patients, doses of 20-40 IU/kg should be administered 2 or 3 times per week. In some cases, such as in patients with gastrointestinal bleeds, higher doses may be necessary.

Paediatric population

Wilate can be used in children of all ages. Dosing is based on the same guidance as for adults and should be adjusted to the clinical condition of the patient, as well as their VWF:RCo and FVIII:C plasma levels. In younger patients, shorter dose intervals or higher doses may be necessary due to lower recovery and shorter half-life compared to adults (see Section 5.2). For the treatment of haemorrhage in children <6 years of age, initial doses of 50 to 80 IU/kg and maintenance doses of 30 to 50 IU/kg are recommended. For initiation of long-term prophylaxis against bleeds in children <6 years of age, doses of 30 to 50 IU/kg administered 2 or 3 times per week should be considered.

Haemophilia A

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII treatment, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

Posology

The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment:

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma level by 1.5-2% of normal activity. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (IU/dl) x 0.5 IU/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery.

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 – 60	Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

Prophylaxis:

For long-term prophylaxis against bleedings in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Continuous infusion:

Prior to surgery, a pharmacokinetic analysis should be performed to obtain an estimate of clearance. The initial infusion rate can be calculated as follows:

Infusion rate (IU/kg/hr) = clearance (mL/kg/hr) x desired steady state level (IU/mL)

After the initial 24 hours of continuous infusion, the clearance should be calculated again every day using the steady state equation with the measured level and the known rate of infusion.

Paediatric population

There are insufficient data to recommend the use of Wilate in haemophilia A in children less than 6 years old.

Method of administration

Intravenous use.

The injection or infusion rate should not exceed 2-3 ml per minute. For children weighing between 6 kg to less than 10 kg, the infusion rate should not exceed 2 ml per minute. **For children weighing less than 6 kg, the infusion rate should not exceed 1 ml per minute.**

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contra-indications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions are possible with Wilate. The product contains traces of human proteins other than factor VIII. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician.
Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock 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), and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as 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 B) should be considered for patients in regular/repeated receipt of human plasma-derived FVIII/VWF concentrates.

It is strongly recommended that every time that Wilate 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.

Von Willebrand disease (VWD)

Thromboembolic events
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.

Inhibitors
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.

Haemophilia A

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII 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 haemophilia and factor VIII inhibitors.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

This medicinal product contains up to 58.7 mg sodium per vial for 450 IU VWF and FVIII/vial, and up to 117.3 mg sodium per vial for 900 IU VWF and FVIII/vial, equivalent to 2.94% and 5.87%, respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population
The listed warnings and precautions apply to both adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII/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.

Haemophilia A

Based on the rare occurrence of haemophilia A in women, experience regarding the treatment during pregnancy and breastfeeding is not available. Therefore, Wilate should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

Wilate has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angiooedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, erythema, pruritus, rash, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, dyspnoea, tingling, vomiting, wheezing) have been observed rarely, and may in some cases progress to severe anaphylaxis (including shock).

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 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.

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

Haemophilia A

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Wilate see section 5.1. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

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

Tabulated list of adverse reactions

The following table shows an overview of adverse reactions observed in clinical studies, post-marketing safety studies, and from other post-marketing sources, categorised according the MedDRA System Organ Class (SOC), Preferred Term Level (PT) and frequency.

Frequencies have been evaluated 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 (SOC)	Adverse Reaction	Frequency
Immune system disorders	Hypersensitivity Anaphylactic shock	Common Very rare
General disorders and administration site conditions	Fever Chest pain	Common Not known
Blood and lymphatic system disorders	Factor VIII inhibiton Von Willebrand's factor inhibitors	Uncommon (PTPs)* Very common (PUPs)* Very rare
Respiratory, thoracic and mediastinal disorders	Cough	Not known
Nervous system disorders	Dizziness	Uncommon
Gastrointestinal disorders	Abdominal pain	Not known
Musculoskeletal and connective tissue disorders	Back pain	Not known

* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

Description of selected adverse reactions

For description of selected adverse reactions, see section 4.4

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 the national reporting system. listed in Appendix V* – [to be completed nationally].

4.9 Overdose

No symptoms of overdose with human factor VIII or VWF have been reported. Thromboembolic events may occur in case of major overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics: blood coagulation factors

Von Willebrand factor and 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 to the level of polymerisation of the protein;

- VWF produces delayed correction of the associated factor VIII deficiency. Administered intravenously, VWF binds 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 VWF (VWF product with a low factor VIII level) restores the FVIII:C level to normal as a secondary effect after first infusion.
  Administration of a factor VIII-containing VWF preparation restores the FVIII:C level to normal immediately after first infusion.

In addition to its role as a factor VIII-protecting protein, VWF mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

Haemophilia A

The factor VIII/von willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient´s circulation. Activated factor VIII (FVIIIa) acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of FVIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Of note, annualized bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

In addition to its role as a factor VIII protecting protein, von Willebrand factor mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

5.2 Pharmacokinetic properties

Von Willebrand disease (VWD)

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

Based on meta-analysis of three pharmacokinetic studies involving 24 evaluable patients (20 adults, 2 adolescents aged 12 to <18 years, and 2 children aged 6 to <12 years) with all VWD types, the following results were observed.

	All VWD types					**VWD type 1**					**VWD type 2**					**VWD type 3**				
Parameter	**N**	Mean	SD	Min.	Max.	**N**	Mean	SD	Min.	Max.	**N**	Mean	SD	Min.	Max.	**N**	Mean	SD	Min.	Max.
Recovery (%/IU/kg)	**24**	1.56	0.48	0.90	2.93	**2**	1.19	0.07	1.14	1.24	**5**	1.83	0.86	0.98	2.93	**17**	1.52	0.32	0.90	2.24
AUC (0-inf) (h*%)	**23**	1981	960	593	4831	**2**	2062	510	1701	2423	**5**	2971	1383	1511	4831	**16**	1662	622	593	2606
T 1/2 (h)	**24**	23.3	12.6	7.4	58.4	**2**	39.7	18.3	26.7	52.7	**5**	34.9	16	17.5	58.4	**17**	18	6.2	7.4	30.5
MRT (h)	**24**	33.1	19	10.1	89.7	**2**	53.6	25.9	35.3	71.9	**5**	53.5	24.6	27.8	89.7	**17**	24.7	8.5	10.1	37.7
Clearance (mL/h/kg)	**24**	3.29	1.67	0.91	7.41	**2**	2.66	0.85	2.06	3.27	**5**	1.95	1.02	0.91	3.31	**17**	3.76	1.69	1.83	7.41

Key: AUC = area under the curve; MRT = mean residence time

Based on PK assessments in 10 children under 6 years of age, the following results were observed for VWF:RCo.

	All VWD types					**VWD type 2**					**VWD type 3**				
Parameter	**N**	Mean	SD	Min.	Max.	**N**	Mean	SD	Min.	Max.	**N**	Mean	SD	Min.	Max.
Recovery (%/IU/kg)	**10**	1.31	0.25	0.84	1.62	**4**	1.22	0.34	0.84	1.62	**6**	1.37	0.17	1.07	1.59
AUC (0-inf) (h*%)	**10**	1100	532	531	2259	**4**	1282	856	531	2259	**6**	978	161	729	1166
T 1/2 (h)	**10**	11.7	9.6	4.5	36.8	**4**	16.8	14.2	6.2	36.8	**6**	8.3	2.9	4.5	12.1
MRT (h)	**10**	15.6	9.5	7.3	38.9	**4**	19.8	14.1	8.9	38.9	**6**	12.8	4.6	7.3	19.3
Clearance (mL/h/kg)	**10**	8.7	3.6	3.5	15.1	**4**	9.2	5.9	3.5	15.1	**6**	8.4	1.5	6.9	11

Key: AUC = area under the curve; MRT = mean residence time

Haemophilia A

Factor VIII (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous factor VIII. After injection of the product, approximately two thirds to three quarters of the factor VIII remain in the circulation. The level of factor VIII activity reached in the plasma should be between 80-120% of the predicted factor VIII activity.

Plasma factor VIII activity decreases by a two-phase exponential decay. In the initial phase, distribution between the intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 3 to 6 hours. In the subsequent slower phase, the

half-life varies between 8 to 18 hours, with an average of 15 hours. This corresponds to the true biological half-life.

The following results were observed in one clinical study in 12 patients (chromogenic assay, double measurement):

Parameter	Baseline visit		6-month visit	
	Mean	SD	Mean	SD
Recovery %/IU/kg	FVIII:C 2.27	1.20	FVIII:C 2.26	1.19
AUC_{norm} % * h/IU/kg	FVIII:C 31.3	7.31	FVIII:C 33.8	10.9
Half-life (h)	FVIII:C 11.2	2.85	FVIII:C 11.8	3.37
MRT (h)	FVIII:C 15.3	3.5	FVIII:C 16.3	4.6
Clearance mL/h/kg	FVIII:C 3.37	0.86	FVIII:C 3.24	1.04

Key: AUC = area under the curve; MRT = mean residence time; SD = standard deviation

5.3 Preclinical safety data

FVIII and VWF in Wilate are normal constituents of the human plasma and act like the endogenous FVIII/VWF.

Conventional safety testing of these compounds in laboratory animals would not add useful information to the existing clinical experience and therefore is not required.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Sodium chloride, Glycine, Sucrose, Sodium citrate and Calcium chloride

Solvent: Water for injections with 0.1 % Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or administered simultaneously with other intravenous preparation in the same infusion set.

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

6.3 Shelf-life

3 years.

The stability of the reconstituted solution has been demonstrated for 4 hours at room temperature (max. +25°C). Nevertheless, to avoid microbial contamination, the reconstituted solution should be used immediately.

6.4 Special precautions for storage

Store powder and solvent vial in a refrigerator (2-8°C). Keep the vials in the outer carton in order to protect from light. Do not freeze.

The product can be stored at room temperature (max. +25°C) for 2 months. In this case the shelf-life expires 2 months after the product has been taken out of the refrigerator for the first time. The new shelf-life has to be noted on the outer carton by the patient. The reconstituted solution should be used on one occasion only. Any solution remaining should be discarded.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Package sizes:

Wilate 450, 450 IU FVIII and 400 IU VWF

1 package contains:

1 vial with Powder, type I glass, closed with a stopper (bromobutyl rubber) and sealed with a flip off cap

1 vial with Solvent (5 ml Water for Injections with 0.1% Polysorbate 80), type I glass, closed with a stopper (halobutyl rubber) and sealed with a flip off cap

1 equipment pack for intravenous injection (1 transfer set, 1 infusion set, 1 disposable syringe)

2 alcohol swabs

Wilate 900, 900 IU FVIII and 800 IU VWF

1 package contains:

1 vial with Powder, type I glass, closed with a stopper (bromobutyl rubber) and sealed with a flip off cap

1 vial with Solvent (10 ml Water for Injections with 0.1% Polysorbate 80), type I glass, closed with a stopper (halobutyl rubber) and sealed with a flip off cap

1 equipment pack for intravenous injection (1 transfer set, 1 infusion set, 1 disposable syringe)

2 alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Please read all the instructions and follow them carefully!
- Do not use Wilate after expiry date given on the label.
- During the procedure described below, sterility must be maintained!
- Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration.
- The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.
- Use the prepared solution immediately, to prevent microbial contamination.
- Only use the infusion set provided. The use of other injection/infusion equipment can cause additional risks and treatment failure.

Instructions for preparing the solution:

1. Do not use the product directly from the refrigerator. Allow the solvent and the powder in the closed vials to reach room temperature.

2. Remove the flip off caps from both vials and clean the rubber stoppers with one of the provided alcohol swabs.

3. The transfer set is depicted in Fig. 1. Place the solvent vial on an even surface and hold it firmly. Take the transfer set and turn it upside down. Place the blue part of the transfer set on top of the solvent vial and press firmly down until it snaps (Fig. 2 + 3). Do not twist while attaching.

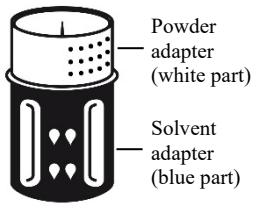


Fig. 1



Fig. 2



Fig. 3

4. Place the powder vial on an even surface and hold it firmly. Take the solvent vial with the attached transfer set and turn it upside down. Place the white part on top of the powder vial and press firmly down until it snaps (Fig. 4). Do not twist while attaching. The solvent flows automatically into the powder vial.

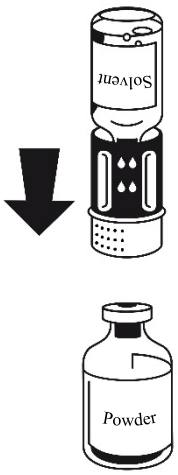


Fig. 4

5. With both vials still attached, gently swirl the powder vial until the product is dissolved.
The dissolving is completed in less than 10 minutes at room temperature. Slight foaming might occur during preparation. Unscrew the transfer set into two parts (Fig. 5). Foaming will disappear.

Dispose the empty solvent vial together with the blue part of the transfer set.

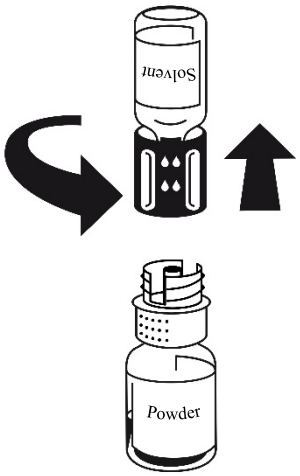


Fig. 5

Instructions for injection:

As a precaution, your pulse rate should be taken before and during the injection. If a marked increase in your pulse rate occurs, reduce the injection speed or interrupt the administration for a short time.

1. Attach the syringe to the white part of the transfer set. Turn the vial upside down and draw the solution into the syringe (Fig. 6).
The solution should be clear or slightly opalescent.
Once the solution has been transferred, firmly hold the plunger of the syringe (keeping it facing down) and remove the syringe from the transfer set (Fig. 7).

   Dispose the empty vial together with the white part of the transfer set.

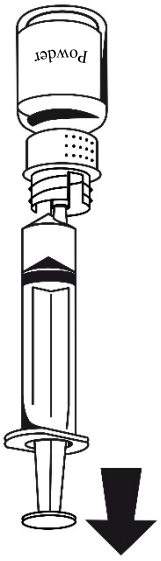


Fig. 6

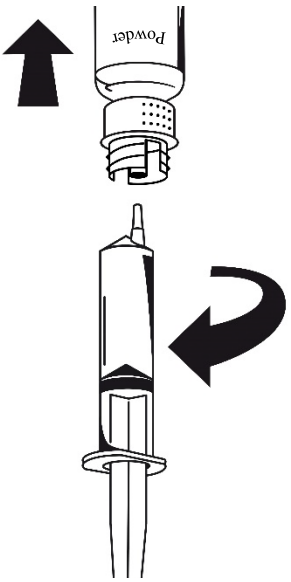


Fig. 7

2. Clean the chosen injection site with one of the provided alcohol swabs

3. Attach the provided infusion set to the syringe.

4. Insert the injection needle into the chosen vein. If you have used a tourniquet to make the vein easier to see, this tourniquet should be released before you start injecting Wilate.
   No blood must flow into the syringe due to the risk of formation of fibrin clots.

5. Inject the solution into the vein at a slow speed, not faster than 2-3 ml per minute in patients weighing 10 kg or more. For patients weighing between 6 kg and less than 10 kg, the infusion rate should not exceed 2 ml per minute. **For patients weighing less than 6 kg, the infusion rate should not exceed 1 ml per minute.**

If you use more than one vial of Wilate powder for one treatment, you may use the same injection needle and syringe again. The transfer set is for single use only.

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

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

To be completed nationally

10 DATE OF REVISION OF TEXT

Last revision: DD.MM.YYYY