INSTRUCTION FOR USE
(Summary of Product Characteristics)

1 NAME OF THE MEDICINAL PRODUCT

Wilate 500, 500 IU VWF/500 IU FVIII, powder and solvent for solution for injection
Wilate 1000, 1000 IU VWF/1000 IU FVIII, 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 500 IU/1000 IU human von Willebrand factor (VWF) and human coagulation factor VIII (FVIII).
The product contains approximately 100 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 ≥ 67 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 100 IU/ml human coagulation factor VIII when reconstituted with 5 ml/10 ml Water for Injections with 0.1% Polysorbate 80.
The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Wilate is ≥ 67 IU FVIII:C/mg protein.
Produced from the plasma of human donors.
Excipient(s) with known effect:
Wilate 500: 11.7 mg sodium per ml reconstituted solution (58.7 mg sodium per vial).
Wilate 1000: 11.7 mg sodium per ml reconstituted solution (117.3 mg 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 VWF:RCo and FVIII:C is 1:1. Generally, 1 IU/kg BW VWF:RCo and FVIII:C 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 VWF:RCo and FVIII:C in the patients by approx. 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.

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

Prevention of haemorrhage in case of surgery or severe trauma:
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 VWF:RCo and FVIII:C 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 bodyweight should be administered 2 or 3 times per week. In some cases, such as in patients with gastrointestinal bleeds, higher doses may be necessary.

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 Unrits (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 to 2% of normal activity. The required dose is determined using the following formula:
Required units = body weight (kg) × desired factor VIII rise (%) (IU/dl) × 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) × 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 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 VWF/factor VIII products.
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 pro-coagulant 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 that 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 500 IU VWF and FVIII/vial, and up to 117.3 mg sodium per vial for 1000 IU VWF and FVIII/vial, equivalent to 2.94% and 5.87%, respectively, of the WHO recommended 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 VWF/factor VIII.

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.
No cases of inhibitors for von Willebrand factor have been reported from clinical studies or from post marketing experience for Wilate so far.
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, categorized according to the MedDRA System Organ Class (SOC), and 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.

MeDRA Standard System Organ Class (SOC)	Adverse Reaction	Frquency
Immune system disorders	Hypersensitivity Anaphylactic shock	Uncommon Very rare
General disorders and administration site conditions	Fever Chest pain	Uncommon Not known
Blood and lymphatic system disorders	Factor VIII inhibition Von Willebrand's factor inhibition	Uncommon (PTPs)* Very common (PUPs)* Very rare
Respiratory, thoracic and mediastinal disorders	Cough	Not known
Nervous system disorders	Dizziness	Not known
Gastrointestinal disorders	Abdominal pain	Not known
Muscoskeletal 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.

4.9 Overdose
No symptoms of overdose with human VWF or factor VIII 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 vonWillebrand 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 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 with all VWD types, the following results were observed.

	All VWD types				
Parameter	N	Mean	SD	Min.	Max.
Recovery (%/IU/kg)	**24**	1.56	0.48	0.90	2.93
AUC (0-inf) (h*%)	**23**	1981	960	593	4831
T 1/2 (h)	**24**	23.3	12.6	7.4	58.4
MRT (h)	**24**	33.1	19	10.1	89.7
Clearance (mL/h/kg)	**24**	3.29	1.67	0.91	7.41

	VWD type 1				
Parameter	N	Mean	SD	Min.	Max.
Recovery (%/IU/kg)	**2**	1.19	0.07	1.14	1.24
AUC (0-inf) (h*%)	**2**	2062	510	1701	2423
T 1/2 (h)	**2**	39.7	18.3	26.7	52.7
MRT (h)	**2**	53.6	25.9	35.3	71.9
Clearance (mL/h/kg)	**2**	2.66	0.85	2.06	3.27

	VWD type 2				
Parameter	N	Mean	SD	Min.	Max.
Recovery (%/IU/kg)	**5**	1.83	0.86	0.98	2.93
AUC (0-inf) (h*%)	**5**	2971	1383	1511	4831
T 1/2 (h)	**5**	34.9	16	17.5	58.4
MRT (h)	**5**	53.5	24.6	27.8	89.7
Clearance (mL/h/kg)	**5**	1.95	1.02	0.91	3.31

	VWD type 3				
Parameter	N	Mean	SD	Min.	Max.
Recovery (%/IU/kg)	**17**	1.52	0.32	0.90	2.24
AUC (0-inf) (h*%)	**16**	1662	622	593	2606
T 1/2 (h)	**17**	18	6.2	7.4	30.5
MRT (h)	**17**	24.7	8.5	10.1	37.7
Clearance (mL/h/kg)	**17**	3.76	1.69	1.83	7.41

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
VWF and FVIII in Wilate are normal constituents of the human plasma and act like the endogenous VWF/FVIII.
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 6 months. In this case the shelf-life expires 6 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 500, 500 IU VWF and 500 IU FVIII
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 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 1000, 1000 IU VWF and 1000 IU FVIII
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 with the medical devices (1 disposable syringe, 1 transfer set (1 double-ended needle and 1 filter needle), 1 infusion set)
2 alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Instructions for reconstitution:
1. Warm the Powder and Solvent in the closed vials up to room temperature. This temperature should be maintained during reconstitution.
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.

7 NAME AND ADDRESS OF PHARMACEUTICAL COMPANY
7.1 Marketing authorisation holder
Pharmaniaga Marketing Sdn Bhd (198401005734)
No. 7, Lorong Keluli 1B,
Kaw. Perindustrian Bukit Raja Selatan,
Seksyen 7, 40000 Shah Alam,
Selangor Darul Ehsan, Malaysia.

7.2 Manufacturer
Octapharma Pharmazeutika Produktionsges.m.b.H.
Vienna, Austria

8 DATE OF REVISION OF THE TEXT
Last revision: 03-08-2020

9 LEGAL CATEGORY
For prescription only.