Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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 containing nominally 900 IU human coagulation factor VIII and 800 IU human von Willebrand factor (VWF) per vial.

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

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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 FVIII deficiency).

4.2 Posology and method of administration

Treatment should be initiated 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 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 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.

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 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 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

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

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

One IU of FVIII activity is equivalent to that quantity of FVIII in one ml of normal human plasma.

The calculation of the required dosage of FVIII is based on the empirical finding that 1 IU FVIII:C/kg BW raises the plasma level by 1.5-2% of normal activity. The required dosage is determined using the following formula:

Required IU = BW (kg) x desired FVIII 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.

Treatment scheme for Haemorrhages and Surgery

Degree of haemorrhage/ Type of surgical procedure	**FVIII 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 disability are resolved.
Life threatening haemorrhages	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.

Major	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 FVIII activity of 30% to 60% (IU/dl).

Prophylaxis:

For long-term prophylaxis against bleedings in patients with severe haemophilia A, doses of 20 to 40 IU Wilate/kg BW should be given 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/h) = clearance (mL/kg/h) 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.

During the course of treatment, appropriate determination of FVIII:C levels is ad-vised to guide the dose to be administered and the frequency of repeated infu-sions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C) is indispensable. Individual patients may vary in their response to FVIII treatment, achieving different levels of *in vivo* recovery and demonstrating different half−lives.

Patients should be monitored for the development of FVIII neutralising antibodies (inhibitors). If the expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a FVIII inhibitor is present. In patients with high levels of inhibitor, FVIII 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. See also 4.4.

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

Method of administration

For intravenous injection after reconstitution with the enclosed solvent. See 6.6.

The injection or infusion rate should not exceed 2-3 ml per minute.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

As with any intravenous infusion of a plasma-derived 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 in-cluding 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.

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 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 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

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.

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

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 occurence 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.

Haemophilia A

The formation of neutralising antibodies (inhibitors) to FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Modified Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic FVIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with FVIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory test. (see also 4.8).

Cases of recurrent inhibitor (low titre) have been observed after switching from one FVIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor patients carefully for inhibitor occurrence following any product switch.This medicinal product contains up to 5.1 mmol sodium (117.3 mg) per dose for 900 IU FVIII and 800 IU VWF/vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other medicinal products are known.

4.6 Fertility, 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.

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

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

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angiooedema, 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.

System Organ Class	Uncommon	Rare	Very rare
Immune system disorders	hypersensitivity reaction		anaphylactic shock
General disorders and administration site conditions		fever	
Investigations		FVIII inhibitors	VWF inhibitors

uncommon (> 1/1,000, < 1/100)

rare (>1/10,000, <1/1,000)

very rare (<1/10,000), including isolated reports

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.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. 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.

Haemophilia A

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

The experience with Wilate in previously untreated patients (PUPs) is limited. In a clinical trial involving 24 PUPs with a minimum of 50 exposure days treated with Wilate, only three patients with a persistent and clinically manifest inhibitor above 5 BU/ml could be detected. Three patients developed low titre, transient inhibitors without any clinical manifestations, and two patients had a low titre inhibitor on a single occasion with no follow-up result.

See also section 4.2. There were no inhibitor developments observed in previously treated patients.

For safety with respect to transmissible agents, see 4.4

4.9 Overdose

No symptoms of overdose with human FVIII 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 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 after first infusion.
Administration of a FVIII-containing VWF preparation restores the FVIII:C level to normal immediately after first infusion.

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

Haemophilia A
The FVIII/VWF complex consists of two molecules (FVIII and VWF) with different physiological functions. When infused into a haemophilia patient, FVIII binds to VWF in the patient´s circulation. Activated FVIII (FVIIIa) acts as a cofactor for activated factor IX (FIXa), accelerating the conversion of factor X to activated factor X (FXa). FXa 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 a result of accidental or surgical trauma. By replacement therapy the plasma levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

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					**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

Haemophilia A

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

FVIII: C 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 measurements):

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

Wilate 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 can be used because treatment failure can occur as a consequence of FVIII/VWF adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf life

3 years.

The stability of the reconstituted solution has been demonstrated for 12 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 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.

6.5 Nature and contents of container

Package sizes:
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 (chlorobutyl rubber) and sealed with a flip off cap

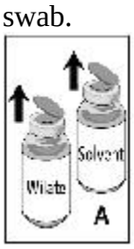
1 equipment pack with the medical devices (1 disposable syringe, 1 transfer set [1 double-ended needle and 1 filter needle], 1 infusion set)

2 alcohol swabs

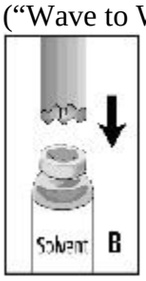
6.6 Special precautions for disposal and other handling

1. Warm the solvent and the powder in the closed vials up to room temperature. 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 (Fig. A) and disinfect the rubber stoppers with an alcohol swab.



3. Place the solvent vial on a flat surface. Attach the double-ended needle with the wavy edging on the solvent vial (“Wave to Water”) and push down as far as will go (Fig. B).



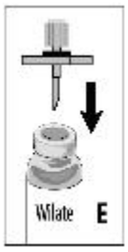
4. Place the concentrate vial on a flat surface. Remove the protective cover from the double-ended needle, making sure not to touch the exposed tip of the needle. Hold the solvent vial with the double-ended needle upside-down and quickly perforate the centre of the concentrate vial rubber stopper with the needle and push down as far as will go (Fig. C). The vacuum inside the concentrate vial draws in the solvent.

5. Remove the solvent vial and the double-ended needle from the powder vial (Fig. D). Wilate dissolves quickly therefore only slowly rotate the vial.

The solution is clear to slightly opalescent. Cloudy solutions or solutions with aggregates must not be used.

Injection:

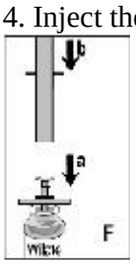
1. Remove the protective cover from the filter and perforate the rubber stopper of the concentrate vial (Fig. E).



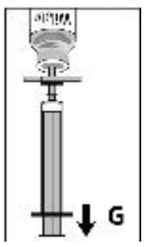
2. Retract the piston of the syringe to draw in air.

3. Remove the closure from the filter and attach the syringe to the filter (Fig. Fa).

4. Inject the air into the vial (Fig. Fb).



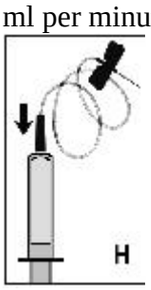
5. Turn the vial with the attached syringe upside-down and draw the solution up into the syringe (Fig. G).



6. Remove the syringe from the filter.

7. Clean the intended injection site with an alcohol swab.

8. Attach the Butterfly to the syringe (Fig. H) and immediately inject the preparation intravenously. Injection speed: 2-3 ml per minute



9. If the patient receives more than one vial of the concentrate, the same butterfly can be used. The syringe can also be used for several concentrate vials. Always use a new filter when drawing up the solution.

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

7 MARKETING AUTHORISATION HOLDER

Octapharma Ltd
The Zenith Building, 26 Spring Gardens
GB-Manchester M2 1AB
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 521/17/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th March 2010

10 DATE OF REVISION OF THE TEXT

October 2010