Clinical Research & Development

wilate®

WIL-20

Surveillance of the Safety and Efficacy of wilate® in patients with von Willebrand disease

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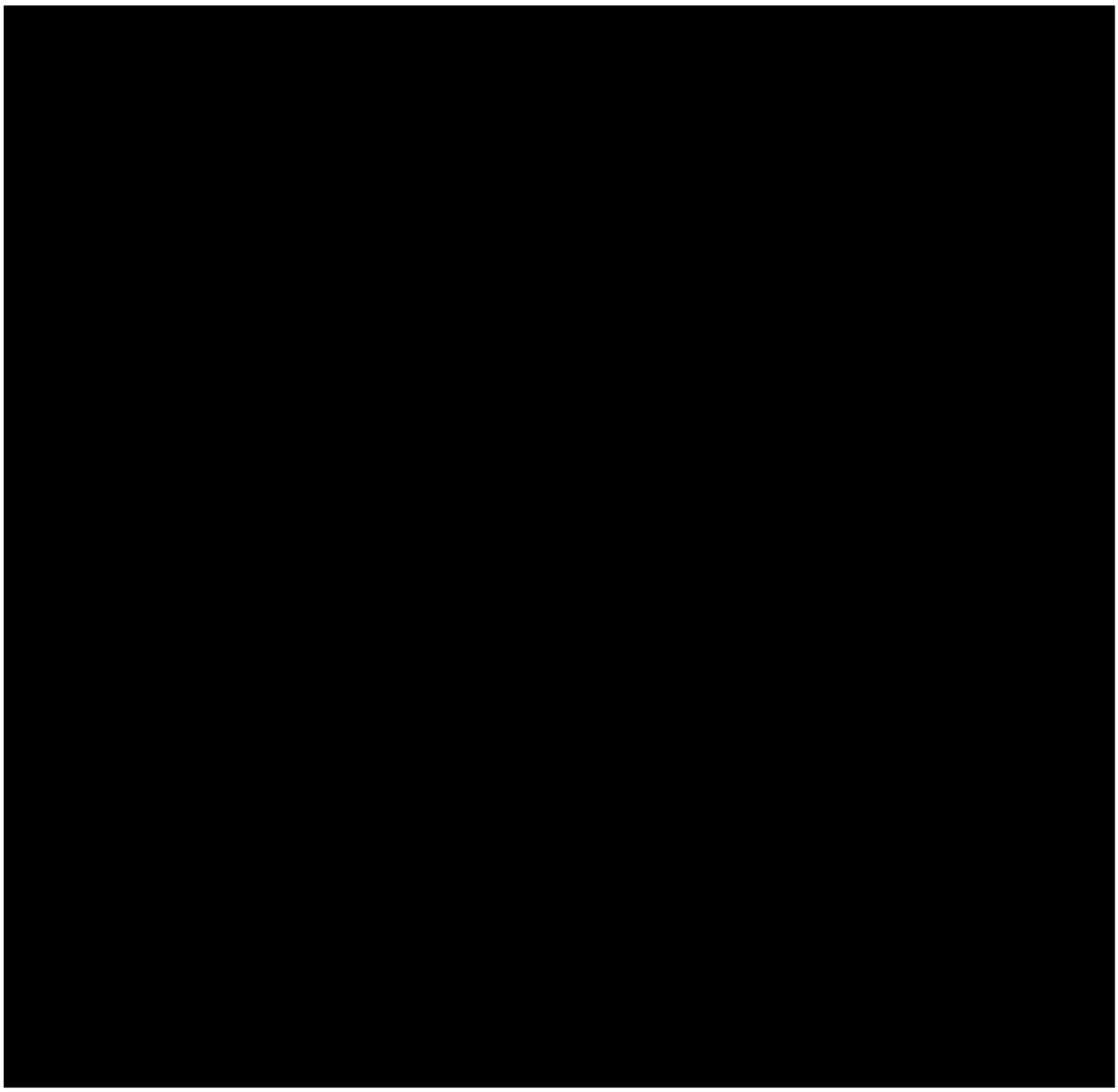
Document Type:	Observational Surveillance Protocol
Development Phase:	Post-marketing
Marketing authorisation holder	Octapharma AG Seidenstrasse 2 8853 Lachen Switzerland
Version Number:	04 (with Protocol Amendment No.2 and 3 incorporated) US country specific version
Release Date:	[28.08.2012]

PROTOCOL AUTHORIZATION

This observational surveillance will be conducted in compliance with the protocol, and the applicable regulatory requirements.



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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CRF	Case Report/Record Form
CRP	C reactive protein
DD	D-dimer
DDAVP	1-deamino-8-D-arginine vasopressin
ED	Exposure days
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
F1+2	Prothrombin fragments 1 and 2
FVIII	Factor VIII
GCP	Good clinical Practice
HAV	Hepatitis A virus
Hb	Hemoglobin
HBV	Hepatitis B virus
Hc	Hematocrit
HIV	Human immunodeficiency virus
IN	Investigator notification
IU	International Unit
PTPs	Previously treated patients
PUPs	Previously untreated patients
RBC	Red blood count
SAE	Serious adverse event
SPC	Summary of product characteristics
VRS	Verbal rating scale
VWD	Von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	VWF antigen
VWF:RCo	VWF Ristocetin Co-factor activity
WBC	White blood count

Surveillance protocol synopsis

Title:

Surveillance of Safety and Efficacy of wilate® in patients with von Willebrand disease

Objectives:

Primary objective:

Primary objective is to collect information concerning t the safety and tolerability of wilate® in routine clinical use.

Secondary objective:

Secondary objective is to collect information concerning the clinical outcome of wilate® administration in routine clinical use.

Population:

VWD patients of any gender, age, or VWD type, previously treated (PTPs) or previously untreated patients (PUPs), who have been prescribed wilate ® in the course of the physician's medical practice.

Investigational and reference therapy:

wilate® - human coagulation factor VIII and human von Willebrand factor (VWF)

Design:

Open-label, prospective, multicentre, multinational, post-marketing, observational, non-interventional surveillance

Efficacy assessments:

Assessment of the outcome of wilate® administration will be based on a 4-point hemostatic efficacy scale as "excellent", "good" "moderate" or "none". The frequency of bleeding episodes in total and per bleeding site, days of treatment of bleeding episodes in total and per bleeding site, exposure days and consumption of wilate® per event, per patient and in total will be calculated.

Safety/Tolerability assessments:

Assessment of safety will be based on recorded Adverse Drug Reactions during the full course of the observation. Assessment of tolerability will be based on a 3 point Verbal Rating Scale.

Immunogenicity

As a recommended assessment, this study will observe development of inhibitors against VWF in response to wilate® treatment (by an ELISA assay). Inhibitor assessment is recommended to be performed before and after first wilate® application, and then the every 3 months during the full course of observation.

Thrombogenicity

As a recommended assessment, this study will observe the coagulation parameters based on assessment of prothrombin fragments 1 and 2 (F1+2) and D-dimer (DD) by latex enhanced immunoturbimetric test. Thrombogenicity assessment is recommended to be performed before first wilate® application, 1 hour after application, 3 and 24 hours after application and every 3 months during the full course of observation. It is also recommended to perform thrombogenicity assessment for all interventional procedures.

Data analysis:

Descriptive statistics will be used as method for data analysis.

1 Background

wilate® is a freeze-dried preparation consisting of the two active ingredients: human plasma-derived coagulation Factor VIII (FVIII) and von Willebrand Factor (VWF). In the United States wilate® is indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. (1) wilate® has not been granted the indication for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients or the treatment of Hemophilia A. Full prescribing information for wilate® in the US is provided in Appendix II.

The hereditary form of von Willebrand's disease (VWD) is a common coagulation disorder with an estimated worldwide prevalence of 0.9-1.3%. Only a part of this patient population requires treatment, as there is great variability of geno- and phenotypes. The three main types of VWD are: type 1, 2 and 3. They are associated with quantitative (type 1 and 3) and qualitative defects (type 2) of the VWF. VWF/FVIII concentrates are administered mainly to patients with type 3, but patients with type 1 or 2 may also need regular or occasional substitution. Generally, the substitution frequency is very variable.

New biotechnological methods and chromatographic materials have been introduced in the development and production of wilate®. The result is a highly purified concentrate that contains FVIII/VWF complex in its natural form and in its physiological ratio of close to 1:1. wilate® is virtually free from low-molecular impurities.

wilate® is double virus-inactivated using the solvent/detergent method and a dry heating process (PermaHeat, 100°C for 2 hours). See appendix II for the approved US package insert.

2 Purpose of the surveillance

This post-marketing surveillance is designed to collect information concerning safety, tolerability, and outcome of wilate® administration in routine clinical use. Documentation of the administration of wilate® in clinical practice will not only improve the efficacy and tolerability knowledge database, but will produce findings that cannot be obtained in the same way in controlled clinical studies. This surveillance will help support the safe and effective use of wilate® thus bringing benefit for both physicians and patients.

3 Objectives

3.1 Primary objective

Primary objective is to collect information concerning the safety and tolerability of wilate® in routine clinical use.

3.2 Secondary objective(s)

Secondary objective is to collect information concerning the (outcome) of wilate® in routine clinical use.

4 Surveillance endpoints

4.1 Primary surveillance endpoint

Incidence of recorded adverse drug reactions (side effects) and wilate® tolerability results assessed by 3 point Verbal Rating Scale (see section 8.10) define primary endpoints.

4.2 Secondary surveillance endpoints

The secondary endpoint is defined as the percentage of the effectiveness ratings “excellent” and “good” based on a 4-point hemostatic efficacy scale (see section 8.6).

5 Surveillance design and duration

This is open-label, prospective, multinational, post-marketing, non-interventional observational surveillance. The observation was started Q4 2009 and to be completed after 5 years, with an individual observation period of 2 years.

6 Population

The surveillance will include 50 subjects. The observed population will consist of clinically diagnosed VWD patients of any type, previously treated (PTPs) or previously untreated patients (PUPs). The surveillance will observe male and female subjects without age limitation. It will include subjects who have been prescribed wilate® by their physician in the course of medical practice.

7 Treatment

7.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. Octapharma assigns the center number to the investigative site. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3. Once assigned to a patient, a patient number will not be reused.

7.2 Observational drug

wilate® is available in the US as a lyophilized powder with a special solvent (water for injection containing 0.1% Polysorbate 80) in the following strengths: 500 IU/vial (+ 5 ml solvent), 1000 IU/vial (+ 10 ml solvent), containing nominally 500 IU FVIII:C/500 VWF:RCo or 1000 IU FVIII:C/1000 VWF:RCo per vial, respectively.

7.3 Treating the patient

7.3.1 Dispensing wilate®

This is an observational, post-marketing surveillance. Subjects documented in this surveillance will receive commercially available wilate®.

7.3.2 Instructions for prescribing and taking wilate®

Patients are treated with wilate® according to the investigator's prescription. For dosage recommendations please refer to the local wilate® package leaflet.

The dosage and duration of treatment depend on the severity of the VWD as well as on the location and extent of bleeding and the patient's clinical condition. The therapeutic decision is at the investigators` discretion.

The ratio of factor VIII:VWF Ristocetin cofactor activity is approximately 1:1. Usual dosage of wilate® to achieve sufficient hemostasis is 20-60 IU/ kg body weight depending on the severity of the bleeding. This should increase the FVIII:C and VWF:RCo plasma level by about 30-50% which will vary depending on individual patient pharmacokinetic characteristics.

The investigator should promote compliance by instructing the patient to take wilate® exactly as prescribed and by stating that compliance is necessary for the patient's safety. The patient should be instructed to contact the investigator if he/she is unable for any reason to receive wilate® as prescribed.

All dosages prescribed and dispensed to the patient and all dose changes during this observational surveillance should be recorded on the Dosage Administration Record CRF.

7.3.3 wilate® dose adjustments and interruptions

Any drug dose adjustment and interruptions are at the discretion of the investigator, according to the location, extent of bleeding and patient's clinical condition.

All changes in wilate® dosage or interruptions should be recorded on the Dosage Administration Record CRF.

7.3.4 Other concomitant treatment

Any other concomitant treatment is at the discretion of the investigator. No interactions with other medicinal products are known (wilate® SPC).

In case of PTPs, a washout period of 7 days after the last infusion of the previous concentrate is recommended before the start of wilate® application.

The investigator should instruct the patient to notify the observational site about any new medications he/she takes after the start of wilate® application. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with wilate® should be listed on the Concomitant Medications/Significant Non-drug Therapies CRF.

7.3.5 wilate® discontinuation

If, for any reason, the investigator or the patient decides to discontinue the treatment the observation of this patient will be terminated.

However, the investigator should make the best efforts to complete and report all observations. The investigator will document the reason(s) for termination in the CRF and complete a Termination Form.

If the reason for discontinuing wilate® therapy is an adverse drug reaction, the specific reaction will also be recorded and is recommended that the investigator make thorough efforts to clearly document the outcome. All serious adverse drug reactions shall be reported to Octapharma to facilitate the Octapharma's compliance with any reporting obligations.

7.3.6 Observation completion

The observation is planned to be finalized after complete documentation of 50 subjects and after completion and submission of all CRFs.

The investigator must also provide follow-up medical care for all patients who are prematurely withdrawn from this observation, or must refer them for appropriate ongoing care.

When the patient has completed all observational assessments, the investigator should inform Octapharma within 10 days and record the core study patient completion in the CRF.

8 Visit schedule and assessments

Table 1 lists all of the assessments recommended by this observation and indicates with an “X” the visits when they should be performed.

Table 1 Assessment schedule

Assessments	Visits			
	Observation Entry	***Subsequent Visits***	***Terminal Visit***	***Interventional treatment [1]***
Anamnestic data [2]	X			X[B]
Weight	X	X		X[B, A]
Residual activity of FVIII / VWF [3]	X			X[B]
Response to DDAVP	X			X[B]
Patient general condition	X			X[B]
Bleeding tendency with severity	X			X[B]
Regularly administered medication(s)	X			X[B, D, A]
Previous treatment with FVIII / VWF	X			X[B]
Concomitant medication [4]	X	X	X	X[B, D, A]
Viral status [5]	X	X[10]	X[10]	X[B]
Vaccination status [6]	X	X		X[B]
Laboratory evaluation [7]	X	X	X	X[B, D, A]
FVIII / VWF measurements before and after wilate® application	X	X		X[B, A]
Current bleeding episodes -Site, Severity, Duration and Efficacy	X	X		X[D. A]
wilate® application [8]	X	X		X[B, D, A]
General wilate® assesment			X	X[A]
Documentation of interventional procedure				X[B]
Assessment of blood loss due to intervention				X[D. A]
Transfusion of blood / components				X[D. A]
Assessment of haemostatic efficacy and tolerability of wilate® [9]		X	X	X[A]
Adverse drug reactions		X	X	X[D. A]

1 - e.g. minor/major surgery, dental care, invasive diagnostic procedures etc..

2 - Anamnestic data include year of birth, gender, height, weight, blood group, general patient condition, VWD type and date of diagnosis

3 - %VWF:RCo; VWF:Ag; FVIII:C

4 - Including all medication taken in the last 7 days before observation entry

5- Hepatitis A, B, C, Parvovirus anbd., HIV anbd.

6 - HAV, HBV vaccine

7 - Hb, Hc, RBC, WBC, Platelets, ALT, AST, Bilirubin, Creatinine, CRP, Erythrocyte Sedimentation Rate (ESR)

8 - Date of administration, batch number, total dose, reason for treatment, tolerability

9 - Assessment of efficacy should be done after each bleeding episode for on demand treatment

10 - Only B19 Parvovirus antb.

B - Before intervention

D - During intervention

A - After intervention

Table 2 Recommended immunogenicity and thrombogenicity assessment schedule

	Week one		3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
	Before first application	After first application								
Inhibitor testing VWF Inhibitor	X	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]
Thrombogenicity testing F1+2 and D-dimer	X	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]	X [2]

Note: All tests will be performed in a central laboratory

1-Inhibitor test should be performed 3 to 4 days (preferably 7 days) after wilate® application

2-Blood samples collected 1 hour, 3 hours and 24 hours after wilate® application

It is recommended that all data obtained from the assessments listed in Table 1 should be documented in the patient's CRFs.

Due to the nature of this non-interventional, observational study design, strict pre-defined visit and time schedule is not required, however the study recommendation is to perform subsequent visits on regular 3 months intervals.

Before patient inclusion there should not be a clinical suspicion for an inhibitor. Recommendation is to perform a VWF inhibitor test to confirm that the patient is inhibitor negative at study entry.

At observation entry the physician will inform the patient about the conduct, implications and goal of this post marketing surveillance. If a patient agrees to participate and provide informed consent, he will receive a patient diary. The physician will explain how to use it and advise patients to bring it at each visit. Patients will be instructed that they should contact the physician in case of any problems that could be related to treatment with wilate®- including all adverse drug reactions - during the whole observation period.

Before the 1st treatment with wilate®, the physician should record all baseline characteristics on appropriate pages of the CRF. These include demographic data, diagnosis, the patient's date of enrolment and intended therapy with VWF/FVIII concentrate, any relevant concomitant medication, medical history, and available baseline laboratory data, including viral markers for HIV and hepatitis A, B, and C. It is recommended that available results should be recorded in the CRF. For PTPs the number of previous exposure days (ED) should be recorded. It is also recommended to document details of patient's treatment of the last 6 months before starting the observation.

It is recommended that any substitution, intolerability, adverse reaction, concomitant medication, major inter-current illness, bleeding episode and surgical procedure throughout the 2-Year observation period should be documented in appropriate CRF sections.

In case interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.) are performed, available related information will be obtained and documented on the respective forms. The information of interest includes a description of the surgical procedure, substitutive treatment, relevant concomitant medication, course and outcome of the surgical procedure, assessment of overall haemostatic effect, details regarding continuous infusion as well as relevant laboratory data.

8.1 Patient Diary

Patients are asked to document data as specified below. For this purpose they will receive a patient diary.

It is recommended to record every treatment with wilate® in the patient diary, regardless whether patients treat themselves at home or receive injections at the participating observational centre. The information of interest is: date and time of each injection, number of units used, batch number(s), indication, patient's and physician's assessment of outcome and of acute tolerability.

Similarly, patients are asked to record all concomitant medication.

The surveillance will observe documented bleeding episodes, indicating the bleeding site, start and stop date of bleeding, severity of bleeding (minor, moderate, or severe) and if appropriate, the amount of wilate® required to treat that episode.

Patients or their parents should assess the outcome of their wilate® treatment in case of bleeding episodes (on demand treatment), using the 4-point hemostatic efficacy scale (see section 8.6):

The tolerability of wilate® injections is assessed by the 3-point Verbal Rating Scale-VRS (see section 8.10).

In addition, each suspected adverse drug reaction related to wilate® therapy should be documented.

8.2 Patient demographics/other baseline characteristics

Before first wilate® application it is recommended to observe and document anamnestic data, (year of birth, gender, height, weight, blood group, general patient condition) VWD type and date of diagnosis, residual plasma level (%) of VWF:RCo, VWF:Ag, and FVIII:C, bleeding time and response to DDAVP.

Bleeding tendency with severity and frequency will also be observed as well as regularly applied medications, previous FVIII/VWF treatment(s), concomitant medications at the start with wilate® treatment and viral status (Hepatitis A, B and C, antibodies against parvovirus B19, HIV antibodies).

Vaccination status (against Hepatitis A and B) and clinical chemistry tests (hemoglobin, hematocrit, RBC, WBC, platelet count, ALT, AST, bilirubin, creatinine, CRP and Erythrocyte Sedimentation Rate-ESR) before wilate® treatment will also be observed if available.

8.3 Treatment exposure

Every wilate® application with date of administration, batch number, total dose applied, and reason for the wilate® treatment and wilate® treatment tolerability will be observed. Laboratory analyses (if performed) before and after first wilate® application and then during the full course of this surveillance will also be observed.

In case of application before, during or after an interventional treatment, date, time, dosage and batch number of wilate® will be observed as well as the wilate® application method (bolus injections or continuous infusion in pre-operative, intra-operative or post-operative application). Above described laboratory sampling in case of wilate® application in pre-operative treatment will also be observed.

Concomitant medication applied during full course of the surveillance will be observed and documented with the generic name of concomitant medication, dosage and mode of administration, with start, end or ongoing concomitant therapy notification. Concomitant medication applied in the last 7 days before the start of observation will be documented.

8.4 Immunogenicity

As recommended assessment, the surveillance will observe inhibitor activity determined by ELISA performed in the central laboratory after the first exposure day (ED), and then on every 3 months during the full course of observation (see table 2). Additional testing should be performed at any time during the course of surveillance if inhibitor development is suspected.

Octapharma will reimburse the costs of laboratory tests performed in the designated central laboratory and all shipment costs.

Before inhibitor testing, a period of at least 3-4 days without injection is recommended, if clinically acceptable. In order to safely exclude the presence of any low titer inhibitors, an injection free period of 7-8 days is preferable. For patients at high risk of bleeding, the injection free period is reduced appropriately.

8.5 Thrombogenicity

As recommended assessment, the study will observe activation of coagulation parameters performed in the central laboratory, based on assessment of prothrombin fragments 1 and 2 (F1+2) and D-dimer (DD) by latex enhanced immunoturbimetric test. Thrombogenicity assessment should be performed before first wilate® application, 1 hour after application, 3 and 24 hours after application and then onwards every 3 months during the full course of observation by the same schedule (1h, 3h and 24 hours after application). It is also recommended to perform thrombogenicity assessment for all interventional procedures.

Octapharma will reimburse the costs of laboratory tests performed in the designated central laboratory and all shipment costs.

8.6 Outcome Assessment

Assessment of the outcome of wilate® administration in treatment of bleeding episodes (on demand treatment) and in interventional procedures will be based on a 4-point haemostatic efficacy scale.

a) Hemostatic efficacy scale applied in treatment of bleeding episodes (on demand treatment) assessed by patients or their parents at the end of each bleeding episode:

- Excellent: bleeding was completely stopped within a reasonable period of time
- Good: bleeding was completely stopped, but time and/or dose slightly exceeded expectation
- Moderate: bleeding could only be stopped by significantly exceeding time and/or dose expectation
- None: bleeding could only be stopped by using other FVIII/VWF-containing products.

b) Hemostatic efficacy scale applied in interventional procedures assessed by physician at the end of the procedure:

- Excellent: Hemostasis clinically not significantly different from normal
- Good: Mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing)
- Moderate/Poor: Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate, controllable bleeding)
- None: Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that is difficult to control)

The frequency of bleeding episodes in total and per bleeding site, days of treatment and numbers of infusions per bleeding episode in total and per bleeding site, exposure days and consumption of wilate® per patient and in total will be calculated.

In addition a comparison of wilate® with previously applied FVIII/VWF preparations should be performed (see also 8.7), based on following parameters: bleeding frequency, concentrate FVIII/VWF consumption and clinical rating.

If the dataset allows, the dose used in different types and severities of bleeds will be correlated to the efficacy and duration of the treatment.

8.7 Bleeding Tendency

Before the first application of wilate® the surveillance will observe and document previous bleeding frequency (number of bleeds per week, per month, per year) and severity of this episodes (severe, moderate, mild). Locations that are affected more frequently will also be observed.

During the course of the observation current bleeding episodes with date of start, site, severity (mild, moderate, severe), duration and outcome should be documented in CRF.

8.8 General patient assessment and previous treatment with FVIII/VWF

At the start of the surveillance anamnestic data together with general patient condition and other clinically relevant diseases will be observed and documented (see section 8.2). Previous treatment with FVIII/VWD concentrates recordings should include concentrates applied in the last 6 months before the observation baseline. These data should include concentrate use for prophylactic or “on demand” treatment with usual dose and application frequency. Total consumption of FVIII/VWF concentrate applied in the last six months and exposure days during the same time will be observed and documented as well as tolerability assessment of previous treatment. Following definition of a 3-point Verbal Rating Scale (VRS) assesses the tolerability of previous treatment:

- Excellent: very good or good overall feeling within or after previous therapy
- Satisfactory: moderate overall feeling within or after previous therapy and/or occurrence of mild reactions (e.g. mild headache, mild dizziness etc.)
- Unsatisfactory: bad overall feeling within or after previous therapy and/or occurrence of moderate or severe adverse drug reactions.

It is recommended to document patients viral and vaccination status at the baseline (see section 8.2). Any changes in vaccination status during the observation period should be recorded.

8.8.1 Laboratory evaluations

The surveillance will follow subsequent laboratory values: Hemoglobin, Hematocrit, WBC, RBC, Platelets, ALT, AST, Bilirubin, Creatinine, CRP and Erythrocyte Sedimentation Rate-ESR. The date and time selection for blood sampling for laboratory evaluations are at the full discretion of the investigator.

The observation will record measurements of FVIII/VWF activity before and after wilate® application, but the choice of laboratory assays used for FVIII/VWF measurements are at the full discretion of the physician. However, its recommended to use VWF:RCo, VWF:Ag and FVIII:C analytical methods.

8.8.2 Days lost from school or work

The surveillance will follow the number of days the patient was not able to attend school or work retrospectively if available at the beginning of observation (estimation is possible, if no precise data are available) and then during the rest of the observation period.

8.9 Assessments in case of hemostasis management before, during or after interventional procedure

8.9.1 Assessment of blood loss / Transfusion

The surveillance will observe and document: date and time of intervention, type and description of intervention (planned or emergency), mode of wilate® administration, consumption, the quantity of blood lost during intervention and in the following five days as well as presence of drainage and quantity of blood lost in drainage system. Any presence of hematoma will also be observed if available.

In case of blood or blood components transfusion; type and volume (ml.) of transfusion (whole blood, RBC, platelets, plasma) applied before, during and/or 5 days after intervention will be observed.

8.10 Safety / Tolerability

Each suspected adverse drug reaction (ADR) during or after wilate® therapy noticed during the full course of the observation should be documented. The documented ADRs will be assessed and reported by the treating physician (for reporting details see section 9.2.).

The tolerability of wilate® injections are assessed by using the following definitions of a 3-point Verbal Rating Scale (VRS):

- Excellent: very good or good overall feeling within or after the wilate® therapy and no adverse drug reactions registered
- Satisfactory: moderate overall feeling within or after the wilate® therapy and/or occurrence of mild reactions (e.g. mild headache, mild dizziness etc.)
- Unsatisfactory: bad overall feeling within or after the wilate® therapy and/or occurrence of moderate or severe adverse drug reactions.

8.10.1 Virus Safety

The surveillance will observe and document the possibility of parvovirus B19 seroconversion after wilate® application. It is recommended to perform B19 testing during subsequent visits including the final visit (see Table 1 Assessment schedule).

9 Safety monitoring

To allow continuous monitoring of the product safety all adverse drug reactions and other safety information as defined below have to be documented and reported to Octapharma.

9.1 Definition of adverse drug reaction and other safety information

Adverse drug reaction (ADR):

Is defined as any adverse event associated with the use of wilate®, whether or not considered drug related.

Serious adverse drug reaction:

ADRs that fulfill at least one of the following criteria:

- results in death
- is life-threatening (this implies that the patient was at an immediate risk of death at the time of the event, and not a hypothetical situation of what could or would have happened if, for example, no treatment had been administered)
- requires in-patient hospitalization or prolongation of existing in-patient hospitalization (hospitalization does not refer to the treatment of an ADR on an out-patient status)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important condition (e.g. suspected transmission of an infectious agent, inhibitor development, thromboembolic events, or other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria)

Other relevant drug safety information:

Any safety information relating to

- pregnancies/breastfeeding,
- drug abuse (persistent, sporadic or intentional excessive use of a medicinal product inconsistent with the SPC or acceptable medical practice),
- overdose (treatment exceeding the medically recommended dose),
- medication errors (prescribing or dispensing error),
- interactions with other medicinal products or devices associated with wilate®, even if no adverse drug reaction occurred.

9.2 Reporting of adverse drug reactions and other safety information

All suspected adverse reactions and other safety information associated with the administration of wilate® have to be reported to the Octapharma Unit using the Case Safety Report Form (see Appendix I).

Serious adverse drug reactions have to be reported immediately by fax or email (within 24 hrs). Non-serious adverse drug reactions and other safety information should be reported to Octapharma, if possible, upon recognition but no later than 10 days.

Patients who carry out home-treatment with wilate® should be asked to inform the treating physician of any adverse drug reaction or other relevant safety information, immediately. The treating physician has to assess the causal relationship for ADRs and report adverse drug reactions and other relevant drug safety information.

More information about possible ADRs and other safety information can be found in the local Summary of Product Characteristics (see Appendix II).

10 Data analysis

10.1 Statistical Analysis

The responsibility for the statistical analyses presented in the final report belongs to: contract research organisation: GASD, Gesellschaft für Angewandte Statistik + Datenanalyse mbH, Am Konvent 8 - 10, 41460 Neuss, Germany.

This is a prospective post-licensure surveillance that will be conducted as an international multi-centre non-interventional surveillance. All items of the CRF will be analyzed by means of descriptive statistical methods.

Standard Patients treatments will be evaluated on total number of wilate® exposure days per year and mean wilate® dose per kg per patient per year.

10.2 Interim analysis

The first interim analysis will take place two years after the enrolment of the first patient, provided that there will be a reasonable number of documented patient-months available. Further interim analyses are planned once a year until surveillance completion.

11 Reference

1. E. Berntorp, J. Windiga and the European Wilate Study Group; Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. 2009 Jan;15(1):122-30

Appendix I: Local Drug Safety nit of Octapharma

Case Safety Report Form (CSRF)

octapharma

Please return the completed and signed form to:
[Enter Local Drug Safety Unit Contact Details]

Case Safety Report Form

Local Log Number _____

Report version	Dates	Report source / type
☐ Initial ☐ Follow-up #	Date initially received (dd/mm/yy)[1]: Date new information (FU) received (dd/mm/yy): Country of Event:	☐ Spontaneous ☐ Regulatory ☐ Consumer ☐ Literature ☒ Non-Interventional study (Study ID: WIL-20) ☐ Pregnancy (please complete Pregnancy report form) ☐ Misuse/abuse/overdose ☐ Other:

1. REPORTER

Reporter	Company reporter
Name: Institution: Address: Telephone: Fax: Email: ☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other:	Name: Institution: Address: Telephone: Fax: Email: ☐ Drug Safety ☐ Sales Representative ☐ Other

2. PATIENT INFORMATION

Initials[2].	Date of Birth (dd/mm/yy):	Height (cm):	☐Caucasoid
☐ Male ☐ Female			☐Mongoloid
☐ Pregnant	Age:	Weight (kg):	☐Negroid
week of gestation:	Age Group[3]:		☐Australoid
			☐Other:

3. SUSPECT PRODUCT(S) [4]

Product /Generic name and Batch No	Conc. of solution	Route	Treatment dosage/ Infusion rate	Start/End	Duration	Indication

Overall treatment regimen with suspect drug(s) (incl. start, frequency, dates):

4. ADVERSE REACTION [5]

Adverse Event/ Diagnosis	Severity	Date (start/end)	Duration (incl Units)	Latency [6] (incl Units)	Outcome
	☐mild ☐moderate ☐severe				☐Recovered ☐Resolving ☐Recovered with sequelae ☐Fatal ☐Unknown
	☐mild ☐moderate ☐severe				☐Recovered ☐Resolving ☐Recovered with sequelae ☐Fatal ☐Unknown
	☐mild ☐moderate ☐severe				☐Recovered ☐Resolving ☐Recovered with sequelae ☐Fatal ☐Unknown

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Case Safety Report Form

Local Log Number _____

Did reaction(s) stop after stopping suspect product [7]?	☐Yes ☐No ☐Unknown ☐NA	
Action taken with respect to suspect product(s)?	☐Drug(s) withdrawn ☐None ☐Unknown	
Did reaction(s) reappear after reintroduction?	☐Yes ☐No ☐Unknown ☐NA	Date(s):
Did patient receive previous treatment with suspect product(s) or similar product(s)?	☐Yes ☐No ☐Unknown ☐NA	
Did patient experience previous adverse reactions with suspect product(s) or similar product(s)[8]?	☐Yes ☐No ☐Unknown ☐NA	If yes, please provide information (dates, type(s) of reaction & other relevant details in Section 9 Detailed Description of Event)

Remedial Therapy [9] ☐None ☐Unknown ☐Yes, please specify below

Laboratory tests performed [10] ☐None ☐Unknown ☐Yes, please specify below

5. CONCOMITANT ILLNESSES AND DISEASES (E.G. ALLERGY, HISTORY, ALCOHOL ABUSE, ETC.)

☐None ☐Unknown ☐Yes, please specify below

6. CONCOMITANT MEDICATION [11]

☐None ☐Unknown ☐Yes, please specify below

7. CASE REPORT CLASSIFICATION / SERIOUSNESS CRITERIA[12]

Case report: ☐ non-serious ☐ serious (please complete section below) ☐ NA

☐Patient hospitalized Date: from to ☐Hospitalization prolonged Date: from to ☐Life threatening ☐Fatal ☐Resulting in persistent or significant disability/incapacity ☐Resulting in congenital anomaly or birth defect ☐Suspected transmission of an infectious agent ☐Other:	Date of death: Autopsy: ☐Yes ☐No ☐Unknown Cause of death:

8. POSSIBLE CAUSE(S) OF REACTION(S) / CAUSALITY ASSESSMENT

Reporter

☐Suspect drug(s) ☐Underlying disease ☐Lack of efficacy/worsening of treated conditions
☐Concomitant medication ☐Administration-related ☐Other:

Causality assessment: (i.e. Relatedness of reaction to administration of suspected Octapharma drug)

☐Reaction is possibly related ☐Reaction is unlikely / not related ☐Unknown
Comment:

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Case Safety Report Form

Local Log Number _____

Company reporter
☐Suspect drug(s) ☐Underlying disease ☐Lack of efficacy/worsening of treated conditions ☐Concomitant medication ☐Administration-related ☐Other:
Causality assessment: (i.e. Relatedness of reaction to administration of suspected Octapharma drug) ☐Reaction is possibly related ☐Reaction is unlikely / not related ☐Unknown Comment:
9. DETAILED DESCRIPTION OF EVENT[13]
10. OTHER COMMENTS [14]
Was Competent Authority(ies) informed? ☐No ☐Unknown ☐Yes, Authority reference #
Has more information been requested from the reporter? ☐Yes ☐No
Is adverse reaction(s) expected according to local product package insert? ☐Yes ☐No Comment:

On behalf of Octapharma: Print Name Date, Signature	Original Reporter: Print Name Date, Signature

[1] To prevent errors resulting from differently used date formats, please state all dates in the format DD/MM/YY
[2] Initials should be in the format "First name/Surname".
[3] Age group: neonate (up to 1 month), infant (> 1 month to < 2 years), child (> 2 years to < 12 years), adolescent (> 12 years to < 16 years), adult (> 16 years to < 65 years), elderly (> 65 years)
[4] Information on treatment that led to the adverse reaction(s) (generally last treatment). If product(s) were taken regularly please enter information in the section below.
[5] The diagnosis/adverse reaction(s) should be stated by the initial reporter. A diagnosis is preferred and the associated events should be described in section 9 Detailed Description of Event
[6] Time since beginning of last treatment with suspect drug(s) which resulted in adverse reaction(s).
[7] Dechallenging information refers to the situation where a direct response (i.e. improvement of adverse reaction(s)) could be noted without patient receiving remedial therapy.
[8] If patient experienced adverse reaction(s) with Octapharma product(s) previously, this may be considered a separate case safety report. Please provide as much information as possible under section 9 Detailed Description of Event.
[9] Provide information on therapy to treat adverse reaction(s). For drugs please include tradename, active ingredient, dosage, route, start/end dates.
[10] Any tests relating to the adverse reaction(s) including results, units, normal range.
[11] Other medication the patient received prior to the adverse reaction(s) or at the time of suspect drug(s) administration including trade name, active ingredient, dosage, route, frequency, indication for use.
[12] The seriousness criteria should not be confused with the nature/degree of the adverse reaction(s) but determines the timeframe of regulatory reporting based on the criteria specified in the section below.
[13] A detailed description of the chronology and outcome of the adverse reaction(s).
[14] Any other information that may be of interest or if available space in the form is insufficient.

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Appendix II: Wilate US Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Wilate safely and effectively. See full prescribing information for Wilate.

Wilate, von Willebrand Factor/Coagulation Factor VIII Complex (Human),
Powder for Solution, for Intravenous Use Only
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
- Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. (1)
- Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients.
- Wilate is not indicated for Hemophilia A

----------DOSAGE AND ADMINISTRATION----------
- **For Intravenous Use Only**

Type of Hemorrhages	Loading Dosage (IU VWF:RCo /kg BW)	Maintenance Dosage (IU VWF:RCo /kg BW)	Therapeutic Goal
Minor	20-40 IU/kg	20-30 IU/kg every 12-24 hours	VWF:RCo and FVIII activity through levels of >30%
Major	40-60 IU/kg	20-40 IU/kg every 12-24 hours	VWF:RCo and FVIII activity through levels of >50%

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleeding, higher doses may be required. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial (3):
  - 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
  - 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL

----------CONTRAINDICATIONS----------
- Hypersensitivity with known anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity reaction (5.1)
- Thromboembolic events associated with von Willebrand factor/Coagulation Factor FVIII (VWF/FVIII) products: plasma levels of FVIII activity should be monitored to avoid sustained excessive FVIII levels, which may increase the risk of thrombotic events (5.2)
- Potential for inducing antibodies to Factor VIII (inhibitors) and antibodies to VWF, especially in VWD type 3 patients (5.3)
- Theoretical risk of infectious agents transmission as the product is made from human plasma (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions in clinical studies on VWD were urticaria and dizziness (each 2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- None known (7).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: No human or animal data. Use only if clearly needed (8.1).

See 17 for PATIENT COUNSELING INFORMATION.
Revised: December 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

Clinical trials to evaluate the safety and efficacy of prophylactic dosing with Wilate to prevent spontaneous bleeding have not been conducted in VWD subjects.

Wilate is not indicated for the prevention of excessive bleeding during and after surgery in VWD patients.

Wilate is not indicated for Hemophilia A.

2 DOSAGE AND ADMINISTRATION

- **For Intravenous Use after Reconstitution**
- Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.
- Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay.
- The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma).

2.1 Dosage in von Willebrand Disease

The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1.

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

2.2 Dosing Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 1.

The careful control of replacement therapy is especially important in life-threatening hemorrhages. **When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity**.[1]

Table 1 Guide to Wilate Dosing for Treatment of Minor and Major Hemorrhages

Type of Hemorrhages	Loading Dosage (IU VWF:RCo /kg BW)	Maintenance Dosage (IU VWF:RCo /kg BW)	Therapeutic Goal
Minor Hemorrhages	20-40 IU/kg	20-30 IU/kg every 12-24 hours*	VWF:RCo and FVIII activity through levels of >30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12-24 hours*	VWF:RCo and FVIII activity through levels of >50%

Treatment guidelines apply to all VWD types

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible, appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

In the unlikely event that a patient who is actively bleeding should miss a dose, it may be appropriate to adopt a dosage depending on the level of coagulation factors measured, extent of the bleeding, and patient's clinical condition.

2.3 Administration

Wilate is administered via intravenous infusion. Wilate is provided with a Mix2Vial™ transfer device for reconstitution of the freeze-dried powder in diluent, a 10-mL syringe, an infusion set and two alcohol swabs.

Instructions for Reconstitution:


Fig.1

1) Warm the Powder and Diluent in the closed vials up to room temperature. This temperature should be maintained during reconstitution. If a water bath is used for warming, care must be taken to avoid water coming into contact with the rubber stoppers (latex-free) or the caps of the vials. The temperature of the water bath should not exceed +37°C (98°F).

2) Remove the caps from the concentrate (Wilate) vial and the diluent vial and clean the rubber stoppers with an alcohol swab.


Fig. 2

3) Peel away the lid of the outer package of the Mix2Vial™ transfer set. To maintain sterility, leave the Mix2Vial™ device in the clear outer packaging. Place the diluent vial on a level surface and hold the vial firmly. Take the Mix2Vial™ in its outer package and invert it over the diluent vial. Push the blue plastic cannula of the Mix2Vial™ firmly through the rubber stopper of the diluent vial (Fig. 1). While holding onto the diluent vial, carefully remove the outer package from the Mix2Vial™, being careful to leave the Mix2Vial™ attached firmly to the diluent vial (Fig. 2).


Fig. 3

4) With the concentrate (Wilate) vial held firmly on a level surface, quickly invert the diluent vial with the Mix2Vial™ attached and push the transparent plastic cannula end of the Mix2Vial™ firmly through the stopper of the concentrate (Wilate) vial (Fig. 3). The diluent will be drawn into the concentrate (Wilate) vial by the vacuum.


Fig. 4

5) With both vials still attached, gently swirl the product vial to ensure the product is fully dissolved to a clear solution. Once the contents of the Wilate vial are completely dissolved, firmly hold both the transparent and blue parts of the Mix2Vial™. Unscrew the Mix2Vial™ into two separate pieces (Fig. 4) and discard the empty diluent vial and the blue part of the Mix2Vial™.

- The powder should be reconstituted only directly before injection. As Wilate contains no preservatives, the solution should be used immediately after reconstitution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- The filtered solution is clear or slightly opalescent, colourless or slightly yellow. If the concentrate fails to dissolve completely or an aggregate is formed, the preparation must not be used.

Instructions for Injection:

1. With the Wilate vial still upright, attach a plastic disposable syringe to the Mix2Vial™ (transparent plastic part). Invert the system and draw the reconstituted Wilate into the syringe.
2. Once Wilate has been transferred into the syringe, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and detach the Mix2Vial™ from the syringe. Discard the Mix2Vial™ (transparent plastic part) and empty Wilate vial.
3. Clean the intended injection site with an alcohol swab.
4. Attach a suitable infusion needle to the syringe.
5. Inject the solution intravenously at a slow speed of 2-4 mL/minute.

- As a precautionary measure, the patient's pulse rate should be measured before and during the injection. If a marked increase in the pulse rate occurs, the injection speed must be reduced or the administration must be interrupted.
- Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

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

3 DOSAGE FORMS AND STRENGTHS

Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:

- 500 IU VWF:RCo and 500 IU FVIII activities in 5-mL
- 1000 IU VWF:RCo and 1000 IU FVIII activities in 10-mL

4 CONTRAINDICATIONS

Wilate is contraindicated for patients who have known anaphylactic or severe systemic reaction to plasma-derived products, any ingredient in the formulation, or components of the container. For a complete listing of ingredients, see Description (11).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed upon use of Wilate, and may in some cases progress to severe anaphylaxis (including shock) with or without fever.[2] Closely monitor patients receiving Wilate and carefully observe for any symptoms throughout the infusion period.

Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, discontinue the administration immediately and contact the physician. Since inhibitor antibodies may occur concomitantly with anaphylactic reactions, patients experiencing an anaphylactic reaction should also be evaluated for the presence of inhibitors.[2]

5.2 Thromboembolic Risk

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity.[1] Monitor plasma levels of VWF:RCo and FVIII activities in patients receiving Wilate to avoid sustained excessive VWF and FVIII activity levels, which may increase the risk of thrombotic events.

5.3 Inhibitor Formation

Patients with VWD, especially type 3 patients, may potentially develop neutralizing antibodies (inhibitors) to VWF. If a patient develops inhibitor to VWF (or FVIII), the condition will manifest itself as an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, perform an appropriate assay to determine if a VWF inhibitor is present. In patients with antibodies against VWF, VWF is not effective and infusion of this protein may lead to severe adverse events. Consider other therapeutic options for such patients. Physicians with experience in the care of patients with hemostatic disorders should direct their management.[3] In all such cases, it is recommended that a center specialized in bleeding disorders be contacted.

Since inhibitor antibodies may occur concomitantly with anaphylactic reactions, patients experiencing an anaphylactic reaction should also be evaluated for the presence of inhibitors.[2]

5.4 Infection Risk from Human Plasma

Wilate is made from human plasma. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent. There is also the possibility that unknown infectious agents may be present in such products. The risk that such products will transmit viruses has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses during manufacture. Despite these measures, such products may still potentially transmit disease. [4]

Record the batch number of the product every time Wilate is administered to a patient, and consider appropriate vaccination (against hepatitis A and B virus) of patients in regular/repeated receipt of Wilate. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Octapharma USA, Inc., telephone # 1-866-766-4860.

5.5 Monitoring and Laboratory Tests

Monitor plasma levels of VWF:RCo and FVIII activities in patients receiving Wilate to avoid sustained excessive VWF and FVIII activity levels, which may increase the risk of thrombotic events, particularly in patients with known clinical or laboratory risk factors.

Monitor for development of VWF and FVIII inhibitors. Perform assays to determine if VWF and/or FVIII inhibitor(s) is present if bleeding is not controlled with the expected dose of Wilate. [5]

6 ADVERSE REACTIONS

The most common adverse reactions to treatment with Wilate in patients with VWD have been urticaria and dizziness.
The most serious adverse reactions to treatment with Wilate in patients with VWD have been hypersensitivity reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trails of another drug and may not reflect the rates observed in clinical practice.

There were 92 VWD patients who received Wilate on 5676 occasions including clinical studies that involved prophylactic use, treatment on demand, surgery, and pharmacokinetics. Their safety data showed that the most common adverse reactions were urticaria and dizziness (each with 2 patients; 2.2%). There were also four patients (4.4%) who showed seroconversion for antibodies to parvovirus B19 not accompanied by clinical signs of disease. Seroconversion has not been reported since implementation of minipool testing of plasma used for the manufacture of Wilate.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during the post approval use of Wilate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

Post-marketing adverse reactions reported in patients treated for VWD include hypersensitivity reactions, dyspnea, nausea, vomiting, and cough.

7 DRUG INTERACTIONS

No interactions with other medicinal products are known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Wilate. It is also not known whether Wilate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Wilate should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

Wilate has not been studied in labor or delivery. It should be administered to VWF-deficient women at labor or delivery only if clearly indicated. [6]

8.3 Nursing Mothers

Wilate has not been studied in lactating women.

8.4 Pediatric Use

Eleven pediatric patients with VWD between 5 to 16 years of age (8 type 3, 1 type 2, 2 type 1) were treated with Wilate for 234 bleeding episodes (BEs) in clinical studies. These studies showed that 88% of the BEs were treated successfully in this population (Table 7). No dose adjustment is needed for pediatric patients as administered dosages were similar to those used in the adult population (Table 8).

8.5 Geriatric Use

Although some of the patients who participated in the Wilate studies were over 65 years of age, the number of patients was inadequate to allow subgroup analysis to support recommendations in the geriatric population.

11 DESCRIPTION

Wilate is a human plasma-derived, sterile, purified, double virus inactivated von Willebrand Factor/Coagulation Factor VIII Complex (Human). Wilate is supplied as a lyophilized powder for reconstitution for intravenous injection.

Wilate is labeled with the actual VWF:RCo and FVIII activities in IU per vial. The VWF activity (VWF:RCo) is determined using a manual agglutination method referenced to the current "WHO International Standard for von Willebrand Factor Concentrate". The FVIII activity is determined using a chromogenic substrate assay referenced to the current "WHO International Standard for Human Coagulation Factor VIII Concentrate". The assay methodologies are according to European Pharmacopoeia (Ph.Eur.).

Wilate contains no preservative. The diluent for reconstitution of the lyophilized powder is Water for Injection with 0.1% Polysorbate 80.

No albumin is added as a stabilizer. The resulting specific activity of Wilate is ≥ 60 IU VWF:RCo and ≥ 60 IU FVIII activities per mg of total protein.

The nominal composition of Wilate is as follows:

Component	Quantity/ 5 mL vial	Quantity/ 10 mL vial
VWF:RCo	500 IU	1000 IU
FVIII	500 IU	1000 IU
Total protein	≤ 7.5 mg	≤ 15.0 mg
Glycine	50 mg	100 mg
Sucrose	50 mg	100 mg
Sodium chloride	117 mg	234 mg
Sodium citrate	14.7 mg	29.4 mg
Calcium chloride	0.8 mg	1.5 mg
Water for injection	5 mL	10 mL
Polysorbate 80	1 mg/mL	1 mg/mL

Wilate is derived from large pools of human plasma collected in U.S. FDA approved plasma donation centers. All plasma donations are tested for viral markers in compliance with requirements of EU CPMP and FDA guidances. In addition, the limit for the titer of human parvovirus B19 DNA in the manufacturing pool is set not to exceed 10^4 IU/mL.

The product is manufactured from cryoprecipitate, which is reconstituted in a buffer and treated with aluminum hydroxide followed by two different chromatography steps, ultra- and diafiltration, and sterile filtration. The manufacturing process includes two virus inactivation steps, namely, treatment with an organic solvent/detergent (S/D) mixture, composed of tri-n-butyl phosphate (TNBP) and Octoxynol-9, and a terminal dry heat (TDH) treatment of the lyophilized product in final container [at +100°C (212°F) for 120 minutes at a specified residual moisture level of 0.7 – 1.6%]. In addition, the ion-exchange chromatography step utilized during Wilate manufacturing also removes some viruses [7]. The mean cumulative virus reduction factors of these steps are summarized in Table 2.

Table 2 Virus Reduction During Wilate Manufacturing

Production Step	Virus Reduction Factor [log_{10}]						
	Enveloped Viruses				Non-Enveloped Viruses		
	HIV-1	SBV	BVDV	PRV	REO 3	HAV	PPV
S/D Treatment	> 7.52	> 8.63	> 4.18	> 8.54	na	na	na
Ion-Exchange Chromatography	nd	nd	nd	nd	1.86 - 2.33	1.16 - 1.93	3.29
TDH Treatment	4.91 - > 5.79	> 5.51	nd	3.99 - 4.87	> 6.40	> 5.69	2.57 - 4.12
Global Reduction Factor	> 12.43 - > 13.31	> 14.14	> 4.18	> 12.53 - > 13.41	> 8.26 - > 8.73	> 6.85 - > 7.62	5.86 - 7.41

na: not applicable
nd: not done (S/D reagents present)
HIV-1: Human Immunodeficiency Virus - 1
SBV: Sindbis Virus
BVDV: Bovine Viral Diarrhea Virus
PRV: Pseudorabies Virus
REO 3: Reovirus Type 3
HAV: Hepatitis A Virus
PPV: Porcine Parvovirus

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VWF and FVIII are normal constituents of human plasma. VWF is a multimeric protein with two key functions. It is an adhesive molecule, which mediates the binding between platelets and damaged sub-endothelial tissues. It is also a carrier protein, involved in the transport and stabilization of FVIII. Patients suffering from VWD have a deficiency or abnormality of VWF. This reduction in VWF concentration in the bloodstream result in a correspondingly low FVIII activity and an abnormal platelet function thereby resulting in excessive bleeding. [8]

The VWF in Wilate is derived from normal human plasma and is expected to behave in the same way as endogenous VWF. Thus, administration of VWF allows correction of the hemostatic abnormalities in VWD patients at two levels:

- The 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 hemostasis, as shown by the shortening of the bleeding time. This effect occurs immediately.
- The VWF induces correction of the associated FVIII deficiency in VWD. Administered intravenously, VWF binds endogenous FVIII (which is produced normally by the patient), and by stabilizing this factor, avoids its rapid degradation. This action is slightly delayed. However, administration of a FVIII-containing VWF preparation like Wilate rapidly restores the FVIII activity level to normal.[8]

12.2 Pharmacodynamics

There have been no specific pharmacodynamic studies on Wilate.

12.3 Pharmacokinetics

An open label, prospective, randomized, controlled, two-arm cross-over Phase 2 study with Wilate and a comparator product was conducted at 6 sites in the US. In this study, pharmacokinetic (PK) profiles of Wilate were determined by FVIII activity, VWF:RCo, VWF:Ag, and VWF:CB.

Each of twenty-two subjects with inherited VWD [Type 1, n=6; Type 2, n=9 (6 Type 2A, 1 Type 2B, and 2 Type 2M); and Type 3, n=7] received an intravenous bolus dose of Wilate containing approximately 40 IU of VWF:RCo/kg BW. Twenty subjects completed the study as per protocol. PK parameters of VWF:RCo and FVIII are summarized in Table 3 and Table 4, respectively.

Table 3 Pharmacokinetic Parameters of VWF:RCo:mean ± SD (range)

Parameters	VWD type I (n = 5)	VWD type II (n = 9)	VWD type III (n = 6)	Total (n = 20)
C_{max} (IU/dL)	74 ± 13 (62 - 91)	77 ± 18 (40 - 100)	79 ± 13 (65 - 102)	76 ± 15 (40 - 102)
$AUC_{(0\text{-}inf)}$ (IU*hr/dL)	1633 ± 979 (984 - 3363)	1172 ± 421 (571 - 1897)	995 ± 292 (527 - 1306)	1235 ± 637 (527 - 3363)
Half-life (hrs)	24.7 ± 17.9 (11.2 - 48.5)	15.3 ± 6.3 (6.0 - 26.4)	9.1± 2.6 (5.7 - 12.9)	15.8 ± 11.0 (5.7 - 48.5)
CL (mL/h/kg)	3.1 ± 1.1 (1.2 - 4.1)	4.1 ± 1.7 (2.0 - 7.1)	4.2 ± 1.4 (3.0 - 6.6)	3.9 ± 1.5 (1.2 - 7.1)
Vss (mL/kg)	81.7 ± 38.5 (15.3 - 74.2)	76.6 ± 35.4 (45.3 - 158.8)	49.4 ± 16.7 (29.7 - 67.1)	69.7 ± 33.2 (29.7 - 158.8)
MRT (hrs)	32.7 ± 25.8 (15.3 - 74.2)	19.7 ± 5.6 (9.9 - 27.1)	11.9 ± 2.9 (9.2 - 15.9)	20.6 ± 14.8 (9.2 - 74.2)
Recovery (%IU/kg)	1.8 ± 0.2 (1.5 - 2.0)	1.8 ± 0.5 (1.0 - 2.4)	2.1 ± 0.3 (1.8 - 2.6)	1.9 ± 0.4 (1.0 - 2.6)

C_{max} = peak concentration; AUC = area under curve; CL = clearance; Vss = volume of distribution at steady state; MRT = mean residence time

The PK parameters reported in Table 3 are based on VWF:RCo values obtained using a modified Behring Coagulation System (BCS) analytical method. The modified BCS was used because of its validated lower variability compared to the standard BCS. The measured concentrations (IU VWF:RCo/mL) are higher by the modified BCS than by the standard BCS analytical method which is used in some clinical laboratories. Dose adjusted C_{max} and AUC determined by this modified BCS method are approximately 1.5 times higher than those by the standard BCS method. No difference has been found in incremental recovery.

Table 4 Pharmacokinetic Parameters of FVIII:C: mean ± SD (range) - chromogenic

Parameters	VWD type I (n = 5)	VWD type II (n = 8*)	VWD type III (n = 6)	Total (n = 19*)
C_{max} (IU/dL)	117.1 ± 12.1 (103 - 135)	147.2 ± 32.6 (102 - 206)	120 ± 23 (91 - 148)	112 ± 23 (59 - 148)
$AUC_{(0\text{-}inf)}$ (IU*hr/dL)	1187 ± 382 (523 - 1483)	1778 ± 1430 (544 - 4821)	2670 ± 854 (1874 - 3655)	2290 ± 1045 (464 - 4424)
Half-life (hrs)	17.5 ± 4.9 (10.9 - 23.8)	23.6 ± 8.3 (12.6 - 34.7)	16.1 ± 3.1 (11.8 - 20.1)	19.6 ± 6.9 (10.9 - 34.7)
CL (mL/h/kg)	4.4 ± 3.7 (2.5 - 11.0)	2.5 ± 0.9 (1.2 - 3.5)	2.0 ± 0.6 (1.4 - 2.8)	2.9 ± 2.1 (1.2 - 11.0)
Vss (mL/kg)	95.0 ± 53.8 (57.1 - 190.0)	79.5 ± 23.1 (52.8 - 116.2)	44.2 ± 10.4 (31.8 - 57.1)	72.4 ± 36.2 (31.8 - 190.0)
MRT (hrs)	24.1 ± 5.5 (17.2 - 31.5)	35.1 ± 14.2 (17.5 - 61.6)	23.0 ± 3.7 (18.0 - 27.7)	28.4 ± 11.1 (17.2 - 61.6)
Recovery (%IU/kg)	1.9 ± 0.5 (1.1 - 2.5)	2.2 ± 0.4 (1.6 - 2.8)	2.5 ± 0.5 (2.0 - 3.0)	2.2 ± 0.5 (1.1 - 3.0)

*One subject with implausible long half-life is not included in the summary table, except for recovery result.
C_{max} = peak concentration; AUC = area under curve; CL = clearance; Vss = volume of distribution at steady state; MRT = mean residence time

Effect of age and VWD type on the pharmacokinetics of Wilate:
Due to small sample size (in age or VWD type subsets) and high PK variability, it is difficult to conclude if age or type of VWD had any impact on the pharmacokinetics of Wilate.

Effect of gender on the pharmacokinetics of Wilate:
Based on PK data of Wilate from 8 males and 12 females, it appears that the females (4.35 ± 1.54 mL/hr/kg) had higher clearance of VWF:RCo than the males (3.16 ± 1.19 mL/hr/kg). The clinical significance of this finding is not known.

14 CLINICAL STUDIES

Clinical efficacy of Wilate in the control of bleeding in patients with VWD was determined in four prospective clinical studies. This included treatment of 1068 bleeding episodes (BEs). Data were obtained from 70 VWD patients, of which 37 were type 3. BEs are summarized in Table 5. The treated BEs were analyzed for efficacy using a set of objective criteria in addition to a subjective 4-point hemostatic efficacy scale (excellent, good, moderate and none). In assessing the efficacy using these objective criteria, the treatment of a bleeding episode was classified as a success only if none of the criteria listed below was fulfilled:

- the episode was additionally treated with another VWF-containing product (excluding whole blood),
- the patient received a blood transfusion during the episode,
- follow-up treatment with a daily dosage of Wilate that was equal or more than 50% (≥ 50%) above the initial dose (for bleeding episodes with more than 1 day of treatment),
- treatment duration of more than 4 days (> 4 days) in cases of severe bleeding (other than gastrointestinal),
- treatment duration of more than 3 days (> 3 days) in cases of moderate bleeding (other than gastrointestinal),
- treatment duration of more than 2 days (> 2 days) in cases of minor bleeding (other than gastrointestinal),
- the last efficacy rating of the bleeding episode was 'moderate' or 'none'.

Among the 70 VWD patients administered Wilate in clinical studies (excluding the PK study), 45 of them received on demand treatment for BEs. Using the above objective criteria, corresponding efficacy for each bleeding event was rated as being successful in 84% of the episodes. In these 45 patients with BEs, 93% of the successfully treated BEs occurred in VWD type 3 patients (n=25).

Table 5 Proportion of successful treatments of bleeding episodes with Wilate (n=45)

			95% CI	
Episodes*	Successful	% Successes	Lower CL	Upper CL
1068	898	84.1	81.8	86.2

*A "bleeding episode" may involve bleeding at multiple sites in this analysis.

The dosing information for the 972 successfully treated "bleeding episodes" (1423 infusions) for regional bleeding is summarized in Table 6. **For the purpose of assigning success/failure to regional bleeding that occurred at the same time, the bleeding at different sites over the same time span would be counted as separate BEs. Thus, the number of these "episodes" would be different from that in the overall evaluation for success/failure of Wilate in the treatment of bleeding episodes in Table 5.**

Table 6 Administered dosages (VWF:RCo in IU/kg) in bleeding episodes* successfully treated with Wilate: Mean ± SD (Range) (n=45)

Location	All Doses considered		Initial Dose		Subsequent Doses	
	# of infusions	Dose: Mean ± SD (Range)	# of infusions	Dose: Mean ± SD (Range)	# of infusions	Dose: Mean ± SD (Range)
Joints	801	26 ± 12 (7 - 69)	542	28 ± 13 (7 - 69)	259	21 ± 10 (7 - 60)
Epistaxis	132	24 ± 11 (8 - 78)	91	25 ± 10 (13 - 78)	41	22 ± 14 (8 - 77)
GI Tract	125	40 ± 20 (9 - 76)	64	43 ± 19 (9 - 76)	61	36 ± 21 (9 - 76)
Oral	41	26 ± 14 (8 - 80)	33	27 ± 14 (10 - 80)	8	24 ± 18 (8 - 60)
Gynecologic	87	27 ± 14 (9 - 77)	52	28 ± 17 (12 - 77)	35	26 ± 9 (9 - 52)
Other**	237	23 ± 12 (10 - 95)	189	24 ± 12 (12 - 95)	48	20 ± 13 (10 - 95)

*For the purpose of this analysis for regional bleeding, bleeding at each site is counted as a separate "episode".
**"Other" Includes mostly muscle bleeds, hematuria, ecchymosis, hematoma and other miscellaneous sites of bleeding

The majority of BEs were treated for 1-3 days. In patients with GI bleeds, the duration for product use to control bleeding could be much longer (up to 7 days).

For pediatric patients (≤16 yrs), a summary of the number of BEs treated and corresponding objective efficacy ratings are provided in Table 7.

Table 7 Efficacy in bleeding episodes in pediatric population (5 to 16 yrs) (n=11) – Proportion of successful treatments of bleeding episodes with Wilate

			95% CI	
Episodes*	Successful	% Successes	Lower CL	Upper CL
234	205	87.6	82.7	91.5

*A "bleeding episode" may involve bleeding at multiple sites in this analysis.

The dosing information for the 211 successfully treated bleeding episodes (289 infusions) is summarized in Table 8. **Multiple bleeding sites are counted as separate episodes.**

Table 8 Administered dosages (VWF:RCo in IU/kg) in bleeding episodes* successfully treated with Wilate in pediatric population (5 to 16 yrs) (n=11): Mean ± SD (Range)

Location	All Doses considered		Initial Dose		Subsequent Doses	
	# of infusions	Dose: Mean ± SD (Range)	# of infusions	Dose: Mean ± SD (Range)	# of infusions	Dose: Mean ± SD (Range)
Joints	158	30 ± 13 (12 - 69)	117	32 ± 13 (14 - 69)	41	25 ± 9 (12 - 62)
Epistaxis	30	27 ± 14 (12 - 77)	25	25 ± 10 (14 - 52)	5	37 ± 25 (12 - 77)
GI Tract	1	22 (N/A)	1	22 (N/A)	0	N/A
Oral	23	25 ± 8 (16 - 52)	21	24 ± 8 (16 - 52)	2	25 ± 13 (16 - 35)
Gynecologic	58	27 ± 13 (12 - 69)	33	27 ± 16 (12 - 69)	25	26 ± 8 (12 - 52)
Other*	19	25 ± 7 (16 - 37)	14	27 ± 7 (19 - 37)	5	19 ± 4 (16 - 26)

*For the purpose of this analysis for regional bleeding, bleeding at each site is counted as a separate "episode".
**"Other" Includes mostly muscle bleeds, hematuria, ecchymosis, hematoma and other miscellaneous sites of bleeding

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16 HOW SUPPLIED/STORAGE AND HANDLING

NDC Number	Size	Protein Amount
67467-181-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
67467-181-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

- Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs.
- Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.
- Components used in the packaging of Wilate contain no latex.

Shelf life

- Store Wilate for up to 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Do not freeze.
- Do not use after the expiration date.
- Store in the original container to protect from light.
- Reconstituted the Wilate powder only directly before injection. Use the solution immediately after reconstitution. Use the reconstituted solution on one occasion only, and discard any remaining solution.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician [*see Warnings and Precautions (5.1)*].
- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities. [*see Warnings and Precautions (5.2)*].
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.[2] [*see Warnings and Precautions(5.3)*].
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded [*see Warnings and Precautions (5.4)*].

Manufactured by:
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U.S. License No. 1646

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