Clinical Research & Development

wilate®

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

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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 document the safety and tolerability of wilate® for prophylaxis and treatment of bleeding in VWD, incl. surgeries

Secondary objective:
Secondary objective is to document the efficacy of wilate® in the treatment of acute bleeding, in the prophylaxis of VWD and in interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).

Population:
VWD patients of any gender, age, or VWD type, previously treated (PTPs) or previously untreated patients (PUPs).

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 efficacy of wilate® in prevention and/or treatment of bleeding episodes and in surgical procedures 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 recommended assessment, this study will observe development of inhibitors against VWF in response to wilate® treatment (ELISA). Inhibitor assessment should be performed before and after first wilate® application, and then every 3 months during the full course of observation.

Thrombogenicity
As recommended assessment, 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 should be performed before and after 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). It is used for the treatment and prophylaxis of bleedings in patients with haemophilia A and in the treatment and prophylaxis of bleeding in patients with von Willebrand disease, incl. major surgeries.

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).

wilate® has been shown to be efficacious and safe in prophylaxis and treatment of bleedings, incl. major surgeries in patients with all types of VWD in several GCP-clinical trials.

2 **Purpose of the surveillance**

This post-marketing surveillance is designed to ensure long-term consistency between data from the pre-licensure clinical studies (where by definition only a limited number of subjects is included) and 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 support the optimal use of wilate® thus bring benefit for both physicians and patients.
3 Objectives

3.1 Primary objective
Primary objective is to document the safety and tolerability of wilate® for prophylaxis and treatment of bleeding in VWD, incl. surgeries.

3.2 Secondary objective(s)
Secondary objective is to document the efficacy of wilate® in the treatment of acute bleeding, in the prophylaxis of VWD and in interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).

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) applied in the treatment of acute bleeding, in the prophylaxis of VWD and in interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).

5 Surveillance design and duration
This is open-label, prospective, multinational, post-marketing, non-interventional observational surveillance. The observation is expected to start within 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 with acute bleeding, subjects on regular VWD prophylactic treatment and subjects undergoing interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).
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 a available a s a yophilised powder w ith a special solvent (water for injection containing 0.1% Polysorbate 80) in the following strengths: 450 IU/vial (+ 5 ml solvent), 900 IU/vial (+ 10 ml solvent), containing nominally 450 IU FVIII:C/400 VWF:RCo or 900 IU FVIII:C/800 VWF:RCo per vial, respectively. And in the new strengths, not yet approved in all countries: 500 IU/vial (+ 5 ml solvent), 1000 IU/vial (+ 10 ml solvent), containing nominally 500 IU F VIII:C/500 V WF: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 20-50 IU/kg body weight. This will increase the FVIII:C and VWF:RCo plasma level by about 30-100%.

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 patients 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.

In case of surgical procedures in patients with suspected risk for thrombotic events, prophylaxis against venous thromboembolism should be instituted, according to the current recommendations.

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 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.

### 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 his 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.

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### 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>
<thead>
<tr>
<th>Visits</th>
<th>Observation Entry</th>
<th>Subsequent Visits</th>
<th>Terminal Visit</th>
<th>Interventional treatment ¹</th>
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<tr>
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<td></td>
<td></td>
<td>X¹B</td>
</tr>
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<td>Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X¹B, A</td>
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<td></td>
<td>X¹B</td>
</tr>
<tr>
<td>Response to DDAVP</td>
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<td></td>
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<td>X¹B</td>
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<tr>
<td>Patient general condition</td>
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<td></td>
<td></td>
<td>X¹B</td>
</tr>
<tr>
<td>Bleeding tendency with severity</td>
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<td></td>
<td></td>
<td>X¹B</td>
</tr>
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<td></td>
<td>X¹B, D, A</td>
</tr>
<tr>
<td>Previous treatment with FVIII / VWF</td>
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<td></td>
<td></td>
<td>X¹B</td>
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<tr>
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<td>X</td>
<td>X</td>
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<td></td>
<td>X¹0</td>
<td>X¹0, X¹B</td>
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<tr>
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<td>X</td>
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<td>X¹B, D, A</td>
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<td>X</td>
<td></td>
<td>X¹D, A</td>
</tr>
</tbody>
</table>

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 anbd.

B - Before intervention
D - During intervention
A - After intervention
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 non-interventional, observational study design strict pre-defined visit and time schedule is excluded, however 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, 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®, it is recommended that the physician records 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 of interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.), 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, a 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 efficacy 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 the ir parents should assess the efficacy 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 cover laboratory tests performed in a 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 on wards every 3 months during the full course of observation by the same schedule (1h, 3h and 24 hour after application). It is also recommended to perform thrombogenicity assessment for all interventional procedures.

Octapharma will cover laboratory tests performed in a central laboratory and all shipment costs.

8.6 Efficacy

Assessment of efficacy of wilate® 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 an efficacy comparison of wilate® with previously applied F VIII/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 Assessments in case of the treatment of acute bleeding and VWD prophylaxis

8.7.1 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 a namestic 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 F VIII/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 observations 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 is 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 undesirable sign, symptom, medical condition, or abnormal laboratory result occurring after starting the wilate® application which is suspected to be related to its administration.
**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 a 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: G ASD, 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