Efficacy and Safety of wilate® in patients with von Willebrand disease – a post marketing surveillance study
wilate® at a glance

- High purity VWF/FVIII-complex
- High-quality VWF
- Double virus inactivated
- Absence of potentially thrombotic FVIII-accumulation after multiple dosing
- Excellent clinical efficacy, safety and tolerability
- New level of convenience
Why participate in WIL-20?

wilate® is a new generation, high-purity, double virus-inactivated concentrate of freeze-dried von Willebrand factor (VWF) and Factor VIII (FVIII) and has been developed specifically for the treatment of VWD.

The production process is optimized to gain a ratio of VWF to FVIII close to the physiological ratio of 1:1 and to maintain a high quality and fully functional VWF. wilate®’s high-quality VWF includes intact VWF triplet structure avoiding increased amounts of proteolyzed VWF as well as the presence of high molecular weight VWF-multimers. wilate® was first launched in 2005 and has shown to be highly effective and safe in on-demand treatment of acute bleeding episodes, prophylaxis and during surgery.¹, ²

Although wilate® has proven an excellent safety and efficacy profile in several trials, it is important to document a larger population of patients in routine use to cover all important aspects of therapy with wilate®.⁴

With your participation, important additional data on wilate’s product safety including immunogenicity, tolerability and efficacy will be documented based upon a larger patient population. This will contribute to further treatment improvements for your patients in the future.

WIL-20 is designed according to the latest EMEA guidelines.⁵

Objectives of WIL-20

This prospective post marketing surveillance is designed to evaluate and document wilate’s haemostatic efficacy and safety in the treatment of acute bleedings, in long-term prophylaxis and in interventional procedures such as surgery, dental care and invasive diagnostic measures. 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. Additionally, safety and tolerability of wilate® during on-demand treatment, prophylaxis and surgery will be assessed.

To further broaden the range of documentation on inhibitor development in VWD patients this trial includes a characterization of inhibitor status to trace the potential development of VWF-inhibitors during the treatment.

Further, coagulation parameters prothrombin fragments 1 and 2, and D-Dimer shall be investigated to collect more information on the theoretical risk of thrombogenic events during therapy, which have not been reported for wilate® so far.

Primary Objectives

- Assessment of efficacy via hemostatic efficacy scale (4 point)

Secondary Objectives

- Assessment of safety and tolerability via adverse drug reaction records
- Observation of inhibitory antibodies development
- Observation of coagulation parameters prothrombin fragments 1 and 2 and D-Dimer
Who will be documented in this surveillance?

- Patients with congenital VWD of any type, age, gender and severity in need of replacement therapy with VWF/FVIII concentrate:
  - previously untreated patients starting on wilate® treatment (on-demand, prophylaxis, surgery)
  - previously treated patients with either wilate® or switching to wilate® from other medications
- Patients with negative inhibitor testing to VWF
- Patients must be HIV negative or have a viral load of <200 particles/µl (~400’000 copies/ml)

Dosage and Treatment Schedule

Dosage and schedule of treatment for individual patients are always at the discretion of the treating physician and should be based on the recommendations as given in the product information leaflet.

For patients starting with therapy, dosage is recommended with reference to predominant bleeding sites.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Mucosal, joints, menorrhagia:</td>
<td>30 IU/kg body weight; 2-3 times/week</td>
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<tr>
<td>Gastrointestinal bleedings:</td>
<td>40 IU/kg body weight; 2-3 times/week</td>
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</tbody>
</table>

wilate® SPC

“Usually, about 20 to 50 IU wilate/kg BW are necessary to achieve adequate haemostasis.”

Design and Duration of WIL-20

- Open-label, prospective, multicentre, multinational, post-marketing, observational, non-interventional surveillance
- Observation period is 24 months
Study procedures in WIL-20

Prior to entry:

- Classification of VWD type and residual activity levels of FVIII / VWF should have been assessed
- Medical history / anamnesis will be documented and prior VWD specific treatment will be recorded
- Bleeding history during 6 months prior to entry to WIL-20 will be documented
- Monitoring of VWF Inhibitor titre will be documented via a central laboratory before entry to WIL-20 (can be continued for full course of the surveillance)
- Coagulation parameters prothrombin fragments and D-dimer will be tested before entry to WIL-20 and during the full course of the surveillance

<table>
<thead>
<tr>
<th>Measure</th>
<th>Observation at study entry</th>
<th>First exposure day</th>
<th>Subsequent visit</th>
<th>Final visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anamnesis / medical and bleeding history</td>
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<tr>
<td>VWD classification, residual FVIII/VWF testing</td>
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<tr>
<td>Inhibitor testing</td>
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<tr>
<td>Thrombogenicity testing</td>
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<td>Laboratory evaluation</td>
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<tr>
<td>Concomitant medication</td>
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<tr>
<td>FVIII/VWF measurements on application</td>
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<tr>
<td>Documentation of interventional procedures and bleeding episodes (when occurring)</td>
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<tr>
<td>Assessment of efficacy</td>
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<td>Adverse drug reactions (patients diary)</td>
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</table>
About wilate®

wilate® is a double virus inactivated, albumin free, highly purified new generation VWF/FVIII concentrate from human plasma. It is virus inactivated by solvent/detergent treatment and terminal dry heating process.

The production process has been optimized to preserve a ratio of VWF to FVIII close to the physiological ratio of 1:1. By using five purification steps during manufacturing, impurities such as the VWF-cleaving protease ADAMTS13 are present only in trace amounts. This ensures a minimum of proteolized VWF in the final product and maintains an intact VWF-triplet structure.

wilate® also contains high molecular weight VWF-multimers with a pattern close to normal human plasma.

Efficacy and safety of wilate® have been proven in several large prospective GCP trials with more than 1000 treated acute bleedings.⁴

<table>
<thead>
<tr>
<th>Site of bleeding</th>
<th>No. of bleeding episodes</th>
<th>Mean dose per infusion [FVIII IU/kg]</th>
<th>Mean no. of treatment days</th>
<th>Excellent/Good Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints</td>
<td>565</td>
<td>28.0</td>
<td>1.67</td>
<td>99%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>94</td>
<td>27.0</td>
<td>1.52</td>
<td>94%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>145</td>
<td>44.1</td>
<td>4.23</td>
<td>82%</td>
</tr>
<tr>
<td>Oral</td>
<td>34</td>
<td>26.3</td>
<td>1.82</td>
<td>94%</td>
</tr>
<tr>
<td>Gynaecologic</td>
<td>62</td>
<td>35.8</td>
<td>1.35</td>
<td>97%</td>
</tr>
<tr>
<td>Other</td>
<td>195</td>
<td>23.4</td>
<td>1.39</td>
<td>99%</td>
</tr>
<tr>
<td>Total</td>
<td>1095</td>
<td>29.3</td>
<td>1.93</td>
<td>96%</td>
</tr>
</tbody>
</table>

Tab.: More than 1000 treatments of acute bleedings documented in GCP trials. Of these 92% in Type 3 patients.
wilate® has been registered in Germany since February 2005 and has recently achieved approval in a total of 26 EU countries, Russia, Canada, Australia, Mexico and the US.

wilate® is supplied in a powdered form for reconstitution and intravenous injection. One vial with freeze-dried substance is reconstituted in a low volume of solvent, either 5 ml (wilate® 450 IU) or 10 ml (wilate® 900 IU).

The product must be stored in a refrigerator at 2–8°C in the original carton to protect the vials from light. Shelf life is 36 month. Do not freeze the product. The product can be stored at room temperature for two months but shelf life expires after this period at room temperature.

For further information on presentation, administration, dosage, route and duration of administration and storage conditions please refer to the local Summary of Product Characteristics, package insert, or contact your local Octapharma representative.

Octapharma supports this important initiative and is prepared to facilitate your participation in the program.

For more information on wilate® or the WIL-20 program, please contact your local Octapharma representative.

References
1. Octapharma AG (2008) SPC WILATE.
Octapharma, a Swiss-based company, is an independent, global plasma fractionation specialist. Its core business is the development, production and sale of high quality plasma derivatives. The company has grown to more than 3,900 employees in 28 countries since its founding in 1983. Octapharma owns five modern, state-of-the-art production facilities in Austria, France, Germany, Sweden and Mexico.

In the highly demanding market of lifesaving plasma products, company success is only possible through reliable product quality and a proven safety record.

Over the past six years, in addition to the plasma-based activities, Octapharma has dedicated increasing resources to recombinant product research and development based on the use of human cell lines. This unique approach sets Octapharma apart from other companies whose recombinant products are based on animal (murine) cells.

Octapharma respects donated human plasma as a scarce and valuable resource. By using leading edge, validated viral inactivation and purification technologies Octapharma aims to achieve the highest production yields and produce products with the highest possible safety margins.