wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

KERRI BORGESE

Switched from Humate-P® to wilate®

At 6 months of age, Kerri Borgese's mother noticed that her infant daughter was bruising just from sitting in a highchair. She alerted their pediatrician, who referred them to a hematologist. Shortly after, Kerri was diagnosed with severe, type 3 von Willebrand disease (VWD).

Despite her diagnosis, Kerri describes her childhood as normal—active, fun, and with few limitations. She credits her parents for doing a great job of making things as normal as possible. "I have an older and a younger sister (both are asymptomatic carriers), and I never felt like I was that different. I wore a helmet and knee pads for biking and sports, but for the most part I felt normal, and I think my parents did a really good job of making it that way."

- Throughout her childhood, Kerri was mostly prescribed Humate-P, and sometimes Alphanate®. Her bleeding was treated as needed (on-demand) for joint bleeds, nosebleeds, and sports injuries.
- With adolescence and adulthood, Kerri experienced heavy and prolonged menstrual bleeding, very common in women with VWD, and was treated more frequently and with higher doses to manage her symptoms.
- Last year (at age 25), Kerri switched to wilate—and with that, a much lower dose to manage her bleeds.

> "I was using so much Humate-P to control my bleeding. It was one of the reasons I wanted to switch. Today, I'm using much less with wilate."

Kerri Today | Living and Thriving with Type 3 VWD

Kerri takes great pride as a pediatric nurse, an avid runner, and a patient advocate. She has been managing her type 3 VWD with wilate for more than 6 months, and with great success. "I just feel a difference on wilate. My joints feel better. If I have an active bleed, it works really well."

Kerri recognizes that women, especially those in their teens, face challenges when it comes to getting information about menstrual bleeding in VWD. "It can be hard to manage. It's a trial and error process. It's definitely something we need more people talking about and raising awareness." To that end, she recommends that everyone living with severe VWD educate themselves about their specific symptoms—and then take control of their therapy. Kerri also recommends that people with severe VWD join the Severe von Willebrand's group on Facebook, which is dedicated to those living with severe type 3 VWD.

Indications and Usage

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated in children and adults with von Willebrand disease for on-demand treatment and control of bleeding episodes, and for perioperative management of bleeding. wilate is also indicated in adolescents and adults with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes, and for on-demand treatment and control of bleeding episodes.

Please see enclosed full Prescribing Information. Please see other side for Important Safety Information.

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

Low Recommended Dosing for All Types of VWD

wilate Offers Low Recommended Loading and Maintenance Dosing for Both Minor and Major Bleeding[1*]

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 to 24 hours[a]	VWF:RCo and FVIII activity trough levels of >30%
Major hemorrhages	40-60 IU/kg	20-40 IU/kg every 12 to 24 hours[a]	VWF:RCo and FVIII activity trough levels of >50%

BW = body weight.

*Based on the Recommended Dosing Guide for wilate®. See Dosage and Administration, section 2.1 of Full Prescribing Information.

[a] This may need to be continued for up to 3 days for minor hemorrhages and 5 to 7 days for major hemorrhages.

The Power of Balance for the Treatment of VWD

- A balanced 1:1 formulation of VWF/FVIII—similar to naturally occurring VWF and FVIII[1]
- Effective control of major and minor bleeding[2]
- Dual viral inactivation steps—solvent/detergent and dry heat treatments[1]
- Simple and convenient to use

Important Safety Information

wilate® is contraindicated in patients with known hypersensitivity reactions, including anaphylactic or severe systemic reactions to human plasma-derived products, any ingredient in the formulation, or components of the container. wilate is made from human plasma and carries the risk of transmitting infectious agents.

The most serious adverse reactions to treatment with wilate in patients with VWD were hypersensitivity reactions. The most common adverse reactions (≥1%) in patients with VWD were hypersensitivity reactions, urticaria, and dizziness. The most common adverse reaction to treatment with wilate in patients with hemophilia A was pyrexia. Seroconversions for antibodies to parvovirus B19 not accompanied by clinical signs of disease have been observed. Monitor plasma levels of FVIII activity to avoid sustained excessive FVIII levels, which may increase the risk of thromboembolic events. Development of neutralizing antibodies to FVIII and to VWF, especially in VWD type 3 patients, may occur.

Please see enclosed full Prescribing Information.

References: 1. wilate®, von Willebrand Factor/Coagulation Factor VIII Complex (Human) full prescribing information. Hoboken, NJ: Octapharma; rev 2019.
2. Berntorp E, et al. Haemophilia. 2009;15:122-130.

Date of preparation: 2/2020. WIL-0231-COT

octapharma®
For the safe and optimal use of human proteins

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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)

Lyophilized Powder for Solution for Intravenous Injection

Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

Indications and Usage (1)	09/2019
Dosage and Administration (2.1)	09/2019
Warnings and Precautions (5)	09/2019

INDICATIONS AND USAGE

WILATE is indicated in children and adults with von Willebrand disease for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

WILATE is indicated in adolescents and adults with hemophilia A for:
- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes (1)

DOSAGE AND ADMINISTRATION

For Intravenous Use Only

VWD
- Use the following formula to determine required dosage (2.1):
  Required IU = body weight (BW) in kg x desired VWF:RCo rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)
- Adjust dosage and duration of the substitution therapy depending on the severity of the VWD, on the location and extent of the bleeding, and on the patient's clinical condition (2.1)
- Dosing recommendations (2.1):

Type of Hemorrhages/ Surgery	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 trough levels of > 30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12-24 hours	VWF:RCo and FVIII activity trough levels of > 50%
Minor Surgeries (including tooth extractions)	30-60 IU/kg	15-30 IU/kg or half the loading dose every 12-24 hours for up to 3 days	VWF:RCo peak level of 50% after loading dose and trough levels of > 30% during maintenance doses
Major Surgeries	40-60 IU/kg	20-40 IU/kg or half the loading dose every 12-24 hours for up to 6 days or more	VWF:RCo peak level of 100% after loading dose and trough levels of > 50% during maintenance doses

In order to decrease the risk of perioperative thrombosis, FVIII activity levels should not exceed 250%.

Hemophilia A
- One International Unit (IU) of factor VIII (FVIII) activity per kg body weight increases the circulating FVIII level by approximately 2 IU/dL (1.7 IU/dL for adolescents and 2.3 IU/dL for adults).
- Use the following formula to determine required dosage (2.1):
  Required IU = body weight (BW) in kg x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)
- Dosing for routine prophylaxis (2.1):

Patients	Dose (IU/kg)	Frequency of infusions
Adolescents and adults	20-40 IU/kg	Every 2 to 3 days

- Individualize dosage based on the patient's weight, type and severity of hemorrhage, FVIII level, presence of inhibitors and the patient's clinical condition (2.1).

DOSAGE FORMS AND STRENGTHS

WILATE is available as a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per single-use 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

Do not use in patients with known hypersensitivity reactions, including anaphylactic or severe systemic reaction, to human plasma-derived products, any ingredient in the formulation, or components of the container (4)

WARNINGS AND PRECAUTIONS
- Anaphylaxis and severe hypersensitivity reactions are possible (5.1).
- Thromboembolic events may occur. Monitor plasma levels of FVIII activity (5.2).
- Development of neutralizing antibodies to FVIII and to VWF, especially in VWD type 3 patients, may occur (5.3).
- WILATE is made from human plasma and carries the risk of transmitting infectious agents (5.4).

ADVERSE REACTIONS

The most common adverse reactions (≥ 1%) in clinical studies on VWD were hypersensitivity reactions, urticaria, and dizziness (6.1)

The most common adverse reaction (≥ 1%) in clinical studies in hemophilia A was pyrexia (fever) (6.1).

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: November 2019

FULL PRESCRIBING INFORMATION: CONTENTS*

FDA-APPROVED PATIENT LABELING

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

WILATE is indicated in children and adults with von Willebrand disease for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

WILATE is indicated in adolescents and adults with hemophilia A for:
- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes

2 DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

2.1 Dose
- Initiate treatment 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 is 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). One IU of VWF:RCo activity is equivalent to the quantity of VWF:RCo in one mL of normal human plasma. One IU of FVIII activity is defined by the quantity of Factor VIII in one mL of normal human pooled plasma. The ratio between VWF:RCo and FVIII activities in WILATE is approximately 1:1.

VWD
- Calculate the required dosage of VWF:RCo, based on the empirical finding that 1 IU VWF:RCo per kg body weight raises the plasma VWF activity by approximately 2% of normal activity or 2 IU/dL, using the following formula:

$$\text{Required IU} = \text{body weight (kg)} \times \text{desired VWF:RCo rise (\%) (IU/dL)} \times 0.5 \text{ (IU/kg per IU/dL)}$$

$$\text{Expected VWF:RCo rise (\% of normal)} = \frac{2 \times \text{administered IU}}{\text{body weight (kg)}}$$

- Adjust the dosage and frequency of administration according to the clinical effectiveness in the individual patient.

Dosing for Hemorrhages

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

Table 1 Dosing for Treatment of Minor and Major Hemorrhages in all VWD types

Type of Hemorrhages	VWF:RCo and FVIII Activity Trough Levels (% of normal)	Loading Dosage (IU VWF:RCo/kg body weight)	Maintenance Dosage (IU VWF:RCo/kg body weight)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor	>30	20-40	20-30	Repeat as needed 12-24	Up to 3 days
Major	>50	40-60	20-40	Repeat as needed 12-24	Up to 5-7 days

- Adjust the dose according to the extent and location of bleeding and the patient's clinical condition. In VWD type 3 patients, those with gastro-intestinal (GI) bleedings may require higher doses.
- Repeat doses as needed based upon repeat monitoring of appropriate clinical and laboratory measures.
- Perform appropriate laboratory tests on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

Dosing for Surgeries

A guide for dosing in minor and major surgeries is provided in Table 2.

Table 2 Dosing for Treatment in Minor and Major Surgeries in all VWD Types

Type of Surgery	Loading Dosage (IU VWF:RCo/kg body weight) (within 3 hours before surgery)	VWF:RCo Peak Levels (% of normal)	Maintenance Dosage (IU VWF:RCo/kg body weight)	VWF:RCo Trough Levels (% of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (including tooth extraction)	30-60	50	15-30 or half the loading dose	>30	12-24	Until wound healing achieved, up to 3 days
Major	40-60	100	20-40 or half the loading dose	>50	12-24 (at least 2 doses within first 24 hours after the start of surgery)	Until wound healing achieved, up to 6 days or more

In order to decrease the risk of perioperative thrombosis, FVIII activity levels should not exceed 250%.
Whereas table 2 provides a dosing range that is expected to provide the desired peak levels of VWF:RCo, the following is an example on how to calculate the loading dose based on a patient's individual IVR which is to be determined pre-surgery.
- Prior to surgery, measure incremental in vivo recovery (IVR) and assess baseline plasma VWF:RCo activity. The IVR for VWF:RCo provides the IU/dL rise per IU/kg body weight infused and can be measured and calculated as follows:
  - Measure plasma VWF:RCo at baseline
  - Infuse 60 IU VWF:RCo/kg of WILATE intravenously at time 0
  - Measure plasma VWF:RCo at 30 minutes after the infusion

  $IVR = (\text{Plasma VWF:RCo}_{30\ min} - \text{Plasma VWF:RCo}_{baseline})/60 IU\ kg$
- Calculation of the loading dose requires four values: the target peak plasma VWF:RCo level, the baseline VWF:RCo level, body weight (BW) in kilograms, and IVR. If the actual IVR calculation exceeds 2.5, use 2.5 to calculate the recommended loading dosing to avoid under-dosing. If IVR is not available, a standardized dose can be calculated based on an assumed VWF:RCo IVR of 2.0 U/dL per IU/kg of WILATE administered.

  Example:

  Assumption: Baseline VWF:RCo value = 10 IU/dL, and VWF:RCo target level = 100 IU/dL = Δ 90 IU/dL

  Assumption: Patient's weight = 75 kg, patient's IVR = 1.8 (IU/dL)/(IU/kg)

  $$\text{Loading Dose} = \frac{90 \text{ IU/dL} \times 75 \text{ kg}}{1.8 \text{ (IU/dL)/(IU/kg)}} = 3{,}750 \text{ IU VWF:RCo}$$

- When possible post surgery, perform appropriate laboratory tests on the patient's plasma once a day after surgery to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained. In order to decrease the risk of perioperative thrombosis, FVIII activity levels should not exceed 250%. [2]

Hemophilia A
- Calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by approximately 2% of normal activity or 2 IU/dL when assessed using the one stage clotting assay. Use the following formula to determine the required dose:

$$\text{Required IU} = \text{body weight (kg)} \times \text{desired Factor VIII rise (\%) (IU/dL)} \times 0.5 \text{ (IU/kg per IU/dL)}$$

$$\text{Expected Factor VIII rise (\% of normal)} = \frac{2 \times \text{administered IU}}{\text{body weight (kg)}}$$

- Dose and duration of therapy depend on the patient's weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors.

  Titrate dose and frequency to the patient's clinical response, individual needs, severity of deficiency, severity of hemorrhage, desired FVIII level, and presence of inhibitor, and the patient's clinical condition. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to WILATE.

Routine Prophylaxis

A guide for dosing WILATE for routine prophylaxis to reduce the frequency of bleeding is provided in Table 3. Exact dosing should be defined by the patient's clinical status and response.

Table 3 Dosing for Routine Prophylaxis

Patients	Recommended Dosage (IU/kg body weight)	Frequency of Infusions
Adolescents and adults	20-40 IU/kg	Every 2 to 3 days

Dosing for Hemorrhages

A guide for dosing in the treatment of hemorrhages is provided in Table 4.

Table 4 Dosing for Treatment of Hemorrhages

Type of Hemorrhages	Recommended dosage (IU/kg body weight)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor	30-40	Repeat every 12-24 hours	At least 1 day, until the hemorrhage has resolved
Moderate	30-40	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved
Major	35-50	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved
Life-threatening	35-50	Repeat every 8-24 hours	Until threat has resolved

- Monitoring parameters
  - Monitor plasma FVIII levels periodically to evaluate individual patient response to the dosage regimen.
  - If dosing studies have determined that a particular patient exhibits a lower/higher than expected response and shorter/longer half-life, adjust the dose and the frequency of dosing accordingly
  - Failure to achieve the expected FVIII:C level or to control bleeding after an appropriately calculated dosage may be indicative of the development of an inhibitor (an antibody to FVIII:C). Quantitate the inhibitor level by appropriate laboratory procedures and document its presence. Treatment with WILATE in such cases must be individualized.

2.2 Preparation and Reconstitution
- 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.
- Reconstitute the powder only directly before injection. Because WILATE contains no preservatives, use the solution immediately after reconstitution.

Instructions for Reconstitution:

1) Warm the concentrate (WILATE) and Diluent in the closed vials up to room temperature. If a water bath is used for warming, avoid water contact with the rubber stoppers 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.

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, remove the outer package from the Mix2Vial™, leaving the Mix2Vial™ attached firmly to the diluent vial (Fig. 2).

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. With both vials still attached, immediately start swirling the concentrate (WILATE) vial to ensure the powder is fully saturated. A slight whirlpool is formed by swirling. In order to avoid foaming, please do not shake the vial.

5) After 30 seconds, 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™. Continue swirling until the powder in the WILATE vial has completely dissolved. This process may take several minutes.

The final solution is clear or slightly opalescent, colorless or slightly yellow. If the concentrate fails to dissolve completely or an aggregate is formed, do not use the preparation.

2.3 Administration

For intravenous injection after reconstitution only
1. Inspect final solution visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
2. Do not mix WILATE with other medicinal products or administer simultaneously with other intravenous preparation in the same infusion set.
3. 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.
4. 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.
5. Clean the intended injection site with an alcohol swab.
6. Attach a suitable infusion needle to the syringe.
7. Measure the patient's pulse rate before and during the injection. If a marked increase in the pulse rate occurs, reduce the injection speed or interrupt the administration.
8. Inject the solution intravenously at a slow speed of 2-4 mL/minute.
9. Dispose unused product or waste material in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

WILATE is available as a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per single-use 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 in patients with known hypersensitivity reactions, including anaphylactic or severe systemic reactions, to human plasma-derived products, any ingredient in the formulation *[see Description (11)], or components of the container.*

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions may occur with WILATE. Signs and symptoms 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, and wheezing that may progress to severe anaphylaxis (including shock) with or without fever.[3] Closely monitor patients receiving WILATE and observe for any symptoms throughout the infusion period.

Because inhibitor antibodies may occur concomitantly with anaphylactic reactions, evaluate patients experiencing an anaphylactic reaction for the presence of inhibitors.[3] *[see Warnings and Precautions (5.3)]*

5.2 Thromboembolic Events

In VWD, continued treatment using a FVIII-containing VWF product may cause an excessive rise in FVIII activity [1], which may increase the risk of thromboembolic events. Monitor plasma levels of VWF:RCo and FVIII activities in patients receiving WILATE to avoid sustained excessive VWF and FVIII activity levels.

5.3 Neutralizing Antibodies

VWD
- Neutralizing antibodies (inhibitors) to FVIII and VWF in patients with VWD, especially type 3 patients, may occur. If a patient develops inhibitor to VWF (or to FVIII), the condition will manifest itself as an inadequate clinical response. Thus, if 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 whether a VWF inhibitor is present.
- In patients with antibodies against VWF, VWF is not effective and WILATE administration may lead to severe adverse events. Consider other therapeutic options for such patients.
- Because inhibitor antibodies may occur concomitantly with anaphylactic reactions, evaluate patients experiencing an anaphylactic reaction for the presence of inhibitors.[3] *[see Warnings and Precautions (5.1)]*

Hemophilia A
- Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained *[see Dosage and Administration (2.1)]*.
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of Wilate. Use Bethesda Units (BU) to report inhibitor levels.

5.4 Transmissible Infectious Agents

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 the product. The risk that WILATE 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, it may still potentially transmit disease. [5]

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., at 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 thromboembolism, particularly in patients with known clinical or laboratory risk factors.
- Monitor for development of VWF and FVIII inhibitors. Perform assays to determine whether VWF and/or FVIII inhibitor(s) is present if bleeding is not controlled with the expected dose of WILATE. [6]

6 ADVERSE REACTIONS

The most common adverse reactions to treatment with WILATE (≥ 1%) in patients with VWD were hypersensitivity reactions, urticaria, and dizziness. The most common adverse reactions to treatment with WILATE (≥ 1%) in previously treated patients with hemophilia A was pyrexia (fever).

Seroconversions for antibodies to parvovirus B19 not accompanied by clinical signs of disease have been observed.

The most serious adverse reactions to treatment with WILATE in patients with VWD and hemophilia A are hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trials Experience

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

A total of 157 VWD subjects (aged 1 to 83 years) received WILATE on 6769 occasions, including clinical studies that involved prophylactic use, treatment on demand, surgery, and pharmacokinetics. Of the 157 subjects, 32 (20.4%) had VWD type 1, 42 (26.8%) had VWD type 2, and 83 (52.9%) had VWD type 3; 96 (61.1%) subjects were female and 61 (38.9%) subjects were male. Overall, subjects received 11,222,241 IU of WILATE during 6355 exposure days. The most common adverse reactions were hypersensitivity reactions (3 subjects; 1.9%), urticaria and dizziness (each with 2 subjects; 1.3%). Five subjects (3.2%) showed seroconversion for antibodies to parvovirus B19 not accompanied by clinical signs of disease. Seroconversion for parvovirus B19 DNA has not been reported since implementation of minipool testing of plasma used for the manufacture of WILATE.

A total of 136 hemophilia A previously treated subjects (aged 11 to 66 years) received WILATE in 5 clinical studies that involved prophylactic use, treatment on demand, surgery and/or pharmacokinetics. All subjects were male. Overall, subjects received 19,317,004 IU of WILATE during 9001 exposure days. The most common adverse reaction was pyrexia (2 subjects; 1.5%). Further adverse reactions included pruritus, headache and sleeping disorder (1 subject; 0.75%). Two out of 55 subjects (3.6%) in the pivotal study of routine prophylaxis in severe hemophilia A had unexplained transient worsening of pre-existing thrombocytosis while on the study.

Immunogenicity

The immunogenicity of WILATE in VWD was specifically assessed in 97 subjects in 3 clinical studies in which subjects received 9,635,041 IU of WILATE during 5575 exposure days. No inhibitors of VWF were detected in these 3 studies. In one of 3 studies, which also assessed FVIII inhibitor development in 15 subjects, no inhibitors of FVIII were detected after administration of a total of 223,290 IU of WILATE over 419 administrations.

The immunogenicity of WILATE in previously treated subjects with hemophilia A was specifically assessed in a pooled analysis that selected from 136 previously treated subjects included in 5 clinical studies those subjects who had at least 150 exposure days at the time of enrollment into the study and had been treated for at least 50 exposure days and 6 months in the study. Eighty three subjects fulfilled these criteria. None of them developed inhibitors to Factor VIII, resulting in a rate of inhibitor development of 0% (95% CI, 0-4.35%).

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to WILATE with the incidence of antibodies to other products may be misleading.

6.2 Postmarketing 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 including dyspnea, hypertension, cough, chest discomfort, and abdominal pain have been reported in patients treated with WILATE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with WILATE use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with WILATE. WILATE was given to four subjects (3 type 3 and 1 type 2B) during labor and delivery in one clinical study. Two subjects underwent vaginal delivery (type 3) and two subjects had a cesarean section (type 3/type 2B). In this study all procedures were uneventful.

In the U.S. general population, regardless of drug exposure, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of WILATE in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WILATE and any potential adverse effects on the breastfed infant from WILATE or from the underlying maternal condition.

8.4 Pediatric Use

Eleven pediatric subjects 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. Treatment success was achieved in 88% of BEs *[see Clinical Studies (14)]*. Efficacy data during surgical prophylaxis were available for 13 pediatric VWD surgery subjects (3 subjects aged 0 to 2 years, 4 subjects aged 2 to 5 years, 3 subjects aged 6 to 12 years, and 3 subjects aged 12 to 16 years). Treatment success was achieved in 22 of 22 surgical procedures (17 minor and 5 major).

Five pediatric subjects with hemophilia A between 12 und 15 years of age were treated with WILATE for routine prophylaxis in one clinical study. The annualized bleeding rate was mean 0.4 (standard deviation 0.9), median 0 (range 0-2) *[see Clinical Studies (14)]*. During 6 months of prophylaxis, one patient experienced one traumatic BE, which was treated successfully with WILATE.

No dose adjustment is needed for pediatric patients as administered dosages were similar to those used in the adult population *[see Clinical Trials (14)]*.

8.5 Geriatric Use

Although some of the subjects who participated in the WILATE studies were over 65 years of age, the number of subjects 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. WILATE is supplied as a lyophilized powder for reconstitution for intravenous injection. The diluent for reconstitution of the lyophilized powder is Water for Injection with 0.1% Polysorbate 80.

WILATE contains no preservative. No albumin is added as a stabilizer. 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.). 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

Von Willebrand Factor/Coagulation Factor VIII complex is the active ingredient in WILATE. It is derived from large pools of human plasma collected in U.S. plasma donation centers. All plasma donations are tested for viral markers in compliance with requirements of EU CPMP and FDA guidance. 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 [8]. The mean cumulative virus reduction factors of these steps are summarized in Table 5.

Table 5 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

WILATE contains von Willebrand factor (VWF) and coagulation factor VIII (FVIII), constituents of normal plasma. VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; it also serves as a stabilizing carrier protein for the procoagulant protein FVIII, an essential cofactor in activation of factor X leading to formation of thrombin and fibrin. Patients suffering from VWD have a deficiency or abnormality of VWF. This reduction in VWF plasma concentration results in correspondingly low FVIII activity and abnormal platelet function, thereby resulting in excessive bleeding. [9] After administration, WILATE temporarily replaces missing VWF and FVIII that are needed for effective hemostasis. When infused into a patient with hemophilia A, FVIII binds to VWF in the patient´s circulation. Activated FVIII (FVIIIa) acts as a cofactor for activated factor IX (FIXa), accelerating the conversion of factor X to activated factor X (FXa). FXa converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Hemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of FVIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

12.2 Pharmacodynamics

There have been no specific pharmacodynamic studies on WILATE.

12.3 Pharmacokinetics

VWD

Pharmacokinetic (PK) profiles of WILATE were determined by FVIII activity, VWF:RCo, VWF:Ag, and VWF:CB obtained from an open label, prospective, randomized, controlled, two-arm cross-over study with WILATE and a comparator product conducted at 6 sites in the US. 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 body weight. Twenty subjects completed the study as per protocol. PK parameters for VWF:RCo and FVIII activities are summarized in Table 6 and Table 7, respectively.

The PK parameters reported in Table 6 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 with the standard BCS. 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 6 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

Table 7 Pharmacokinetic Parameters of FVIII activity: 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

Hemophilia A

The pharmacokinetics (PK) of WILATE were evaluated in 21 (16 adults and 5 pediatric subjects aged 12-15 years) previously treated patients (PTPs) with severe Hemophilia A within a prospective, open-label, multicenter clinical study. The PK parameters (Table 8) were based on plasma Factor VIII activity measured by the one-stage clotting assay after a single intravenous infusion of a 50 IU/kg dose.
The PK profile obtained after 6 months of repeated dosing was comparable with the PK profile obtained after the first dose.

Table 8 Pharmacokinetic Parameters of WILATE in 21 Previously Treated Patients (PTP: Mean ± SD)

PK Parameters	Adults (n=16)	Adolescents (n=5)
C_{max} (IU/dL)	113.82 ± 20.53 (77.43 - 142.00)	83.92 ± 9.40 (77.93 – 100.27)
AUC (IU*hr/dL)	1562.10 ± 451.43 (721.92 - 2271.48)	1009.74 ± 172.26 (816.23 - 1287.76)
AUC_{norm} (IU*hr/dL)	31.24 ± 9.03 (14.44 - 45.43)	20.20 ± 3.45 (16.32 - 25.76)
Half-life (hrs)	10.64 ± 2.69 (6.30 - 15.43)	11.41 ± 1.93 (9.37 – 14.57)
CL (dL/h/kg)	0.035 ± 0.013 (0.02 - 0.07)	0.051 ± 0.008 (0.04 - 0.06)
Vd (dL/kg)	0.53 ± 0.13 (0.36 - 0.82)	0.73 ± 0.13 (0.53 - 0.85)
MRT (hrs)	15.81 ± 3.63 (10.80 - 22.23)	14.39 ± 1.83 (12.85 – 17.30)
Recovery (%IU/kg)	2.27 ± 0.41 (1.54 - 2.83)	1.66 ± 0.17 (1.55 – 1.95)

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

14 CLINICAL STUDIES

VWD

Treatment of Bleeding Episodes

Clinical efficacy of WILATE in the control of bleeding in subjects with VWD was determined in four prospective, open-label, non-controlled clinical studies (excluding PK study). For inclusion in the studies, subjects had to have inherited VWD (any type) that did not respond to desmopressin acetate. Subjects aged ≥12 to ≤65 years were eligible to enter three of the four studies, and subjects aged ≥6 to ≤85 years were eligible for one study. Exclusion criteria included the administration of other plasma-derived or blood products or desmopressin acetate 15 days before study entry, administration of acetylsalicylic acid 7 days before study entry, symptomatic infection, past or present inhibitor activity (3 studies), and severe liver or kidney disease (3 studies). A total of 70 VWD subjects with a mean age of 37 years (range 5–77 years) were enrolled in the studies, of whom 37 were type 3 and 30 were male. The total number of exposure days to WILATE for all investigations across the four studies ranged from 202 to 4917 days. 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) which was determined at the discretion of the investigator. In assessing efficacy using the objective criteria, treatment of a bleeding episode was classified as a success when none of the criteria listed below were met:

- the episode was additionally treated with another VWF-containing product (excluding whole blood)
- the subject received a blood transfusion during the episode
- follow-up treatment with a daily dosage of WILATE that was greater than or equal to 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'

BEs treated with WILATE are summarized for all subjects (n=45) and subjects aged 5–16 years (n=11) in Table 9. Among the 70 VWD subjects administered WILATE in clinical studies (excluding the PK study), 45 received on demand treatment for 1068 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 subjects with BEs, 93% of the successfully treated BEs occurred in VWD type 3 subjects (n=25). In 11 pediatric subjects aged 5–16 years, efficacy was rated as being successful in 87.6% of BEs.

Table 9 Proportion of Successful Treatments of Bleeding Episodes with WILATE

	Number of BEs*	Number of successfully treated BEs	% Successes (95% CI)
All subjects (n=45)	1068	898	84.1 (81.8-86.2)
Subjects 5–16 years (n=11)	234	205	87.6 (82.7-91.5)

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

Dosing information for 972 successfully treated "bleeding episodes" (1423 infusions), and 211 successfully treated bleeding episodes (289 infusions) in subjects aged 5–16 years, for regional bleeding is summarized in Table 10. For the purpose of assigning success/failure to regional bleeding that occurred at the same time, bleeding at different sites over the same time span was counted as separate BEs. Thus, the number of these "episodes" is different from that in the overall evaluation for success/failure of WILATE in the treatment of BEs in Table 9. The majority of BEs were treated for 1-3 days. In subjects with GI bleeds, the duration for product use to control bleeding was longer (up to 7 days).

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Table 10 Administered Dosages (VWF:RCo in IU/kg) in Bleeding Episodes* Successfully Treated with WILATE: Mean ± SD (Range)

Location	All Subjects (n=45)				Subjects 5–16 years (n=11)			
	Initial Dose		Subsequent Doses		Initial Dose		Subsequent Doses	
	# of Infusions	Dose: Mean ± SD (Range)	# of Infusions	Dose: Mean ± SD (Range)	# of Infusions	Dose: Mean ± SD (Range)	# of Infusions	Dose: Mean ± SD (Range)
Joints	542	28 ± 13 (7 - 69)	259	21 ± 10 (7 - 60)	117	32 ± 13 (14 - 69)	41	25 ± 9 (12 - 62)
Epistaxis	91	25 ± 10 (13 - 78)	41	22 ± 14 (8 - 77)	25	25 ± 10 (14 - 52)	5	37 ± 25 (12 - 77)
GI Tract	64	43 ± 19 (9 - 76)	61	36 ± 21 (9 - 76)	1	22 (N/A)	0	N/A
Oral	33	27 ± 14 (10 - 80)	8	24 ± 18 (8 - 60)	21	24 ± 8 (16 - 52)	2	25 ± 13 (16 - 35)
Gynecologic	52	28 ± 17 (12 - 77)	35	26 ± 9 (9 - 52)	33	27 ± 16 (12 - 69)	25	26 ± 8 (12 - 52)
Other**	189	24 ± 12 (12 - 95)	48	20 ± 13 (10 - 95)	14	27 ± 7 19 - 37)	5	19 ± 4 (16 - 26)

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

Prevention of Bleeding in Surgery (Perioperative Management)

A prospective, open-label, single-arm, uncontrolled, multi-center clinical study was conducted to investigate the safety and hemostatic efficacy of WILATE in 28 subjects (19 female and 9 male) who underwent 30 surgeries. Two female subjects underwent 2 surgeries each. Subjects ranged in age from 12 to 74 years (median = 36). Three subjects were between 12 and 17 years old and 4 were 65 years or older. Six subjects had type 1 VWD, 1 had type 2A, 1 type 2B, and 20 had type 3 VWD. One type 1 and one type 3 subject had 2 surgeries each.

Twenty-one surgeries were classified as major (e.g. orthopedic joint replacement, cesarean section and vaginal deliveries, laminectomy, tonsillectomy, appendectomy, 3rd molar extractions) and 9 were classified as minor (e.g. menisectomy, teeth extractions other than 3rd molars, septoplasty, biopsy). Seven surgeries (3 major, 4 minor) were performed in type 1 VWD subjects, 2 surgeries (1 major, 1 minor) were performed in type 2 (A/B) VWD subjects, and 21 surgeries (17 major, 4 minor) were performed in type 3 VWD subjects. The types of surgery for the 9 minor procedures were: dental (n=5, 55.6%); orthopedic (n=2, 22.2%); ophthalmologic (n=1, 11.1%); and ear, nose and throat (n=1, 11.1%). The types of surgery for the 21 major procedures were: orthopedic (n=8, 38.1%); obstetric/gynecological (n=5, 23.8%); gastrointestinal (n=4, 19.0%); dental (n=2, 9.5%); and ear, nose and throat (n=2, 9.5%). The type of surgery according to VWD type were: VWD type 1 (n=7) – dental (n=4, 57.1%), orthopedic (n=2, 28.6%), and ear, nose and throat (n=1, 14.3%); VWD type 2 (A/B) (n=2) – orthopedic (n=1, 50%), and obstetric/gynecological (n=1, 50%); VWD type 3 (n=21) – orthopedic (n=7, 33.3%), gastrointestinal (n=4, 19.0%), obstetric/gynecological (n=4, 19.0%), dental (n=3, 14.3%), ear, nose and throat (n=2, 9.5%), and ophthalmologic (n=1, 4.8%).

Dosing was individualized based on in-vivo recovery results performed before surgery. Mean total loading dose per infusion was 51.4 IU/kg (median 52.1 IU/kg; range 27-77 IU/kg). Major surgeries required a mean loading dose of 54.7 IU/kg (median 55.5 IU/kg; range 36-69 IU/kg) in comparison with a mean loading dose of 41.9 IU/kg (median 37.5 IU/kg; range 27–77 IU/kg) for minor surgeries. Mean total maintenance dose per infusion was 28.5 IU/kg (median 28.5 IU/kg; range 8-63 IU/kg). Major surgeries required a mean maintenance infusion of 29.6 IU/kg (median 30 IU/kg; range 8-63 IU/kg) in comparison with a mean maintenance infusion of 21.6 IU/kg (median 20.6 IU/kg; range 14-38 IU/kg) for minor surgeries.

Efficacy of WILATE in surgical procedures was assessed by the surgeon at the conclusion of surgery and by the investigator-hematologist at 24 hours following completion of the final maintenance dose. Efficacy of WILATE was assessed using a stringent and objective 4-point ordinal efficacy scale (excellent, good, moderate, or none) based on estimated expected versus actual blood loss, transfusion requirements and post-operative bleeding and oozing. A rating of excellent or good was required to declare the outcome a success. An independent data monitoring committee (IDMC) additionally conducted an independent post hoc adjudication of intra- and post-operative assessments made by the surgeon/investigator-hematologist. In situations where the IDMC's assessment differed from that of the surgeon and/or investigator-hematologist, the IDMC assessment took priority.

The overall efficacy of WILATE treatment for surgical procedures in this study was 96.7%. Treatment with WILATE was successful in all minor surgeries and in 95.2% of major surgeries (Table 11). It was also successful in all surgical procedures in VWD type 3 and type 2 subjects and in 85.7% of procedures in VWD type 1 subjects (Table 12). One failure was reported in a VWD type 1 subject undergoing lumbar laminectomy (major surgery) who experienced slightly greater blood loss (25 mL) than the expected maximum (20 mL).

Table 11 Hemostatic Efficacy Assessment by Severity of Surgery as Adjudicated by the IDMC (n=30)

Efficacy grade	Minor (n=9)			Major (n=21)			All surgeries (n=30)		
	n (%)	Rate	98.75% CI	n (%)	Rate	98.75% CI	n (%)	Rate	98.75% CI
Success	9 (100)	1.000	0.569, 1.000	20 (95.2)	0.952	0.704, 1.000	29 (96.7)	0.967	0.784, 1.000
Failure	0			1 (4.8)			1 (3.3)		

CI = confidence interval; IDMC = Independent Data Monitoring Committee; n = number of surgeries; rate = overall success rate.

Table 12 Hemostatic Efficacy Assessment by Type of VWD as Adjudicated by the IDMC (n=30)

Efficacy grade	VWD type 1			VWD type 2			VWD type 3		
	n (%)	Rate	98.75% CI	n (%)	Rate	98.75% CI	n (%)	Rate	98.75% CI
Overall IDMC assessment Success	6 (85.7)	0.857	0.328, 0.999	2 (100)	1.000	0.079, 1.000	21 (100)	1.000	0.785, 1.000
Failure	1 (14.3)			0			0		

CI = confidence interval; IDMC = Independent Data Monitoring Committee; n = number of surgeries; rate = overall success rate; VWD = von Willebrand Disease.

In this study, actual blood loss (median) was lower than the expected maximal estimated blood loss in all types of surgeries. The actual blood loss was also lower than the average predicted blood loss in minor surgeries and equal in major surgeries (Table 13).

Table 13 Expected and Actual Estimated Blood Loss during Surgery

Estimated Blood Loss	Minor Surgery (n = 9)	Major Surgery (n= 21)
Expected Maximum - Median (range) mL	50 (1-200)	500 (20-2000)
Expected Average – Median (range) mL	20 (1-100)	100 (5-1500)
Actual - Median (range) mL	15 (1-50)	100 (0-1200)

Intra-operative transfusion was predicted in 5 subjects, but actually given in only 2. One subject received platelets intra-operatively for previously existing thrombocytopenia and one subject who underwent abdominal hysterectomy received one infusion of rejuvenated (in biochemical solution) packed red blood cells intra-operatively which was planned pre-surgery.
Three subjects received transfusions following surgery due to anemia and low hemoglobin values seen post-operatively.

Hemophilia A

Routine prophylaxis

The efficacy of WILATE in routine prophylaxis was evaluated in a prospective, open-label, multicenter clinical study in which adult subjects and pediatric subjects aged 12-15 years were treated during 6 months of prophylaxis with 20-40 IU/kg WILATE, mean dose 32 IU/kg. Within the group of 55 subjects, of which 50 adults and 5 pediatric subjects, there were 30 (54.6%) subjects with 0 bleeding episodes, 12 (21.8%) subjects with 1 bleeding episode, 4 (7.3%) subjects with 2 bleeding episodes, 4 (7.3%) subjects with 3 bleeding episodes, and 5 (9%) subjects with 5 or more bleeding episodes. Annualized bleeding rates for all bleeding episodes, treated and untreated, are summarized in Table 14.

Table 14 Annualized Bleeding Rate in Adult and Pediatric Subjects under Prophylaxis

	Adults (n=50)	Pediatric Subjects (n=5)
Annualized bleeding rate (per subject) - spontaneous bleeds	1.67 ± 3.11 (median 0, range 0-11.76)	0 (median 0, range 0-0)
Annualized bleeding rate (per subject) for all types of bleeds	2.39 ± 3.77 (median 0, range 0-15.69)	0.4 ± 0.89 (median 0, range 0-2)

Treatment of bleeding episodes

The study presented above also provided data on the efficacy of WILATE in the treatment of bleeding episodes. The break-through bleeds were treated with WILATE doses adjusted to the severity of the bleed. Treatment efficacy was assessed by the patient (together with the investigator in case of on-site treatment) using the predefined criteria using an ordinal scale of excellent (abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection), good (definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an injection, requiring up to two injections for complete resolution), moderate (probable or slight beneficial effect within approximately 12 hours after the first injection, requiring more than two injections for complete resolution), or none (no improvement within 12 hours, or worsening of symptoms, requiring more than two injections for complete resolution).

In the per protocol population (n=52), 57 bleeding episodes were treated with WILATE, of which 15 (26.3%) bleeding episodes were minor (e.g. early onset muscle and joint bleeds with no visible symptoms, such as little or no change in the range of motion of affected joint, mild restriction of mobility and activity, scrapes, superficial cuts, bruises, superficial mouth bleeds, and most nose bleeds), 32 (56.1%) were moderate (e.g. advanced soft tissue and muscle bleeds into the limbs, bleeding into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot, or finger), 10 (17.5%) were major (e.g. complicated joint bleeds, bleeds of the pelvic muscles, eyes), and 0 (0%) were life-threatening (e.g. bleedings in the abdomen, digestive system or chest, central nervous system bleeds, bleedings in the area of the neck or throat or pharynx, or other major trauma). Forty-one bleeds (71.9%) were spontaneous and 16 (28.1%) were traumatic. Thirty-six bleeding episodes (63.2%) were managed with one WILATE injection, 12 (21.1%) were managed with two injections, 7 (12.3%) were managed with 3 injections, and 2 (3.6%) required more than 3 injections. The mean dose of WILATE per injection was 34 IU/kg. Treatment efficacy was judged as excellent for 16 (28.1%) bleeding episodes, good for 32 (56.1%) bleeding episodes and moderate for 9 (15.8%) bleeding episodes. Therefore, 84.2% of all bleeding episodes were treated successfully. The one bleeding episode in one subject younger than 16 years (bleeding in finger) was treated with a single injection of 62.81 IU/kg of WILATE with excellent efficacy (successful treatment).

Further efficacy data in the treatment of bleeding episodes is available from a pooled analysis of 37 subjects with hemophilia A included in 3 additional clinical studies. These subjects had at least 150 exposure days at the time of enrollment into the study and had been treated for at least 50 exposure days and 6 months in the study. The analysis encompassed 986 bleeding episodes, of which 936 (94.9%) were treated successfully.

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- WILATE is supplied in packages comprising of 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.

Kit NDC Number	Size	Protein Amount
68982-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
68982-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

- 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 are not made with natural rubber latex.

Storage and Handing

- Store WILATE for up to 36 months at +2°C to +8°C (36°F to 46°F) in the original containers to protect 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.
- Reconstitute the WILATE powder only directly before injection. Use the solution immediately after reconstitution and discard any remaining solution.

17 PATIENT COUNSELING INFORMATION

- Advise the patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- 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, advise patients to discontinue the administration immediately and contact their physician to administer appropriate emergency treatment [*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.[3] [*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)*].

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