wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

THE POWER OF BALANCE

Understanding von Willebrand Disease & Its Treatment

PATIENT & CAREGIVERS GUIDE

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.

octapharma®

For the safe and optimal use of human proteins

Please see accompanying full Prescribing Information.

Understanding von Willebrand Disease

Von Willebrand disease (VWD) is an inherited bleeding disorder that affects the blood's ability to clot.[1] VWD is caused by problems with a protein in the blood called von Willebrand factor (VWF). When there is not enough VWF in the blood, or when it does not function properly, the blood takes longer to clot. VWF also carries and protects Factor VIII (FVIII), which is another important protein that helps blood to clot.[1]

Types of VWD

The 3 main types of VWD are Types 1, 2, and 3.[1] In general, bleeding becomes progressively more severe from Type 1 to Type 3. But this is not always the case—bleeding can be mild, moderate, or severe with any type of VWD.

- **Type 1 VWD**[2,3]

  In Type 1 VWD, the VWF functions properly, but levels in the blood are too low. Type 1 is the most common type, affecting approximately 60%-80% of people with VWD. Although Type 1 is typically the mildest type, those with Type 1 VWD can have episodes of serious bleeding.

- **Type 2 VWD**[2,3]

  In Type 2 VWD, there is some type of defect in the VWF protein. Type 2 is the second-most common type, affecting approximately 15%-30% of people with VWD. There are different subtypes of Type 2 VWD depending on the type of defect in the VWF protein. Type 2 VWD subtypes are Types 2A, 2B, 2M, and 2N. Symptoms of Type 2 VWD are usually moderate, but serious bleeding can occur.

- **Type 3 VWD**[1-3]

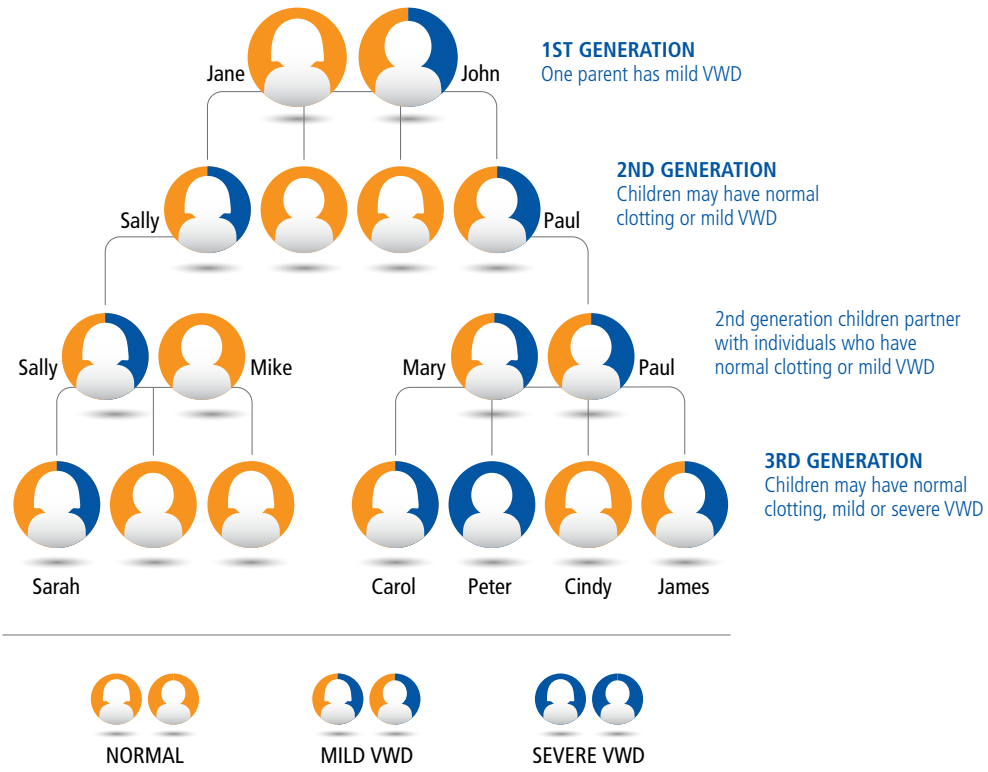
  In Type 3 VWD, there is very little to no VWF present in the body and decreased levels of FVIII. Type 3 VWD is the rarest type, affecting about 5%-10% of people with VWD. This is the most serious type of VWD and symptoms are generally more severe. People with Type 3 VWD can have more serious bleeding issues, such as bleeding into muscles or joints, sometimes even without an injury.

Genetics of VWD[4]

VWD is almost always inherited, meaning that parents pass the gene for the disorder on to their children.Type 1 or Type 2 VWD can occur if only one parent passes the gene on, while Type 3 VWD occurs only if both parents pass the gene on.Because VWD is inherited, it often affects several members of the same family, both males and females.

Occasionally, VWD in a sibling can occur spontaneously from a genetic mutation.[4] In that case, other children in the family would not inherit it.

Three Generations of a Family with VWD



VWD Symptoms and Diagnosis[2,4]

VWD occurs equally in men and women. The most common symptom is abnormal bleeding. In some people with VWD, however, the bleeding is so mild they don't even know they have the disease. In others, the bleeding can be quite severe.

Bleeding symptoms of VWD include:
Frequent large bruises from minor bumps or injuries
Frequent or hard-to-stop nosebleeds
Long-lasting bleeding from the gums after a dental procedure such as an extraction
Heavy or extended menstrual bleeding in women
Blood in the stool that comes from bleeding in the intestines or stomach
Blood in the urine that comes from bleeding in the kidneys or bladder
Heavy bleeding after surgery or childbirth

How VWD Is Diagnosed

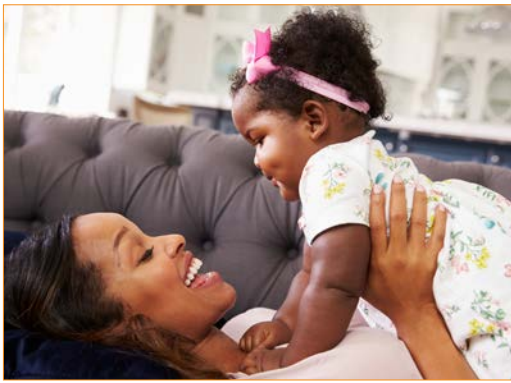
Diagnosing VWD can be difficult and some doctors might not be familiar with it.

To diagnose VWD, your doctor or a hematologist who specializes in bleeding disorders will review your personal and family history of bleeding. If the medical history suggests VWD, specific blood tests can help confirm the diagnosis.

VWD Treatment[2]

Treatment usually depends on the specific type of VWD and its severity. Most cases of VWD are mild enough that treatment may only be necessary when:

- You're having surgery
- You're having dental work
- You need it to treat accidental injuries



Desmopressin

Desmopressin, also called DDAVP, is a man-made (synthetic) version of a hormone the body normally produces. DDAVP is often used to prevent or treat bleeding episodes in people with Type 1 and occasionally some people with Type 2 VWD. It works by causing the body to release more VWF into the bloodstream. But if VWF levels are still too low, or if the VWF protein being released is defective, DDAVP might not be sufficient to control bleeding.

Purified VWF/FVIII Concentrates

For people who don't achieve adequate bleeding control with DDAVP or those with more severe Type 2 and Type 3 VWD, infusion of a purified VWF/FVIII concentrate is the usual treatment. These products increase the levels of both VWF and FVIII to provide bleeding control.

Antifibrinolytics and Fibrin Sealants

Antifibrinolytics help stop an enzyme that dissolves blood clots. They help prevent the breakdown of clots that have formed.

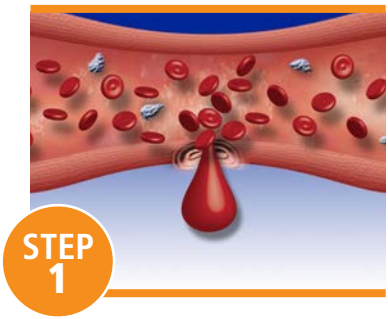
Examples: Tranexamic acid, aminocaproic acid

Fibrin sealants create a fibrin "net" to help hold platelets together in a clot. They may be used during dental extractions and surgery.

VWF and FVIII Are Both Important to Maintaining Hemostasis[5,6]

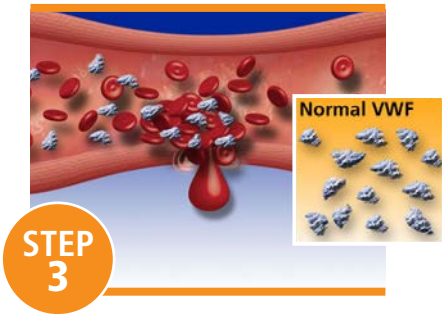
Hemostasis is the process that stops bleeding at the site of an injury while allowing the blood to flow normally elsewhere in the circulation. When you have an injury that bleeds, VWF acts as a "glue" to help the blood clot and close up the wound. In patients with VWD this "glue" is missing or may not work very well.

Normal Clotting[4]

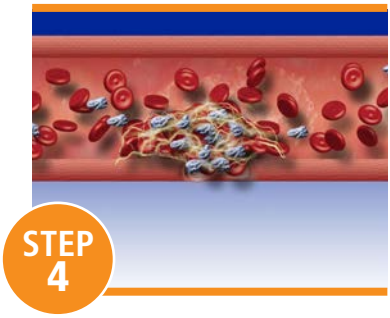


When a blood vessel is damaged, it tightens to slow the flow of blood out of the vein.

Platelets are very small cell fragments in the blood. They stick to the inside of the blood vessel and plug holes at the injury site.

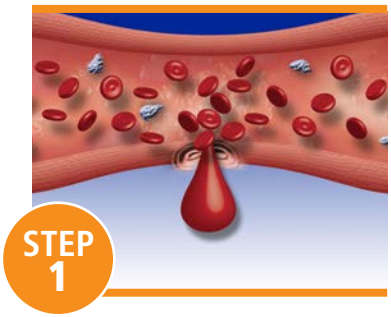


VWF acts as a glue to hold the platelets in place at the site of injury.

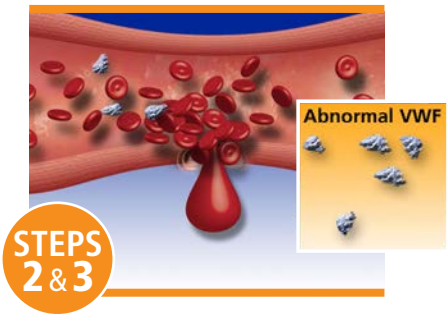


The clump of platelets provides a surface where blood clotting can occur. Clotting proteins (like FVIII) in the blood gather on the surface of the platelets to form a thick fibrin mesh that holds the clot in place, similar to a scab.

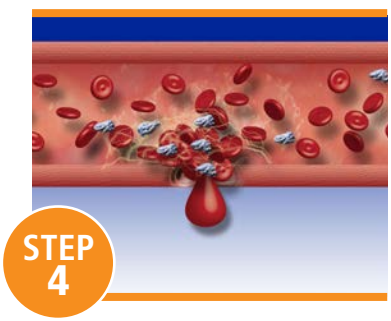
How VWD Affects Clotting[4]



When a blood vessel is damaged, the blood vessels tighten normally.



A person with VWD may not have enough VWF in the blood, or it may not work normally, so the VWF can't hold the platelets in place. The platelets do not form a clump.



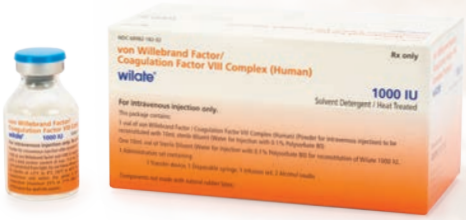
The VWF carries FVIII, a protein needed to make a solid clot. When VWF is low, so is FVIII. Without normal levels of FVIII, a solid clot takes a very long time to form.

IT IS BECAUSE people with VWD can have different levels of VWF and/or FVIII deficiency, that infusion of a purified VWF/FVIII concentrate may be the appropriate treatment.

What is wilate®?

wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated in children and adults with VWD for on-demand treatment and control of bleeding episodes, and for the management of bleeding during surgery.[7]

wilate is also is 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.



What is the Power of Balance?

wilate contains *equal* amounts of VWF and FVIII.[7] This means that the ratio of VWF to FVIII is **balanced** at 1 to 1. This is similar to the ratio of VWF and FVIII that occurs naturally in the body.

For patients with VWD, wilate offers a number of benefits:[7-9]

- Low recommended dosing*
- Low risk of FVIII accumulation during repeat dosing in surgery
- Effective control of major and minor bleeding
- An advanced purification process that minimizes impurities
- Two viral inactivation steps: solvent/detergent (S/D) and dry heat treatment
- Simple and convenient to use

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

Important Safety Information
The most common adverse reactions to treatment with wilate® (≥1%) in patients with VWD were hypersensitivity reactions, urticaria (hives), and dizziness. The most serious adverse reactions to treatment with wilate in patients with VWD have been hypersensitivity reactions. The most common adverse reaction to treatment with wilate in patients with hemophilia A was pyrexia (fever).

Please see accompanying full Prescribing Information.

Low Recommended Loading and Maintenance Dosing

wilate Dosing in Minor and Major Bleeds for All VWD Types[7]

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

RCo, ristocetin cofactor; BW, body weight.
*Based on the Recommended Dosing Guide for wilate. See Dosage and Administration, section 2.1 of full Prescribing Information.

Humate-P® VWF:RCo Dosing Recommendations by VWD Type[10]

VWD Type	Severity of Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 VWD–Mild (baseline VWF:RCo activity typically >30%)	Minor (eg, epistaxis, oral bleeding, menorrhagia)	Typically treatable with desmopressin.
	Minor (when desmopressin is known or suspected to be inadequate) Major† (eg, severe or refractory epistaxis, GI bleeding, CNS trauma, traumatic hemorrhage)	Loading dose 40-60 IU/kg. Then 40-50 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-50 IU/kg daily for up to 7 days.
Type 1 VWD–Moderate or Severe (baseline VWF:RCo activity typically <30%)	Minor (eg, epistaxis, oral bleeding, menorrhagia)	40-50 IU/kg (1 or 2 doses).
	Major (eg, severe or refractory epistaxis, GI bleeding, CNS trauma, traumatic hemorrhage)	Loading dose 50-75 IU/kg. Then 40-60 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-60 IU/kg daily for up to 7 days.
Type 2 VWD (all variants) and Type 3 VWD	Minor (clinical indications above)	40-50 IU/kg (1 or 2 doses).
	Major (clinical indications above)	Loading dose 60-80 IU/kg. Then 40-60 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-60 IU/kg daily for up to 7 days.

†For major bleeds in all types of VWD where repeated dosing is required, monitor and maintain the patient's FVIII level according to the guidelines for hemophilia A therapy.

Please see accompanying full Prescribing Information.

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von Willebrand Factor/Coagulation Factor VIII Complex (Human)

What Is Factor VIII Accumulation?

Your levels of FVIII may increase when repeat doses of VWF/FVIII products are given, such as before and after surgery, possibly leading to FVIII accumulation.[9]

- FVIII accumulation can increase the risk of a blood clot, also called a venous thromboembolism (VTE)
- When repeat doses of a VWF/FVIII product are given, this can lead to a temporary rise in FVIII levels—which may increase the chance of a VTE
- VWD patients undergoing surgery who need repeated treatment with a VWF/FVIII concentrate will require special monitoring of their FVIII levels[7,10]

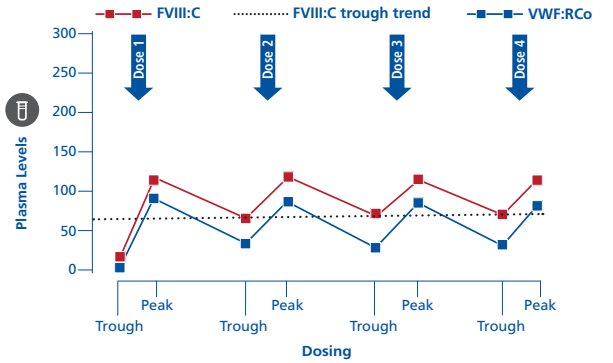
In a clinical trial with VWD patients undergoing surgery, there was **NO FVIII ACCUMULATION** after repeat dosing with wilate[9]

Important Safety Information

Anaphylaxis and severe hypersensitivity reactions are possible. 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. Development of neutralizing antibodies to FVIII and to VWF, especially in VWD type 3 patients, may occur.

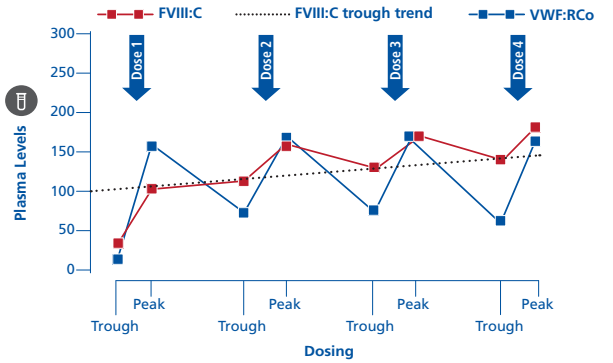
Please see accompanying full Prescribing Information.

VWF and FVIII Plasma Levels with wilate and Humate-P in Patients Undergoing Surgery[9,11]



With wilate

No accumulation of FVIII were observed after repeat dosing in VWD patients undergoing surgery



With Humate-P

FVIII levels may increase after repeat dosing in surgery, potentially increasing the risk of FVIII accumulation

If you have VWD and are planning to have surgery,
TALK TO YOUR HEMATOLOGIST ABOUT WILATE

Important Safety Information

Hypersensitivity or allergic reactions have been observed upon use of wilate and may in some cases progress to severe anaphylaxis (including shock) with or without fever.

Please see accompanying full Prescribing Information.

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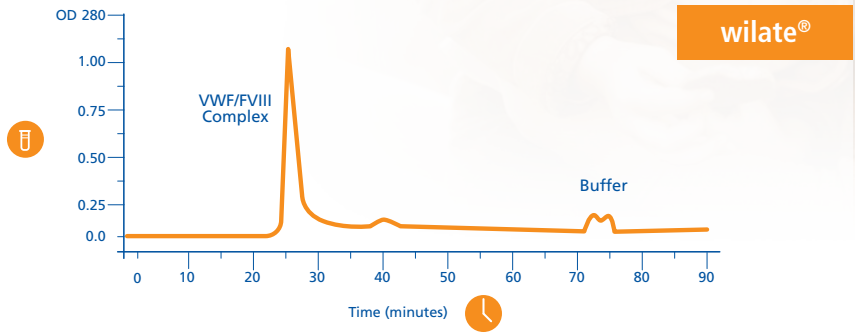
wilate is a High Purity VWF/FVIII Product

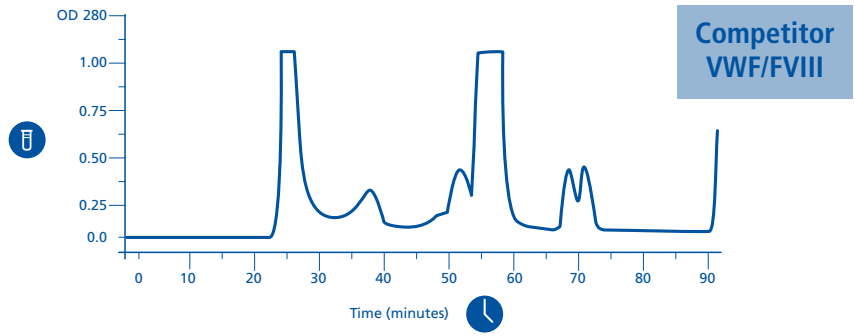
The extensive purification processes of wilate include a step called size exclusion chromatography. This step minimizes impurities and helps reduce the risk of side effects.[7]

wilate shows a single peak containing only the native (natural) VWF/FVIII complex.[12]



- No albumin is added to wilate

Plasma Proteins May Cause Clinical Side Effects



Important Safety Information
wilate® is made from human plasma and carries the risk of transmission of infectious agents, eg, viruses and, theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent.
Please see accompanying full Prescribing Information.

Octapharma Has High Standards for Safety

Octapharma maintains stringent standards for the plasma used in all of its human protein therapies. wilate is derived exclusively from pools of human plasma collected in US Food and Drug Administration (FDA)-licensed plasma donation centers. All donated plasma is subject to individual unit testing for evidence of a wide range of viruses, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Any plasma with evidence of these viruses is rejected.

Dual Viral Inactivation

The carefully selected and tested plasma then undergoes 2 separate viral inactivation steps—the S/D treatment and the PermaHeat process.

S/D Process[13]	PermaHeat Process[13]
• An established and proven method for inactivating infectious enveloped viruses • Effective against HIV, HBV, HCV, and West Nile Virus	• Uses dry heat (100°C, for 2 hours) to inactivate viruses. Developed to supplement the S/D process • Inactivates a broad spectrum of both enveloped and non-enveloped viruses

Important Safety Information
wilate is contraindicated for patients who have known anaphylactic or severe systemic reaction to plasma-derived products, any ingredient in the formulation, or components of the container.
Please see accompanying full Prescribing Information.

wilate®
von Willebrand Factor/Coagulation Factor VIII Complex (Human)

wilate Offers Simple and Convenient Usage

wilate is available in 2 vial sizes, 500 or 1000 IU, with a Mix2Vial® needle-free transfer device.

- wilate is rapidly dissolved in a small injection volume—to help save time during administration
- Includes Mix2Vial transfer device—a quick and easy way to mix wilate with less risk of accidental sticks and a built-in filter for a fast and easy process
- wilate has a recommended infusion rate of 2 to 4 mL/minute

wilate 1000 IU

1000 IU VWF:RCo and **1000 IU FVIII** activities in 10 mL

wilate 500 IU

500 IU VWF:RCo and **500 IU FVIII** activities in 5 mL

- Store up to 36 months in a refrigerator (+2°C to +8°C or 36°F to 46°F) protected from light from the date of manufacture
- Within this period, wilate may be stored up to 6 months at room temperature (maximum of +25°C or 77°F)
- Once stored at room temperature, the product must not be returned to the refrigerator

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Octapharma Programs and Support Services

Patient Assistance Made Simple

WILATE FREE TRIAL PROGRAM	A great opportunity for people with VWD and their providers to try wilate at no cost.
CO-PAY ASSISTANCE PROGRAM	Offers savings to eligible patients on some of the out-of-pocket costs associated with therapy.
REIMBURSEMENT SERVICES	Experienced, knowledgeable professionals providing insurance and reimbursement support to providers, patients, and families.

Call 800-554-4440 for more information about Co-Pay Assistance, Reimbursement Services, and the wilate Free Trial program.

For general information, please dial our Customer Service Department at 866-766-4860 or email us at uscustomerservice@octapharma.com.

Contact Information

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Customer Service	**uscustomerservice@octapharma.com**
Medical Affairs	**usmedicalaffairs@octapharma.com**
Free Trial, Co-Pay Assistance, and Reimbursement	**usreimbursement@octapharma.com**

For all inquiries relating to drug safety, or to report adverse events, please contact our Local Drug Safety Officer:

Tel: 201-604-1137 | **Cell:** 201-772-4546 | **Fax:** 201-604-1141
or contact the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**

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THE POWER OF BALANCE

- A balanced 1:1 formulation of VWF/FVIII
- Effective control of major and minor bleeding[8]
- Low recommended dosing*[7]
- No accumulation of FVIII during repeat dosing in surgery[9]
- High purity

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

www.wilateusa.com

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References: 1. Nichols WL, et al. Haemophilia. 2008;14:171-232. **2.** World Federation of Hemophilia. What is von Willebrand disease?. Available at: http://www1.wfh.org/publication/files/pdf-1330.pdf. **3.** Mannucci PM. N Engl J Med. 2004;351:683-694. **4.** Canadian Hemophilia Society. von Willebrand disease. Available at: https://www.hemophilia.ca/von-willebrand-disease. **5.** Gale AJ. Toxicol Pathol. 2011;39(1):273-280. **6.** Centers for Disease Control. What is von Willebrand disease? Available at: https://www.cdc.gov/ncbddd/vwd/facts.html. **7.** wilate® full Prescribing Information. Hoboken, NJ: Octapharma; rev September 2019. **8.** Berntorp E, et al. Haemophilia. 2009;15:122-130. **9.** Srivastava A, et al. Haemophilia. 2017;23(2):264-272. **10.** Humate-P® full Prescribing Information. Kankakee, IL: CSL Behring; rev September 2017. **11.** Lethagen S, et al. J Thromb Haemost. 2007;5:1420-1430. **12.** Stadler M, et al. Biologicals. 2006;34:281-288. **13.** Farrugia A. Guide for the assessment of clotting factor concentrates. World Federation of Hemophilia. Last updated 2008. Available at: http://www1.wfh.org/publication/files/pdf-1271.pdf.

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