wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

THE POWER OF BALANCE

Your Guide to Understanding von Willebrand Disease and Its Treatment

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 not indicated for the treatment of hemophilia A.

Please see Important Safety Information on page 15.
Please see accompanying Full Prescribing Information.

octapharma®

For the safe and optimal use of human proteins

Understanding von Willebrand Disease

Von Willebrand disease (VWD) is an inherited bleeding disorder that affects the blood's ability to clot.[1-3] VWD is caused by problems with a special protein in the blood called von Willebrand factor (VWF). When there is not enough VWF in the blood, or when it does not work the way it should, the blood takes longer to clot. VWF also carries and protects factor eight (FVIII), which is another important protein that helps blood to clot.

Types of VWD

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

- **Type 1 VWD**[1,4,5]

  In Type 1 VWD, the VWF works the way it should, but there is just not enough of it. Type 1 is the most common type, affecting 60% to 80% of people with VWD. While it is usually the mildest type, it is possible to have serious bleeding.

- **Type 2 VWD**[5]

  In Type 2 VWD, there is something wrong with the way the VWF works because there is a defect in the VWF protein. Type 2 is the second most common type, affecting 15% to 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**[3,5]

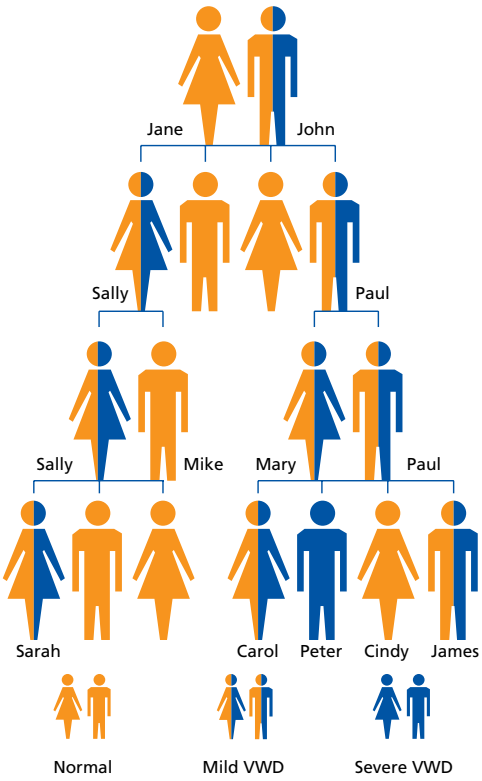
  In Type 3 VWD there is very little or no VWF present in the body. Type 3 VWD is the rarest type, affecting about 5% to 10% of people with VWD. This is the most serious type of VWD and symptoms are usually more severe. People with Type 3 VWD can have more serious bleeding issues, such as bleeding into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

Genetics of VWD

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

Occasionally, one of a baby's genes can undergo a change, called a genetic mutation.[2] The baby's parents do not carry this defective gene, so other children in the family would not inherit it.

Three generations of a family with VWD[2]



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VWD Symptoms and Diagnosis

VWD occurs equally in men and women. The most common symptom is bleeding. In some people with VWD, 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[6]:
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 your stool that comes from bleeding in your intestines or stomach
Blood in your urine that comes from bleeding in your kidneys or bladder
Heavy bleeding after surgery or childbirth

How VWD is Diagnosed

Diagnosing VWD can be complicated. It is a relatively rare condition, and some doctors might not be familiar with it.

To diagnose VWD, your doctor or a doctor who specializes in bleeding disorders, called a hematologist, will review your personal and family history of bleeding.[1] If the medical history suggests VWD, specific blood tests can be used to help make the diagnosis.

VWD Treatment

Treatment usually depends on the specific type of VWD and how severe it is. Most cases of VWD are mild enough that you might only need treatment 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. It 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 release of more VWF into the bloodstream. But if enough VWF cannot be released or if there is something wrong with the VWF protein being released, 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 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.

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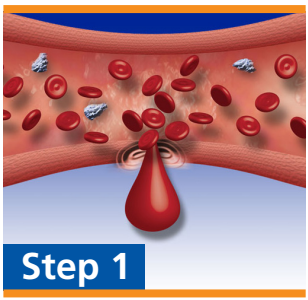
VWF and FVIII Are Both Important to Maintaining Hemostasis[7-9]

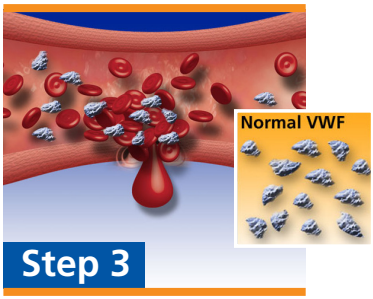
Hemostasis is the process that stops bleeding at the site of an injury while allowing the blood to flow normally elsewhere in the circulation.[9] When you have an injury that bleeds, VWF acts as a "glue" to help the blood clot and close up the wound. In patients with VWD this "glue" is missing or may not work very well.

Normal Clotting[2]

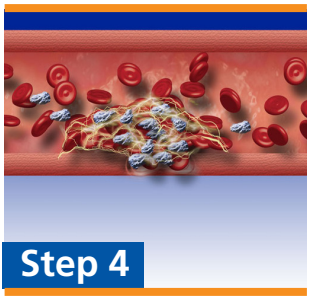


Step 1: When a blood vessel is damaged, it tightens to slow the flow of blood out of the vein.

Step 2: Platelets are very small cells in the blood. They stick to the inside of the blood vessel and plug holes at the injury site.

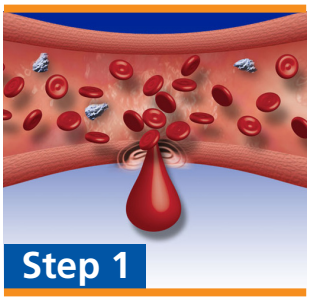


Step 3: VWF acts as a glue to hold the platelets in place at the site of injury.

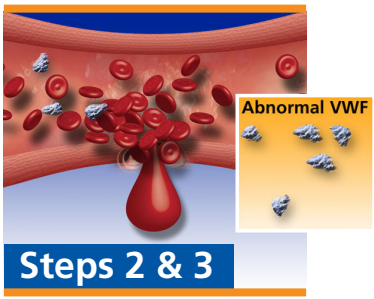


Step 4: The clump of platelets provides a surface where blood clotting can happen. Clotting proteins (like FVIII) in the blood gather on the surface of the platelets to form a thick fibrin mesh that holds the clot in place, similar to a scab.

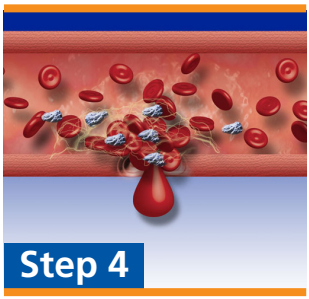
How VWD Affects Clotting[2]



Step 1: When a blood vessel is damaged, the blood vessels tighten normally.



Steps 2 & 3: A person with VWD may not have enough VWF in the blood, or it may not work normally. So, the VWF cannot act as the glue to hold the platelets in place. The platelets do not form a clump.



Step 4: The VWF carries FVIII in the blood. FVIII is 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 appropriate treatment.

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Developed Specifically For the Treatment of VWD

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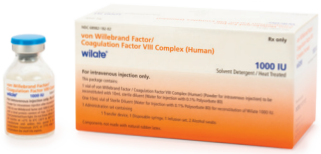
wilate® is the first treatment developed specifically for VWD.[7,8,10]

- Some products that are used to treat VWD were originally developed for hemophilia A



Because wilate® was developed specifically for the treatment of VWD, it has several features that make it well suited to treat this condition.

- A balanced formulation with a 1:1 ratio of VWF:FVIII
- An advanced purification process that minimizes impurities
- Effective control of major and minor bleeding[11]
- Low recommended dosing[7*]
- Two viral inactivation steps using solvent/detergent and dry heat treatments
- Simple and convenient to use

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

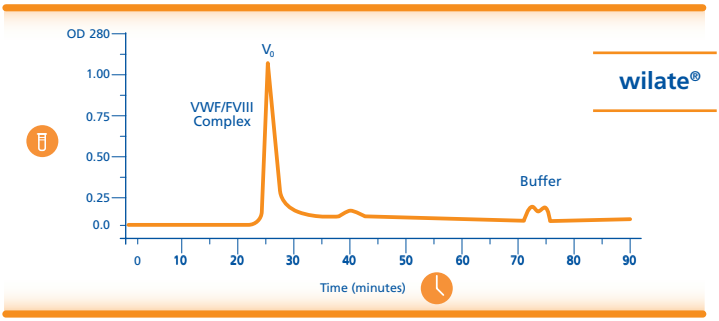
A balanced 1:1 formulation of VWF/FVIII.[7,10,11] wilate® contains equal amounts of VWF and FVIII. Another way of saying this is that the ratio of VWF to FVIII is 1 to 1. This is important because it is similar to the ratio of VWF and FVIII that occurs naturally in the body. This balance of factors may help optimize the dosage that's needed for treatment.

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

High Purity

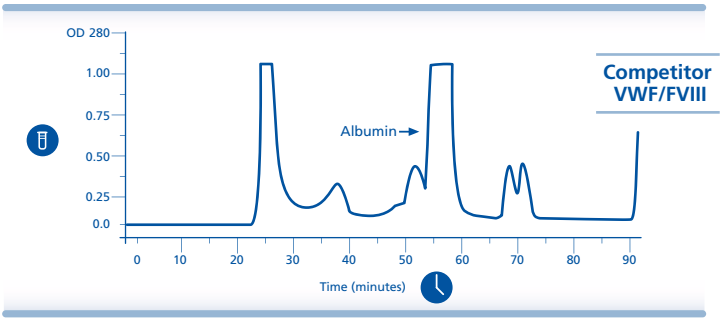
The extensive purification processes of wilate® include a step called size exclusion chromatography. This step minimizes impurities and helps reduce the risk of side effects.[7,11,12]

When the results of the advanced size exclusion chromatography are analyzed, wilate® shows a single peak containing only the native (natural) VWF/FVIII complex.[11,12]



- No albumin is added to wilate®

Added plasma proteins may cause clinical side effects[11]



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 additional Important Safety Information on page 15.
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Low Recommended Dosing*

wilate® offers low recommended dosing for all types of VWD. The appropriate dose of wilate® is based on your weight and how severe your bleeding is.[7] Most bleeds are treated for 1 to 3 days, but severe bleeding may need longer treatment. Your doctor will prescribe the correct dose for you.

wilate® Dosing for the Treatment of 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%

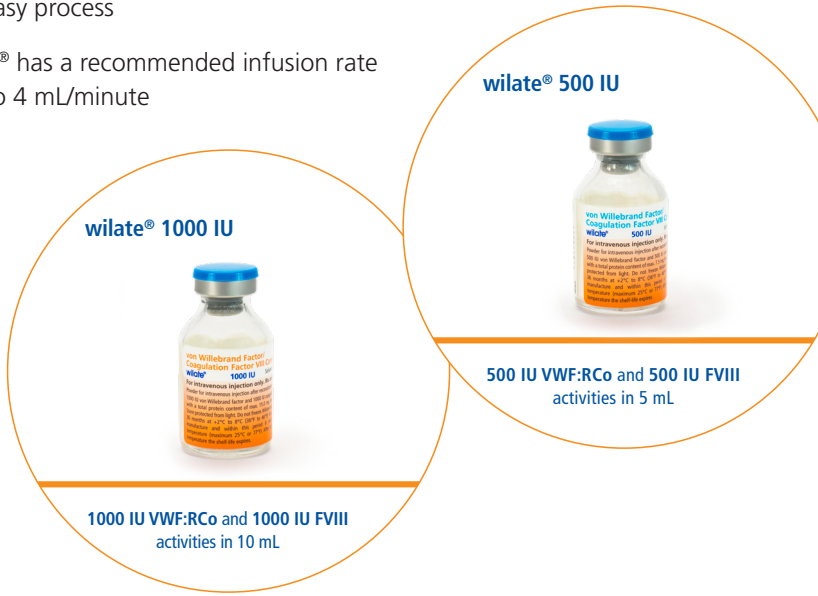
RCo, ristocetin cofactor; BW, body weight.
*Based on the Recommended Dosing Guide for wilate®. See Dosage and Administration, section 2.1 of full Prescribing Information.

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.

Simple and Convenient

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



- 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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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 Solvent Detergent (S/D) treatment and the PermaHeat process.

Solvent Detergent Process	PermaHeat Process
• An established and proven method for infectious enveloped viruses[13]	• An optimized heat inactivation process (100°C, for 2 hours) developed to supplement the S/D process
• Destroys membrane of lipid-coated viruses (HIV, HBV, HCV, and West Nile Virus)	• Inactivates a broad spectrum of both lipid-coated and non-lipid-coated 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.

About Octapharma—Manufacturer of wilate®

One of the largest plasma product manufacturers in the world, Octapharma is committed to the advancement of human protein therapies. The company provides a complete range of safe and effective human protein therapies. Octapharma was the first manufacturer to apply the S/D process to large-scale production of FVIII concentrate. With more than 30 years of experience in the development of coagulation products, Octapharma has become a global company with a comprehensive portfolio of human protein therapies.

In addition to hematology products for the treatment of bleeding disorders, Octapharma also specializes in immune therapy, intensive care, and emergency medicine. Currently, patients in over 80 countries around the world are treated with Octapharma products.

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Octapharma Programs and Support Services

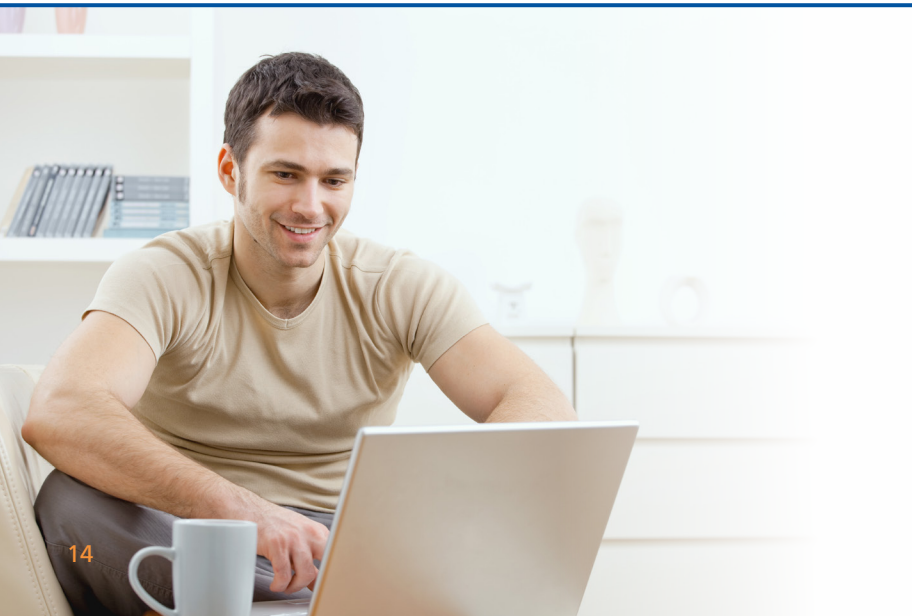
For general information, please dial our Customer Service Department at 866-766-4860 or email us at uscustomerservice@octapharma.com.

Patient Assistance Made Simple

- **wilate® Free Trial Program**
  A great opportunity for people with VWD and their providers to experience the safety, efficacy, and convenience of wilate® at no cost. For more information or to get started call: **800-554-4440**

- **Co-Pay Assistance Program**
  Offers savings to eligible patients on some of the out-of-pocket costs associated with your therapy. For more information call: **800-554-4440**

- **Reimbursement Services**
  Experienced, knowledgeable professionals providing insurance and reimbursement support to providers, patients, and families. For more information call: **800-554-4440**



Important Safety Information

Contraindications and Adverse Reactions

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.

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.

Warnings and Precautions

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.

When using a factor VIII (FVIII)-containing von Willebrand factor (VWF) product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity. Monitor plasma levels of VWF:RCo and FVIII activities in patients receiving wilate® to avoid sustained excessive VWF and FVIII activity levels, which may increase the risk of thrombotic events.

Patients with VWD, especially Type 3 patients, may potentially develop neutralizing antibodies (inhibitors) to VWF, manifesting as an inadequate clinical response. Since inhibitor antibodies may occur concomitantly with anaphylactic reactions, patients experiencing an anaphylactic reaction should also be evaluated for the presence of inhibitors.

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.

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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- A balanced 1:1 formulation of VWF/FVIII—similar to naturally occurring VWF and FVIII
- High purity
- Effective control of major and minor bleeding[11]
- Low recommended dosing[7*]
- Dual viral inactivation steps—solvent/detergent and dry heat treatments
- Simple and convenient to use

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

www.wilateusa.com

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.

References: 1. National Heart, Lung, and Blood Institute. von Willebrand Disease. Last update 2010. Available at: http://www.nhlbi.nih.gov/health/dci/Diseases/vWD/vWD_All.html. Accessed May 1, 2018. **2.** Canadian Hemophilia Society. An Introduction to von Willebrand disease. Last update 2010. Available at: http://www.hemophilia.ca/en/bleeding-disorders/vonwillebrand-disease/. Accessed May 1, 2018. **3.** Nichols WL, et al. Haemophilia. 2008;14:171-232. **4.** World Federation of Hemophilia. von Willebrand disease (VWD). Last update 2008. Available at: http://www1.wfh.org/publication/files/pdf-1330.pdf. Accessed May 1, 2018. **5.** Mannucci P. N Engl J Med. 2004;351:683-694. **6.** Nichols WL, et al. Am J Hematol. 2009;84:366-370. **7.** wilate®, von Willebrand Factor/Coagulation Factor VIII Complex (Human) full prescribing information. Octapharma USA, Inc; August 2010. **8.** Kessler CM, et al. Thromb Haemost. 2011;106:279-288. **9.** Gale AJ. Toxicol Pathol. 2011;39(1):273–280. **10.** Stadler M, et al. Biologicals. 2006;34:281-288. **11.** Berntorp E, et al. Haemophilia. 2009;15:122-130. **12.** Data on file. Octapharma USA, Inc; 2011. **13.** Farrugia A. Guide for the assessment of clotting factor concentrates. World Federation of Hemophilia. Last update 2008. Available at: http://www1.wfh.org/publication/files/pdf-1271.pdf. Accessed May 1, 2018.

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For the safe and optimal use of human proteins