

The Diagnosis and Management of von Willebrand Disease

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Continuing Education Objectives

After reading this monograph, the participant should be able to:

1. Describe the pathophysiology of von Willebrand factor (VWF) and its role in von Willebrand disease (VWD)
2. Differentiate between the three types of VWD by symptoms and diagnosis
3. List the available treatment options for VWD based upon type and severity of the disease
4. Explain the role of home infusion and specialty pharmacy providers in the care and management of VWD patients

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About the Author

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A graduate of the University of Rhode Island, Lima is also the past President of the American Society of Health-System Pharmacists (ASHP) Section of Home Care Practitioners. She has lectured at national pharmacy and nursing meetings and has published extensively on the clinical and practical aspects of home infusion and specialty pharmacy. Her work has appeared in numerous pharmacy and nursing journals and pharmaceutical texts.

No strangers to von Willebrand disease, Lima and her family all have VWD. She and her son Benjamin have Type 1 moderately severe VWD, her husband Peter has mild Type 1, and her youngest son, Nik has severe Type 3 VWD.

Author Disclosure Statement:

- Hetty Lima is a consultant member of the US Nurse Advisory Board for Octapharma, this continuing education activity's commercial sponsor.
- Hetty Lima does not discuss off-label drug usage in this article.
- Hetty Lima briefly discusses the investigational use of recombinant VWF products in the drug pipeline but does not mention brand or generic names, or the company performing the investigation.

Von Willebrand disease (VWD) is the most common congenital bleeding disorder and has a prevalence of one to two percent of the general population.^{1,2} VWD is caused by a defect in the concentration, function, and or structure of the von Willebrand factor (VWF) and presents with varying clinical manifestations. The disease was first described in 1926 by Dr. Erik von Willebrand, a Finnish internist, who reported a bleeding disorder that affected 23 out of 66 family members (16 of whom were female) living on the Åland Islands between Finland and Sweden. This family was prone to severe bleeding, and three of four children died due to hemorrhaging before the age of four. The index case was a five-year-old female with severe mucocutaneous bleeding who bled to death at age 13 at menarche. Initially, von Willebrand called the disease “pseudohemophilia;” however, he noted that this disease was clearly different from hemophilia due to its autosomal inheritance pattern, and that the disorder affected both men and women. He also recognized that bleeding symptoms were greater in children and women of childbearing age.³

Named after its discoverer, von Willebrand disease (VWD) affects approximately three million individuals in the United States. VWD presents with mucocutaneous bleeding, an autosomal pattern of inheritance, and a prolonged bleeding time despite having a normal platelet count and clotting time.⁴ It affects people of all ethnic backgrounds; more than two-thirds of individuals with VWD are asymptomatic or mildly symptomatic.⁵

VWD is caused by a lack of or defect in the von Willebrand factor (VWF), a blood protein that initiates the first step in the coagulation process.⁶ VWF is one of the largest proteins in the blood and is composed of a large number of protein sequences that form multimers (chains) of varying lengths and molecular weight. VWF is stored in the endothelial cells (Weibel-Palade bodies) and in platelets. It mediates adhesion of platelets to sites of vascular injury through its interaction with platelet glycoprotein 1b (GP1b). Additionally, VWF serves as a carrier protein for factor VIII and may facilitate the transportation of factor VIII to the site of vascular injury.⁶ VWD is attributed to an issue with primary hemostasis—the inability to form a platelet plug that prevents blood from flowing from the injured blood vessel. Conversely, hemophilia is a bleeding disorder attributed to a problem involved with secondary hemostasis in which the normal formation of a fibrin clot does not occur. The fibrin clot serves to strengthen and stabilize the platelet plug.⁷

Clinical Manifestations

Von Willebrand disease is characterized by variable mucosal bleeding particularly in the mouth, nose, throat, gastrointestinal (GI) tract, and skin surfaces. Oftentimes, menorrhagia and post-partum hemorrhage are the only presenting symptoms and these symptoms can be quite severe.^{5,8} There are five hallmark signs of bleeding associated with VWD:⁸

1. Easy bruising with indurations
2. Menorrhagia
3. Frequent or prolonged nosebleeds (epistaxis)
4. Prolonged bleeding following injury, childbirth, and surgery
5. Prolonged bleeding/mucous membrane bleeding during dental work

Oftentimes bleeding is caused by injury, other times there may be no obvious cause. In most cases, VWD is a mild disorder

with relatively few—if any—symptoms, which is why the disease is so highly undiagnosed. Many individuals do not realize that they have the disease until another family member is diagnosed or they experience surgery or major physical trauma.

Prevalence, Incidence, and Classification

Von Willebrand disease shows a worldwide distribution and affects approximately one percent of the world’s population. Patients with bleeding symptoms presenting to primary care physicians show a prevalence of 1 in 1,000; the prevalence of severe VWD requiring occasional blood transfusions is approximately 1 in 10,000 individuals. VWD also affects other animal species including dogs and pigs.⁹

Von Willebrand Disease is classified into three major types. Disease severity and treatment depend on the type of VWD that the individual has.¹⁰ The disease is classified based upon VWF multimer differentiation or abnormal multimers. VWD is classified into three types as follows:^{11,12}

- **Type 1 VWD** is the most common and mildest form of VWD and affects approximately 70 to 80 percent of persons with VWD. Type 1 VWD is due to a quantitative defect of VWF. The VWF functions normally, but levels are reduced to 20 to 50 percent of normal values, thus, a wide range of severities can be seen.¹² Type 1 is generally inherited as an autosomal dominant trait with incomplete penetrance – thus the levels of VWF and resulting symptoms can vary among affected family members.⁷
- **Type 2 VWD** involves a qualitative defect in the VWF and affects 15 to 20 percent of patients with VWD. Unlike Type 1 patients, Type 2 VWD patients produce normal levels of VWF; however, their VWF is structurally and functionally dysfunctional. There are four distinctive subgroups of Type 2 VWD:^{7,11}
- **Type 2A VWD** accounts for approximately 75 percent of cases of Type 2 VWD. VWF-dependent platelet adhesion is decreased because patients do not have a sufficient quantity of high molecular weight (HMW) multimers.

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- ▶ **Type 2B.** The VWF that patients have is defective causing an increase in spontaneous binding of VWF to platelets which further leads to the degradation and depletion of functional HMW multimers. Patients lack medium to high VWF multimers. The increase in platelet aggregation leads to mild to moderate thrombocytopenia.
- ▶ **Type 2M** VWD is inherited via an autosomal dominant pattern but is not very common. Not associated with multimer defects, Type 2M is similar to Type 2B, but with decreased platelet-function and absence of HMW multimers. There is a reduced binding of VWF multimers with platelets
- ▶ **Type 2N** VWD is inherited as an autosomal recessive gene that causes mutations that inactivate the binding site of VWF to factor VIII. Similar to mild hemophilia A with a reduced half-life of factor VIII by approximately five to 20 percent of normal.
- ▶ **Type 3** is the rarest and most severe form of VWD and is inherited as a recessive trait with the individual receiving one defective gene from the mother and the father. The incidence is one to three per million and is caused by a reduced or complete absence of VWF. The prevalence of Type 3 VWD is higher in geographic areas where consanguineous marriages are frequent.⁹ There is also a corresponding reduction in the level of factor VIII (3-10 u/dL).⁶ These individuals experience frequent, severe, life-threatening bleeds similar to individuals with hemophilia, and must be treated immediately. Individuals with Type 3 VWD can develop inhibitors to VWF after receiving intravenous VWF containing factor products.

Some individuals develop VWD later in life due to the formation of antibodies that attack and destroy the VWF. Acquired VWD is usually seen in individuals with underlying autoimmune disorders such as systemic lupus erythematosus (lupus), rheumatoid arthritis, and certain types of cancer. Additionally, certain drugs such as valproic acid and ciprofloxacin can induce VWD.⁴

Diagnosis

Diagnosis is based on patient symptoms and family history since most cases follow an autosomal dominant pattern of inheritance (see Exhibit 1). However, spontaneous genetic mutations of VWD occur in approximately 30 percent of all cases.

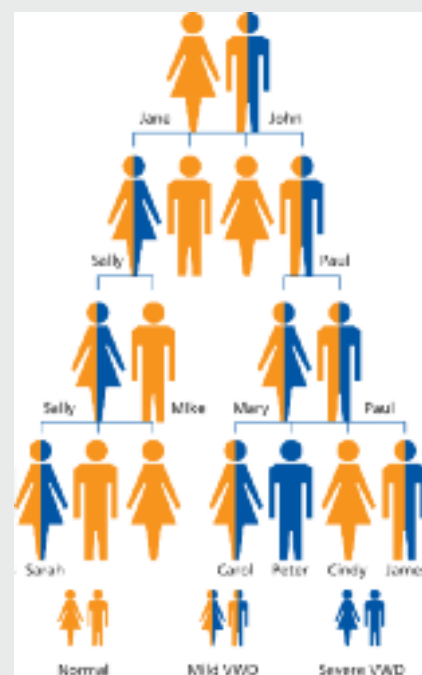
Initial screening for a bleeding disorder starts with obtaining a detailed personal and family history. VWD guidelines published by the U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute, (NHBLI), and National Institutes of Health offer a detailed algorithm and questionnaire for performing the initial evaluation of VWD. The questionnaire provides an initial evaluation strategy to determine which patients would most benefit from further diagnostic evaluation.⁴

Initial laboratory values screening often includes: platelet count, complete blood count (CBCP), prothombin time (PT),

and activated partial thromboplastin time (aPPT). Frequently, a patient's initial laboratory values screening are often normal.⁵ Individuals with VWD may have a normal PT, unless they have very low levels of factor VIII. Activated partial thromboplastin time (aPPT) may also be normal in VWD, and thus can result in false negatives in many patients. These basic coagulation tests are generally considered to be inadequate for detecting mild forms of VWD. In individuals whose personal and family histories are strong enough to indicate a potential VWD diagnosis, additional diagnostic labs should be ordered (see Exhibit 2).

Since VWD is highly variable, repeated laboratory testing is often needed to confirm diagnosis. Additionally, there is a high degree of lab test variability that may cause false negatives. An individual's levels of VWF may fluctuate; fluctuating levels are seen with: stress and anxiety, exercise, pregnancy, estrogen therapy, cold temperatures, systemic inflammation, infection, and ABO blood type.¹¹ Several of these variables affect VWF levels by releasing adrenaline from the stored sites within the blood vessel endothelium—which in turn, releases stored levels of VWF.^{11,13,14} Genetic factors such as ABO blood type affect the amount of plasma VWF. Individuals with Type O blood have approximately 25 percent lower levels of VWF than individuals with other blood types regardless of whether or not they have VWD.¹⁴ A thorough assessment of available diagnostic tests and results commonly seen by type of von Willebrand Disease is readily available in the NIH Clinical Practice Guideline titled "The Diagnosis, Evaluation and Management of von Willebrand Disease," which can be accessed at the NIH website.^{4,5}

Exhibit 1
Family History Inheritance Pattern of von Willebrand Disease



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von Willebrand Disease Case Studies

Confirming the diagnosis of VWD via lab testing is not always easy and may require repeated rounds of testing. Oftentimes, a detailed family history relative to bleeding tendencies will also facilitate the diagnosis. Case study #1 illustrates the difficulties of confirming a diagnosis of VWD.

Case Study, #1 - HL

- Female, age 40 presents with a lifelong history of menorrhagia, anemia, and easy bruising
- Positive maternal familial history for the above (mother, maternal grandmother)
- Three miscarriages all in the first trimester (note: although VWD does not definitively cause miscarriages, there appears to be an increased propensity for spontaneous abortions in the first trimester)
- Two children; experienced significant postpartum hemorrhage with each delivery
- Diagnosed with Type 1 moderate to severe VWD as a result of work up on her youngest son NL

Case Study Patient #2 - NL

- Diagnosed with severe Type 3 VWD at age 8 during a work up of the entire family. The entire family was being evaluated for unknown bleeding episodes following a detailed personal history that seemed to indicate a bleeding disorder.
- Normal circumcision (note: oftentimes, hemophilia and VWD are suspected or diagnosed upon circumcision)
- Lifelong history of easy bruising and excessive bleeding, particularly, tongue and mouth bleeds
- Once NL started walking, he developed huge swollen hematomas on his forehead and legs as he bumped into things.
- During this time, the family moved around the country and NL was brought to pediatricians in three different locations (Illinois, Washington, DC and Massachusetts). Each time (despite very visible bruises) each pediatrician stated “there is nothing abnormal in NL’s labs.”
- One dentist remarked that NL’s gums bled ‘more than usual’ for a child his age
- Due to an elongated aPTT, NL was brought to a hemophilia treatment center (HTC) in Chicago, IL for more comprehensive testing. The result of NL’s tests appears below:

| | Patient Value | Lab Reference |
|---------------|---------------|----------------------------|
| aPTT | 45 sec’s | 26-38 seconds |
| F VIII | 30 | 50-200 IU/dL |
| VWF:AG | 8 | 36-157 IU/dL |
| VWF RCoF | <10 | 45-200 IU/dL |
| VWF Multimers | None Seen | Level too low to interpret |
| Bleeding Time | 30+ mins. | 3.5 – 9.5 mins. |

After completing two rounds of comprehensive laboratory testing specifically for VWD and after undergoing eight years of check-up’s, screenings, and general testing, a definitive diagnosis of VWD was made: not only did NL have Type 3 von Willebrand, both of his parents (including HL, from Case Study #1) and his sibling also had VWD. NL inherited a defective gene from each of his parents and he also had Type O blood. This case illustrates the difficulties in confirming a diagnosis of von Willebrand and is highlighted in the family genogram.

Neither of NL’s parents was aware of the fact that they had VWD despite each parent having a family history of bleeding tendencies common to VWD (menorrhagia, easy and frequent bruising, epistaxis etc). Once the diagnosis of VWD was confirmed, the family received appropriate education and instruction in the self-management of the disease. HL (Case Study #1), her husband PL, and their son BL were prescribed intranasal Stimate® to treat their bleeding episodes. Their youngest son NL (Case Study #2) was prescribed intravenous clotting factor containing VWF and the family was taught to perform peripheral ‘self-infusion’ of clotting factor at home. Their medications were delivered to their home by a national, specialty pharmacy. Oral aminocaproic acid syrup was also prescribed for the boys and maintained at home to treat mouth bleeds or prior to any dental procedures.

Case Study - Family Genogram

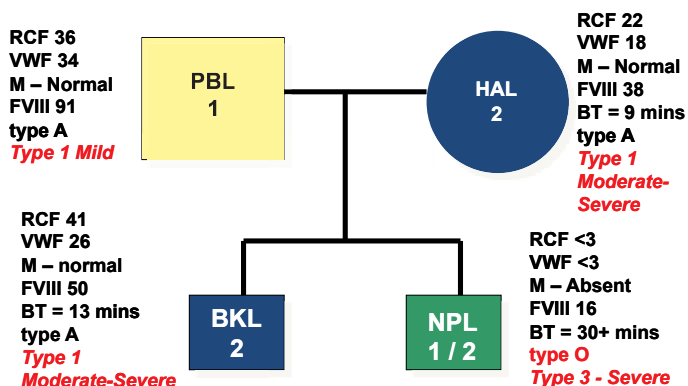


Exhibit 2 Standard Laboratory Tests for von Willebrand Disease^{9,11}

| TEST | PURPOSE |
|--|---|
| Factor VIII Clotting Activity (FVIII:C). | Measures the functional activity of factor VIII. Normal ranges are 50-150 IU/dL |
| VWF Antigen (VWF:Ag) | An immunoassay protein quantification that measures the total amount VWF. Normal ranges are 50 to 200 m/dL |
| von Willebrand Ristocetin Co-factor and/or collagen binding capacity (VWF:RCo and/or VWF:CB) | Measures the agglutination of normal platelets in the presence of ristocetin, thus, measuring the functional activity of VWF. Normal ranges are 50 to 200 m/dL. |
| von Willebrand Factor (VWF) Multimer Analysis | Measures the quantity and molecular structure of the VWF molecule and provides a visualization of how well the VWF monomer is joined in chains (multimerized). Analysis of the VWF multimers is necessary to ensure an accurate classification of the disease |
| Ristocetin-Induced Platelet Aggregation (RIPA). | Measures the sensitivity of VWF relative to Ristocetin. Useful in distinguishing Type 2B from 2A VWD |

Drugs and foods that affect platelet function can also mask the diagnosis of VWD and may include (but are not limited to): aspirin, NSAIDs, guaifenesin, quinine and penicillin, fish high in omega-3 fatty acids, vitamin E, and herbs such as ginkgo biloba, ginseng, and echinacea.^{11,13}

Treatment Options

Treatment goals for VWD include adjunctive measures to achieve hemostasis and focus on correcting the patient's bleeding time, replacing the plasma levels of VWF and factor VIII to correct the coagulation abnormality.^{7,11} Treatment goals can be achieved via three strategies to prevent and control bleeding:⁴

1. Increase the plasma concentration of VWF by stimulating the release of endogenous VWF from storage sites within blood vessel endothelium through the use of desmopressin.
2. Replace VWF by intravenous infusions of plasma-derived, virally inactivated VWF concentrates.
3. Promote hemostasis and wound healing without significantly altering the plasma concentration of VWF via the use of adjunctive agents.

In late-2009, the U.S. Food and Drug Administration (FDA) approved two new medications for von Willebrand disease: tranexamic acid (Lysteda™) and von Willebrand Factor/Coagulation Factor VIII Complex (Human), or wilate®, which received “orphan drug status” as a fractionated plasma product. These new treatments for VWD will be discussed in the appropriate pharmacologic class of treatment options.

The following is a summary of VWD treatment options. Dosing and more specific information is detailed in Exhibit 3.

- Desmopressin Acetate (DDAVP).** DDAVP is a synthetic derivative of the anti-diuretic hormone vasopressin. DDAVP causes the release of VWF and factor VIII from storage sites within the endothelium of the blood vessels. DDAVP is indicated for Type 1 VWD and mild hemophilia A, some Type 2A, but is not indicated for Types 2 and Type 3 VWD. A test dose of DDAVP is usually given in a controlled medical setting (during a non-bleeding state) in order to determine patient response. For DDAVP to be considered effective, a three- to five-fold increase in a patient's VWF/FVIII over baseline within one hour following administration is required.⁴ Dosage forms include a parenteral (intravenous and subcutaneous) and intranasal form.

DDAVP is available as a highly concentrated (1.5 mg/mL) intranasal spray (Stimate®). Clinicians should take care not to dispense the generic DDAVP spray, as it is a much weaker concentration (0.1 mg/mL), and is indicated for diabetes insipidus. Generic DDAVP nasal spray will not stop bleeding. Side effects of DDAVP include flushing, mild tachycardia, headaches, and dizziness, and are related to the release of adrenaline. Hyponatremia and fluid overload can occur generally in the elderly and in children less than two years old. Regulate the patient's fluid intake for at least 24 hours following DDAVP administration.⁷

- Factor Concentrates.^{7,11}** Factor concentrates are indicated for individuals with Type 2A, 2B, and 3 or for those patients where desmopressin is not effective or is contraindicated including individuals with Type 1 VWD prior to surgery or injury. Factor concentrates work by raising the patient's plasma levels of VWF and factor VIII. Since currently marketed clotting factor for VWD is plasma-derived, the products are screened for hepatitis, HIV, and other viruses. VWF clotting factor products have undergone extensive viral inactivation to eliminate the risks of infusion-related viral transmission. These products contain HMW multimers of VWF. Unlike clotting factor products for hemophilia which are dosed by international units (IU) each vial of factor concentrate is labeled with the activity expressed in both von Willebrand ristocetin co-factor international units (VWF:RCo I.U.) and factor VIII international units (F VIII I.U.).

For patients with VWD, the dosage to be administered is based on the patient's body weight in kilograms (kg) and is normally ordered in ristocetin co-factor units (VWF:RCo I.U.).

Exhibit 3

Treatment Options and Dosages for von Willebrand Disease (VWD)^{7,11}

Desmopressin Acetate (DDAVP)^{4,15}

- ▶ IV: 0.3 mcg/kg in 25 – 50 mL 0.9% sodium chloride infused over 30 minutes.
- ▶ SQ: 0.3 mcg/kg over 30 minutes; may be administered subcutaneously without the addition of NS. Peak VWF and FVIII levels are attained 90 minutes after IV administration and last in the plasma for approximately eight to 10 hours.⁴
- ▶ *Intranasal*: Use highly concentrated (1.5 mg/mL) DDAVP nasal spray (Stimate[®]). For pediatric patients weighing <50 kg, the recommended dose one puff (150 mcg) into one nostril. For adults whose weight is greater than 50 kg, the recommended dose is 300 mcg or one spray in each nostril.¹⁵

VWF/Factor VIII Concentrate:

- ▶ *Antihemophilic factor/von Willebrand factor complex*. Dose will vary by patient's weight and type of hemorrhagic incident. Usual dosing guide:

$$\text{RCoF Dose (IU)} = \frac{\text{Body Weight (kg)} \times \% \text{ Target increase in VWF plasma level}}{1.5 \text{ Recovery Rate}^{16}}$$

Antifibrinolytics^{5,16-19}

- ▶ *Aminocaproic Acid (Amicar[®])*: Available as 500 mg tablets and a 250mg/mL liquid
IV: 50 to 100 mg/kg
Orally: Every six to 12 hours followed by maintenance doses of 100 mg/kg every six hours for three to seven days, maximum of 6 gm/ dose
- ▶ *Tranexamic acid (Cyklokapron[®])*: Intravenous dosage form is available in a concentration of 100 mg/mL. Prior to teeth extractions, the dosage is 10 mg per kg of body weight three to four times daily for two to eight days. Dosages and frequency of administration must be adjusted in patients with moderate to severe impaired renal function.¹⁸
- ▶ *Tranexamic acid (Lysteda[™])*: was approved in November 2009 and is indicated for the treatment of cyclic heavy menstrual bleeding or menorrhagia. Menorrhagia is oftentimes a chief complaint in women with von Willebrand disease. Lysteda[™] is convenient because it is a sustained release tablet that allows for less frequent dosing than the standard dose formulation. Although tranexamic acid tablets are one of the first-line treatments for menorrhagia in many countries throughout the world, this is the first time the oral tablet is available in the U.S.

*Both medications can be used as a mouthwash, dilute 10% IV solution with NS.

Adjunctive Therapies

- ▶ *Oral contraceptive agents (OCAs)*: to control menorrhagia. OCAs help regulate and reduce the duration of menstrual bleeding. Estrogen increases the level of fibrinogen, prothrombin, FVII, FVIII, and VWF, and thus, promotes hemostasis.⁷
- ▶ *Progesterone IUD*
- ▶ *Topical hemostatic agents* applied to exposed bleeding sites are an adjunctive treatment for VWD and include: topical thrombin, Liquid Band Aid[®], Nosebleed QR[™], UrgentQR[™], topical phenylephrine (Neosynephrine[®]) for nosebleeds

Specialty pharmacy and home care clinicians should be cautious and verify the type of units prescribed with the patient's physician. The ratio of VWF:RCo to FVIII and quantity of VWF multimers will vary among factor products, therefore, the dose and frequency of administration of these products will also vary. The prescribed quantity of factor will also vary depending on the type of VWD the patient has as well as the severity of the bleeding episode. The goal of factor treatment is to achieve a therapeutic level of 100 IU/dL of VWF:RCo and generally, for the first three days of treatment, a nadir of 50 IU/dL VWF:RCo. Initial dosing recommendations are summarized in Exhibit 4. Additionally, the surgical and non-surgical indications for VWF containing clotting factors are not the same; refer to Exhibit 5. After administration, patients and their caregivers are instructed to document the lot number(s), expiration date(s), factor concentrate name and total number of units infused on "bleed or infusion logs." This information

can be found on the factor concentrate's box and provides the hemophilia treatment center (HTC) staff with valuable information regarding the patient's pattern of bleeds.

Recombinant versions of VWF (or rVWF) clotting factor have been studied in animals, and preliminary research indicates that rVWF are comparable to plasma-derived (pdVWF) factor. Clinical trials of rVWF are ongoing.⁷

- ▶ **Antifibrinolytics.** Antifibrinolytics are useful agents for the treatment of mucosal bleeds in the mouth, tongue, and nose. Digestive enzymes present in the saliva make the treatment of mouth bleeds difficult. Hematologists also prescribe antifibrinolytics for menorrhagia.

Exhibit 4 VWF Clotting Factor Concentrates – Initial Dosing Recommendations for Prevention & Management of Bleeding⁴

| | Minor Surgery / Bleeding | Major Surgery / Bleeding |
|---|--|--|
| Loading Dose of VWF:RCo in IU/dL | 30 – 60 U per kg | 40 – 60 U per kg |
| Maintenance Dose | 20-40 U / kg every 12 to 48 hours | 20-40 U / kg every 8 to 24 hours |
| Monitoring | VWF:RCo and FVIII trough and peak, at least once | VWF:RCo and FVIII trough and peak, at least daily |
| Therapeutic Goal | Trough VWF:RCo and FVIII > 50 IU/dL for 3 to 5 days | Trough VWF:RCo and FVIII > 50 IU/dL for 7 to 14 days |
| Safety Parameter | Do not exceed VWF:RCo 200 IU/dL or FVIII 250-300 IU/dL | Do not exceed VWF:RCo 200 IU/dL or FVIII 250-300 IU/dL |
| | May alternate with DDAVP for latter part of treatment | |

Conclusion

Effective management of VWD is a life-long effort that requires comprehensive care from skilled clinicians. Specialty pharmacy/home infusion providers are uniquely positioned to train and educate families with VWD about the importance of being compliant with their medication regimens particularly, pre-treating prior to activities where excessive bleeding may occur (sports, dental procedures and extractions, elective surgery). Additionally, specialty infusion pharmacies are qualified to augment the training provided by the patient's HTC staff in an effort to make the patient and their caregivers independent with self infusion.

Once properly diagnosed and treated, individuals with VWD can lead normal and productive lives. The aforementioned family leads a very active, athletic lifestyle. Both sons are in college where they participate in numerous intramural and extracurricular sports, and the parents are active in cycling, hiking, and running.

Oftentimes, complications arise because the individual doesn't realize that he or she has VWD until surgery or major trauma occurs. When presented with a patient who has extensive bleeding patterns, the clinician should ask if other members in the family also have unusual bleeding tendencies. To address this public health concern, several VWD public awareness initiatives have been launched by the Centers for Disease Control (CDC) and the National Hemophilia Foundation (NHF) to spread knowledge of and to encourage testing for VWD.

Hemophilia Treatment Centers

In 1973, the National Hemophilia Foundation (NHF) launched a two-year campaign to establish the creation of a nationwide network of hemophilia diagnostic and treatment centers. The idea was based upon providing a range of comprehensive services for patients and families within one treatment facility. By 1975, hemophilia treatment centers (HTCs) were founded with federal funding from the Health Resource Services Administration (HRSA) and Centers for Disease Control (CDC) in an effort to improve clinical outcomes for all patients with bleeding disorders, regardless of their insurance status or ability to pay. Patients are usually referred to their nearest HTC upon initial diagnosis, although—as pointed out in Case Study #2—they can play a pivotal role in pinpointing difficult diagnoses.

Today, there are approximately 141 federally funded HTCs across the country that coordinate care for bleeding disorder patients—in the home, the outpatient setting, and in acute care facilities. A 2001 study found that patients experienced 40-percent fewer hospital stays for bleeding-related events when receiving treatment coordinated by an HTC than patients seen in other care facilities.²⁰ Additionally, patients seen in HTCs were 40-percent less likely to die of a hemophilia-related complication.²⁰ The comprehensive care model utilized in HTCs has been described as the model of the future for coordinated, proactive health-based treatment of chronic disease.

Exhibit 5

VWD - FDA Approved Treatment Options^{16, 21-24}

| Product | Type 1 Non-surgical | Type 1 Surgical | Type 2 Non-surgical | Type 2 Surgical | Type 3 Non-surgical | Type 3 Surgical | Hemophilia A | Surgical Use Comments |
|--|---------------------|-----------------|---------------------|-----------------|---------------------|-----------------|-------------------------|--|
| von Willebrand Factor/Factor VIII Concentrate Alphanate® | | ✓ | | ✓ | | No | ✓ | For patients unresponsive or where desmopressin is contraindicated only; not approved for severe Type 3 VWD undergoing major surgery |
| von Willebrand Factor/Factor VIII Concentrate Humate-P® | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | For mild to moderate VWD in patients with inadequate or unresponsive to desmopressin and patients with severe Type 3 VWD |
| Koate-DVI®* | | | | | | | ✓ | |
| DDAVP Nasal Spray Stimate® | | | | | | | ✓ (Mild, FVIII > 5%) | May be used prophylactically for minor surgical procedures and postoperatively |
| von Willebrand Factor/Factor VIII Concentrate wilate®** | ✓ | | ✓ | | ✓ | | | Not indicated for the prevention of excessive bleeding during and after surgery in VWD patients. |

* Contains VWF and FVIII, however, product is only approved for hemophilia A

** Indicated for treatment of spontaneous and trauma-induced bleeding episodes in patients with severe VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.²³

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Exhibit 6
von Willebrand Factor/Factor VIII Product Comparison (adapted from²⁵)

| | Alphanate® | Humate-P® | wilate® |
|--|--|---|--|
| FDA Approved Indications | <ul style="list-style-type: none"> - Surgical and/or invasive procedures in patients with VWD in whom desmopressin (DDAVP) is either ineffective or contraindicated - Not indicated for severe Type 3 patients undergoing major surgery - Prevention and control of bleeding in patients with factor VIII deficiency due to hemophilia A or acquired factor VIII deficiency | <ul style="list-style-type: none"> - Spontaneous and trauma-induced bleeding episodes in patients with severe VWD. - Patients with mild to moderate VWD where use of desmopressin is known or suspected to be inadequate - Prevention of excessive bleeding during and after surgery - Adults only: Treatment and prevention of bleeding in hemophilia A | <ul style="list-style-type: none"> - Spontaneous and trauma-induced bleeding episodes in patients with severe VWD. - Patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated - Not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients. Not indicated for hemophilia A |
| VWF:RCo | Not less than (NLT) 0.4 IU per 1 IU of FVIII:C | 72-224 IU per mL | 90 IU per mL |
| Factor VIII | 40-80 IU per mL | 40-80 IU per mL | 90 IU per mL |
| VWF:RCo/FVIII Ratio (approx) | 0.4 : 1 (Varies) | 2.4 : 1 | 1 : 1 |
| Half-Life (hours) | VWF: 7.46 ± 3.20 (mean) FVIII: 13.03 ± 2.12 (mean) | VWF: 11 (range 3.5-33.6) (median) FVIII: Not available for VWD patients | VWF: 15.8 ± 11 (mean) FVIII: 19.6 ± 6.9 (mean) |
| Loading Dosage (IU VWF:RCo/kg Body Weight (BW)) | Hemorrhage prophylaxis for surgical and invasive procedures of VWD; except Type 3 undergoing major surgery - Adult: 60 IU/kg - Pediatric: 75 IU/kg | Type 1 VWD Mild <i>Major hemorrhage: 40-60 IU/kg (1 dose)</i> Type 1 Moderate/Severe <i>Minor hemorrhage: 40-50 IU/kg (1-2 doses)</i> <i>Major hemorrhage: 50-75 IU/kg (1dose)</i> Type 2 (all variants) and Type 3 VWD <i>Minor hemorrhage: 40-50 IU/kg (1-2 doses)</i> <i>Major hemorrhage: 60-80 IU/kg (1 dose)</i> Prevention of Excessive Bleeding During & After Surgery <i>Major: 100 IU/dL VWF:RCo target peak plasma level</i> <i>80-100 IU/dL FVIII:C target peak plasma level</i> <i>Minor: 50-60 IU/dL VWF:RCo target peak plasma level</i> <i>40-50 IU/dL FVIII:C target peak plasma level</i> | Minor hemorrhage: 20-40 IU/kg for one dose Major hemorrhage: 40-60 IU/kg for one dose |

Exhibit 6 (continued)
von Willebrand Factor/Factor VIII Product Comparison (adapted from²⁵)

| | Alphanate® | Humate-P® | wilate® |
|--|--|---|--|
| Maintenance Dosage (IU VWF:RCo/kg BW) | Hemorrhage prophylaxis for surgical and invasive procedures of VWD; except Type 3 undergoing major surgery - Adult: 40-60 IU/kg every 8-12 hours as clinically needed. Dosing may be reduced after third postoperative day - Pediatric: 50-75 IU/kg every 8-12 hours as clinically needed. Dosing may be reduced after third postoperative day | Minor hemorrhage: None Type 1 VWD Mild Major hemorrhage: 40-50 IU/kg every 8-12 hours for 3 days; then daily for up to a total of 7 days Type 1 Moderate/Severe Major hemorrhage: 40-60 IU/kg every 8-12 hours for 3 days; then daily for up to a total of 7 days Type 2 (all variants) and Type 3 VWD Minor hemorrhage: None Major hemorrhage: 40-60 IU/kg every 8-12 hours for 3 days; then daily for up to a total of 7 days Prevention of Excessive Bleeding During & After Surgery <i>Major:</i> VWF:RCo and FVIII:C target peak plasma level: >50 IU/dL up to 3 days post surgery, >30 IU/dL after day 3 <i>Minor:</i> VWF:RCo target peak plasma level: >30 IU/dL up to 3 days post surgery FVIII:C after day 3, >30 IU/dL day 3 | Applies to All VWD Types: Minor hemorrhage: 20-30 IU/kg every 12-24 hours up to 3 days Major hemorrhage: 20-40 IU/kg every 12-24 hours up to 5-7 days |
| Rate of Administration | Do not exceed 10 mL/minute | 4 mL/minute | 2-4 mL/minute |

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Providing Counseling to Your Patients Living With von Willebrand Disease

If you have von Willebrand disease (VWD), you can take steps to prevent bleeding and stay healthy. You should:

- ▶ Avoid over-the-counter medicines that can affect blood clotting, including aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs).
- ▶ Always check with your doctor before taking any medicines.
- ▶ Tell your doctor, dentist, and pharmacist that you have VWD. Your dentist can talk to your doctor about whether you need medicine before dental work to reduce bleeding. You also may want to tell people like your employee health nurse, gym trainer, and sports coach about your condition.
- ▶ Consider wearing a medical ID bracelet or necklace if you have a serious form of VWD (for example, Type 3). In case of a serious accident or injury, the health care team treating you will know that you have VWD.
- ▶ Exercise regularly and maintain a healthy weight. Exercise helps keep muscles flexible. It also helps prevent damage to muscles and joints. Always stretch before exercising.