Overview of von Willebrand Disease (VWD) and Its Treatment

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CSL Behring at-a-Glance

- Global leader in plasma protein biotherapeutics industry
- Owns and operates ZLB Plasma, one of world’s largest plasma collection networks
- 8,000+ employees in 19 countries
- Headquartered in King of Prussia, Pennsylvania, USA
- Three manufacturing facilities
- Six research facilities
Global Portfolio covering different Therapeutic Areas

<table>
<thead>
<tr>
<th>Critical Care</th>
<th>Immunology</th>
<th>Coagulation</th>
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<tr>
<td>Albumin Solutions</td>
<td>Polyvalent Immunoglobulins</td>
<td>Recombinant factor VIII</td>
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<td>Carimune® NF</td>
<td>Helixate® FS/NexGen</td>
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<td>Sandoglobulin®</td>
<td>Factor VIII:C/VW factor</td>
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<td>Sandoglobulin® NF Liquid</td>
<td>Haemate® P, Humate-P®</td>
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<td>Sanglopor®</td>
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<td>Redimune®</td>
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<td>Vivaglobin®</td>
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<td>Hyperimmunes</td>
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<td>Cytogam®</td>
<td>Other Products</td>
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Product availability varies from country to country, depending on registration status.

Products licensed in Canada, Products under Special Access Program in Canada.
CSL Behring Manufacturing

**Marburg Plant** (Marburg, Germany)
- 1,700 employees
- Core products: coagulation factors, critical care and immunoglobulins
- Specialty products: hyperimmunes

**Bern Plant** (Bern, Switzerland)
- 800 employees
- Core products: immunoglobulins
- Specialty products: IVIg, albumin, anti-D

**Kankakee Plant** (Kankakee, IL)
- 575 employees
- Core products: coagulation factors, alpha₁-proteinase inhibitor
- Specialty products: Monoclate-P®, albumin, pastes
Åland Islands – young woman bled to death 3rd period
“pseudohemophilia” 1926
vWD – Von Willebrand’s Disease

Most common inherited bleeding disorder,\(^1\) occurring in about 1 in every 100 people;\(^1\) occurs equally in males and females\(^2\)

Abnormality/deficiency of blood protein\(^2\)

Easy bruising and excessive mucosal bleeding

Functions of the VWF Molecule

Mediate platelet adhesion

Facilitate platelet aggregation

Bind and protect factor VIII (FVIII)

Normal Clot Formation

Hemostasis (blood clots at site of injury and bleeding stops)
• Part 1: Primary hemostasis (after-vessel injury and constriction of the blood vessel)

VWF binds to collagen at the site of vessel injury, initiating clot formation while platelets also rush to the injury site

VWF begins to bind with blood platelets (working as a glue, continuing clot formation (platelet adhesion))

Bleeding stops due to platelet bridges that have formed a plug (platelet aggregation)

Reference: Data on file, CSL Behring.
Normal Clot Formation (cont)

- Part 2: Secondary hemostasis

Clotting factors are activated (clotting cascade) and fibrin is released (usually results in long-term blood clotting)

Successful completion of both parts results in the final step of the clotting process: formation of a stable hemostatic plug

Reference: Data on file, CSL Behring.
The Roles of Multimers in Blood Clotting

VWF multimers contain sites for collagen and platelet binding

HMWMs bind more readily to collagen and platelets than low molecular weight (LMW) multimers

Greater number of binding sites (A3 for collagen and A1 for platelets) with high molecular weight VWF (HMW-VWF)

HMW-VWF encourages formation of a stable hemostatic plug

Impaired hemostatic plug with LMW-VWF

Reference: Data on file, CSL Behring.
Diagnosing VWD: Overview

Three components of diagnosis:

- Personal history of excessive mucocutaneous bleeding
- Family history of excessive bleeding
- Laboratory evaluation

Diagnosing VWD: Variability

Fluctuating VWF levels may be due to:¹

- Exercise
- Infection
- Pregnancy
- Stress
- Hormone therapy
- Recent surgery
- Medications

ABO blood type affects VWF levels

- Blood group O individuals have levels 20% to 25% lower than other individuals²

Need for repeat testing

- Significant variability of VWF and FVIII values requires that testing must be repeated at least twice before diagnosis is confirmed or refuted²

# Diagnosing VWD: Specific Assays

Specific assays for accurately diagnosing VWD and determining the subtype

<table>
<thead>
<tr>
<th>Diagnostic assay</th>
<th>Purpose of assay</th>
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<tr>
<td>VWF activity (VWF: ristocetin cofactor [RCO])</td>
<td>Provides a measurement of VWF function(^1)</td>
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<td>VWF multimers</td>
<td>Analyzes the quality and provides a measurement of VWF multimers—essential for determining subtype(^2,3)</td>
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<td>FVIII clotting activity (FVIII:C)</td>
<td>Determines the degree of FVIII activity(^1)</td>
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<td>VWF antigen (VWF:Ag)</td>
<td>Measures the quantity of VWF(^2,4)</td>
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<td>Ristocetin-induced platelet aggregation (RIPA)</td>
<td>Provides a measurement of VWF function(^5)</td>
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<tr>
<td>Platelet function analyzer 100 (PFA-100)</td>
<td>Identifies the presence of VWD through primary hemostasis simulation(^6)</td>
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</table>

**References:**
Diagnosing VWD: Type

VWD can be caused by a **quantitative** or **qualitative** defect in VWF

Quantitative types:

- **Type 1**
  - Most common type (80% of all cases)
  - Mildest form—in most cases only mild bleeding tendency

- **Type 3**
  - Has a prevalence of 1 to 3 per million in most populations
  - Most severe type (severe recurrent mucocutaneous bleeding; frequent soft tissue and musculoskeletal bleeding)

Diagnosing VWD: Type

Qualitative types:

• **Type 2**
  
  — Clinical manifestations similar to those of type 1 VWD
  
  — Divided into 4 subgroups:
    
    Type 2A: Low VWF:RCo to VWF:Ag ratio with absent high molecular weight multimers (HMWMs)
    
    Type 2B: Enhanced binding of VWF for platelet receptors
    
    Type 2M: Loss-of-function equivalent of type 2B VWD
    
    Type 2N: Only laboratory abnormality is often a reduced plasma FVIII level

Treatment Options: Non-replacement

<table>
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<th>Drug</th>
<th>Type</th>
<th>How taken</th>
<th>Useful in</th>
<th>Notes</th>
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<tr>
<td>Desmopressin acetate</td>
<td>Synthetic hormone¹</td>
<td>Injection or nasal spray¹</td>
<td>Most patients with type 1 and some with type 2A VWD¹</td>
<td>Should not be used in patients with type 2B VWD</td>
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<tr>
<td>Oral contraceptives</td>
<td>Birth control pills</td>
<td>By mouth</td>
<td>Women who have heavy menstrual bleeding¹</td>
<td>Hormones in the pills can increase VWF and FVIII activity¹</td>
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<tr>
<td>Antifibrinolytic drugs</td>
<td>Aminocaproic acid; tranexamic acid²</td>
<td>Injection or by mouth²</td>
<td>VWD patients to stop bleeding following minor surgery, tooth extraction, or an injury¹</td>
<td>Can be used alone or with desmopressin and replacement therapy¹</td>
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</table>

Depending on the type of VWD; the severity of an injury; the severity of nose, menstrual, or post-childbirth bleeding; or the extent of a medical or dental procedure, the physician may prescribe one or more of these treatments.

## Treatment Options: Replacement

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<thead>
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<th>Drug</th>
<th>Type</th>
<th>How taken</th>
<th>Useful in</th>
<th>Notes</th>
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</table>
| Replacement therapy| Concentrate of VWF and FVIII\(^1\)        | Infusion (IV) | - Patients who cannot tolerate desmopressin or who need prolonged treatment\(^1\)  
- Patients with type 1 VWD who do not respond to desmopressin\(^1\)  
- Patients with any variant of type 2 VWD\(^1\)  
- Patients with type 3 VWD\(^1\) | Effective in a wide range of patients, including those with severe VWD |

Humate-P® Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized

Humate-P® is indicated for:

- Adult patients for treatment and prevention of bleeding in hemophilia A

- Adult/pediatric patients for treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease

- Mild and moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate.
Humate-P®: High-Quality VWF

- The clinical efficacy of a VWF concentrate is related to the quality of its multimers—the more high molecular weight (HMW) multimers, the better\(^1\) and is 96% similar to NHP
- HMW-VWF demonstrates increased hemostatic activity\(^1\)
- HMW-VWF is associated with
  - High specific activity\(^1\)
  - VWF:RCo activity
  - Collagen-binding activity
- HMW-VWF is associated with shortened bleeding time\(^2\)

Humate-P®: High-Quality VWF (Part 1)

Densitometric analysis of various von Willebrand factor/factor VIII concentrates

Humate-P®: High-Quality VWF (Part 2)

The mainstay of VWD treatment is the replacement of the deficient protein [VWF]

Quantity: High ratio of VWF:RCo to FVIII

International unit (IU) activity of VWF:RCo and FVIII per vial of Humate-P®

• Humate-P® contains larger amounts of VWF than it does FVIII
  — The average ratio of VWF:RCo to FVIII activity is 2.4 to 1

<table>
<thead>
<tr>
<th>VWF:RCo/vial</th>
<th>FVIII/vial</th>
<th>Ratio</th>
<th>Diluent</th>
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<tr>
<td>1200 IU</td>
<td>500 IU</td>
<td>2.4 to 1</td>
<td>10 mL</td>
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<tr>
<td>2400 IU</td>
<td>1000 IU</td>
<td>2.4 to 1</td>
<td>15 mL</td>
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Humate-P®: Proven Clinical Efficacy

In a retrospective review of Humate-P® treatment in 97 Canadian patients with VWD:

Humate-P®: Pasteurization Proven to Inactivate Enveloped and Non-Enveloped Viruses

The addition of stabilizing agents (which are removed later in the manufacturing process) preserves the high molecular weight von Willebrand factor multimers of Humate-P®.

References:
2. Data on file, CSL Behring LLC.
Humate-P®: Convenience for Healthcare Providers and Patients

Small assay sizes for added convenience

• Less infusion time
• Small vials and packaging
• Less storage space
• 24 month storage at room temperature

Please see accompanying full prescribing information for Humate-P®.
Humate-P®: Convenience for Healthcare Providers and Patients

Mix2Vial™ needle-free transfer device—a simple way to reconstitute Humate-P®

• Fast  Easy Safe
• Less risk of accidental injury
• Less time to prepare product
• Simple process encourages independence
• Built-in filter
• For use with all Luer-Lok™ syringes
# Humate-P®: Dosing for VWD Treatment

Dosing recommendations for the treatment of VWD:

<table>
<thead>
<tr>
<th>Classification of VWD</th>
<th>Hemorrhage</th>
<th>Dosage (IU VWF:RCo/kg body weight)</th>
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<tr>
<td><strong>Type 1</strong></td>
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<tr>
<td>• Mild, if desmopressin is inappropriate (baseline VWF:RCo activity typically &gt;30%)</td>
<td>Major (e.g. severe or refractory epistaxis, CNS trauma, or traumatic hemorrhage)</td>
<td>40 to 50 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of VWF:RCo &gt;50% ; then 40 to 50 IU/kg daily for a total of up to 7 days of treatment</td>
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<tr>
<td>• Moderate or severe (baseline VWF:RCo activity typically &lt;30%)</td>
<td>Minor (e.g. epistaxis, oral bleeding, menorrhagia)</td>
<td>40 to 50 IU/kg (1 or 2 doses)</td>
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<td>Major (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)</td>
<td>40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of VWF:RCo &gt;50% ; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment. Factor VIII:C levels should be monitored and maintained according to the guidelines for hemophilia A therapy</td>
</tr>
<tr>
<td><strong>Types 2 (all variants) and 3</strong></td>
<td>Minor (clinical indications above)</td>
<td>40 to 50 IU/kg (1 or 2 doses)</td>
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<td>Major (clinical indications above)</td>
<td>40 to 80 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of VWF:RCo &gt;50%, then 40 to 60 IU/kg daily for a total of up to 7 days of treatment. Factor VIII:C levels should be monitored and maintained according to the guidelines for hemophilia A therapy</td>
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# Humate-P® von Willebrand Disease Dosage Calculator

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<td>1100</td>
<td>1125</td>
<td>1150</td>
<td>1175</td>
<td>1200</td>
<td>1225</td>
<td>1250</td>
<td>1275</td>
<td>1300</td>
<td>1325</td>
</tr>
</tbody>
</table>

These calculations are to be used only with Humate-P® and are applicable to all VWD types.

**General Rule:** Doses are calculated based on an expected in vivo recovery of 2.0 IU/dL rise in VWF:RCo activity per every IU/kg of VWF:RCo administered.¹

See attached Prescribing Information for full dosing recommendations.

(*) delta IU/dL is defined as Target Level (VWF:RCo) - Baseline level (VWF:RCo)
POP QUIZ:

What is the most severe subtype of vWD?

TYPE 3
POP QUIZ:

What does the “P” in Humate-P stand for?

Pasteurized

When referring to HMW-VWF, what does "HMW" stand for?

High Molecular Weight
POP QUIZ:

How similar is Humate-P when compared to the VWF in Normal Human Plasma?

a) 50%
b) 75%
c) 96%
d) 87%

Thank You

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