BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

**PHARMACY COVERAGE GUIDELINE**

# HEMOPHILIA A FACTOR VIII PRODUCTS:
# ADVATE®
# ADYNOVATE®
# AFSTYLA®
# ALPHANATE®
# ALTUVIIIO™
# ELOCTATE®
# ESPEROCT
# HEMOFIL M®
# HUMATE-P®
# JIVI®
# KOATE®
# KOGENATE FS®
# KOVALTRY®
# NOVOEIGHT®
# NUWIQ®
# OBIZUR®
# RECOMBINATE®
# WILATE®
# XYNTHA®
# Generic Equivalent (if available)

**This Pharmacy Coverage Guideline (PCG):**
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

## Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

## Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG

ORIGINAL EFFECTIVE DATE: 08/15/2024 | ARCHIVE DATE: | LAST REVIEW DATE: | LAST CRITERIA REVISION DATE:

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- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

## Criteria:

➢ **Criteria for initial therapy:** Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Jivi, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Wilate, Xyntha and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual's age is consistent with FDA label

3. Individual has a confirmed diagnosis of **ONE** of the following:
   a. **For Advate, Adynovate, Afstyla, Altuviiio, Eloctate, Esperoct, Hemofil M, Jivi, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha:** Hemophilia A (congenital Factor VIII deficiency) and the request is for **ONE** of the following:
      i. On-demand treatment and control of bleeding episodes given at the time of bleeding
      ii. Perioperative management of bleeding to prevent bleeding for short periods of time
      iii. Routine prophylaxis to reduce the frequency of bleeding episodes

   b. **For Koate:** Hemophilia A (congenital Factor VIII deficiency) and the request is for **ONE** of the following:
      i. On-demand treatment and control of bleeding episodes given at the time of bleeding
      ii. Perioperative management of bleeding to prevent bleeding for short periods of time

   c. **For Alphanate:** Hemophilia A (congenital Factor VIII deficiency) or von Willebrand Disease and the request is for **ONE** of the following:
      i. Control and prevention of bleeding in adult and pediatric individuals with hemophilia A
      ii. Surgical and/or invasive procedures in adult and pediatric individuals with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery

   d. **For Humate-P:** Hemophilia A (congenital Factor VIII deficiency) or von Willebrand Disease and the request is for **ONE** of the following:
      i. Hemophilia A – Treatment and prevention of bleeding in adults
      ii. von Willebrand disease (VWD) – Adults and pediatric individuals in the (1) treatment of spontaneous and trauma-induced bleeding episodes, and (2) prevention of excessive bleeding during and after surgery. This applies to individuals with severe VWD as well as individuals with mild to moderate VWD where the use of desmopressin is known or suspected to be inadequate. It is not indicated for the prophylaxis of spontaneous

bleeding episodes in VWD

e. **For Wilate:** Hemophilia A (congenital Factor VIII deficiency) or von Willebrand Disease and the request is for **ONE** of the following:
   i. Hemophilia A: **ONE** of the following:
      1. On-demand treatment and control of bleeding episodes
      2. Routine prophylaxis to reduce the frequency of bleeding episodes
   ii. von Willebrand disease (VWD): **ONE** of the following:
      1. On-demand treatment and control of bleeding episodes
      2. Perioperative management of bleeding

f. **For Obizur:** Acquired hemophilia A and **BOTH** of the following:
   i. On-demand treatment and control of bleeding episodes with a baseline anti-porcine factor VIII inhibitor titer less than 20 Bethesda Units (BU)
   ii. Individual does not have the FDA label contraindication of congenital hemophilia A with inhibitors

4. For hemophilia A (congenital Factor VIII deficiency) treatment or prevention of bleeding episodes or perioperative management of bleeding individual has been screened for antibody inhibitor and has **ONE** of the following:
   a. No inhibitor to Factor VIII
   b. Low responding inhibitor (less than 5 BU/mL)
   c. High responding inhibitor (greater than or equal to 5 BU/mL) and the requested agent will be used as part of an Immune Tolerance Induction (ITI) regimen

5. **Additional criteria for request for long acting Adynovate, Afstyla, Altuviiio, Eloctate, Esperoct, and Jivi for routine prophylaxis**: Individual has failure after 3-month trial, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following standard half-life products:
   a. Advate
   b. Kogenate FS
   c. Kovaltry
   d. Novoeight
   e. Nuwiq
   f. Recombinate
   g. Xyntha

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance or is not a candidate for a **generic equivalent** (see Definitions section) [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)]

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation

**Initial approval duration**: 6 months

- **Criteria for continuation of coverage (renewal request):** Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Jivi, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Wilate, Xyntha and/or generic equivalent (if available) is considered ***medically necessary*** and

will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual's condition has responded while on therapy with response defined as the following:
    a. Bleeding episodes are controlled
    b. Frequency of bleeding episodes are reduced

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label or intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual is not currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation

**Renewal duration**: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of Non-Cancer Medications**

    2. **Off-Label Use of Cancer Medications**

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**Description:**

Hemophilia A (factor VIII [factor 8] deficiency) and hemophilia B (factor IX [factor 9] deficiency) are X-linked clotting factor deficiencies associated with bleeding of variable severity, ranging from life-threatening to clinically silent. Hemophilia A and B are X-linked disorders that primarily affect males. Females who are heterozygous carriers can be affected and can have factor levels in the hemophilic range. Hemophilia A may also be referred to as classical hemophilia. Hemophilia B is also known as Christmas disease and as Royal disease. Hemophilia C, also known as Rosenthal syndrome, is an inherited autosomal recessive bleeding disorder caused by a deficiency of factor XI [factor 11].

Hemophilia may be characterized as mild, moderate, or severe, based on residual factor activity level which is be expressed either as a percent of normal or in international units (IU)/mL. Factor levels usually correlate with the degree of bleeding symptoms. Severe hemophilia can be defined as <1 percent factor activity, which corresponds to <0.01 IU/mL. Moderate hemophilia can be defined as a factor activity level greater than or equal to 1 percent of normal and less than or equal to 5 percent of normal (corresponding to greater than or equal to 0.01 and less than or equal to 0.05 IU/mL). Mild hemophilia is usually defined as a factor activity level of 6 percent of normal and less than 40 percent of normal (greater than or equal to 0.05 and less than 0.40 IU/mL). Individuals with more severe hemophilia are more likely to have spontaneous bleeding, severe bleeding, and first bleeding episode at an earlier age.

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# HEMOPHILIA A FACTOR VIII PRODUCTS

Untreated individual with hemophilia is characterized by spontaneous bleeding including intracranial bleeding, muscle, and joint bleeding (usually in severe disease), immediate or delayed bleeding or prolonged oozing after injuries, tooth extractions, or surgery, or renewed bleeding after initial bleeding has stopped. Intermittent oozing may last for days or weeks after tooth extraction. Prolonged or delayed bleeding or wound hematoma formation after surgery is common. The leading cause of death is intracranial bleeding and the major cause of disability from bleeding is chronic joint disease.

Another complication in severe hemophilia is the development of alloantibodies (inhibitors) that block the factor activity. Inhibitors can also develop in individuals with moderate and mild hemophilia. These inhibitory antibodies develop in response to administration of exogenous factor and occur in approximately 30 percent of patients with severe hemophilia A and 5 to 15 percent with severe hemophilia B. Inhibitors decrease responsiveness to factor infusions and may lead to anaphylactoid reactions.

Treatment of hemophilia involves infusion of the deficient clotting factor to a level that achieves adequate blood clotting in an effort to prevent complications associated with the disorder.

Individuals with mild or moderate hemophilia may be treated with replacement therapy as needed (episodic infusion therapy) to treat a bleeding episode that has already started. Some individuals with mild or moderate hemophilia may receive prophylaxis (either short or longer term) for prevention of bleeding during activities before a specific activity. Individuals with severe hemophilia may receive regular infusions (prophylactic therapy) to prevent bleeding episodes before they occur.

Referral to a hemophilia treatment center (HTC) for assessment, education, genetic counseling, and treatment is recommended. These specialized centers provide comprehensive care for individuals with hemophilia including the development of specific treatment plans, monitoring and follow-up of affected individuals and state-of-the-art medical care. To locate a hemophilia treatment center, visit the Centers for Disease Control and Prevention website at: https://www.cdc.gov/ncbddd/hemophilia/HTC.html. For young children with severe or moderate hemophilia B, assessments every six to 12 months at an HTC is recommended. Older children and adults with severe or moderate hemophilia benefit from at least annual assessment at an HTC. For individuals with mild hemophilia B, assessment at an HTC every one to two years may be sufficient.

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**Definitions:**

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

**Hemophilia Treatment Centers**
Individuals with hemophilia significantly benefit from receiving care from a federally recognized hemophilia treatment center. These specialized centers provide comprehensive care for individuals with hemophilia including the development of specific treatment plans, monitoring and follow-up of affected individuals and state-of-the-art medical care.

To locate a hemophilia treatment center, visit the Centers for Disease Control and Prevention website at:
https://www.cdc.gov/ncbddd/hemophilia/HTC.html

**Selected available factor VIII products for hemophilia A**

| Product name | Approximate Half-life (hours) | Characteristics |
|---|---|---|

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# HEMOPHILIA A FACTOR VIII PRODUCTS

| | | |
|---|---|---|
| **Standard half-life products** | | |
| Advate | 9 to 12 | Recombinant |
| Hemofil M | 15 | Plasma-derived; mAb-purified |
| Kogenate FS | 11 to 15 | Recombinant |
| Koate | 16 | Plasma-derived; chromatography-purified |
| Kovaltry | 12 to 14 | Recombinant |
| Novoeight | 8 to 12 | Recombinant |
| Nuwiq | 12 to 17 | Recombinant |
| Recombinate | 15 | Recombinant |
| Xyntha | 8 to 11 | Recombinant |
| **Long-lasting products** | | |
| Adynovate | 13 to 16 | Recombinant; PEGylated |
| Afstyla | 10 to 14 | Recombinant; single chain |
| Altuviiio | 40 to 48 | Recombinant; Fc-VWF-XTEN fusion |
| Eloctate | 13 to 20 | Recombinant; Fc fusion |
| Esperoct | 17 to 22 | Recombinant; glycoPEGylated |
| Jivi | 17 to 21 | Recombinant; PEGylated |

**Types of prophylaxis for patients with hemophilia A or B**

| Type of treatment | Definition |
|---|---|
| Episodic (on demand) treatment | Replacement factor given at the time of bleeding |
| Continuous (regular) prophylaxis: | Replacement factor given to prevent bleeding for at least 45 of 52 weeks (85%) of a year |
| Primary prophylaxis | Continuous prophylaxis started before age three years and before the second large joint bleed |
| Secondary prophylaxis | Continuous prophylaxis started after two or more large joint bleeds but before the onset of chronic arthropathy |
| Tertiary prophylaxis | Continuous prophylaxis started after the onset of arthropathy to prevent further damage |
| Intermittent (periodic) prophylaxis | Replacement factor given to prevent bleeding for short periods of time such as during and after surgery |

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# HEMOPHILIA A FACTOR VIII PRODUCTS

## Classification of inherited von Willebrand disease (VWD)

| Type | Clinical features | Laboratory findings | Comments on treatment |
|---|---|---|---|
| **Type 1** (partial quantitative deficiency) | ▪ Accounts for approximately 75% of individuals with VWD<br>▪ Variable bleeding severity from mild to severe<br>▪ AD inheritance | ▪ VWF activity and antigen decreased concordantly<br>▪ Factor VIII activity normal or reduced<br>▪ RIPA decreased (may be normal in mild disease)<br>▪ Multimer electrophoresis: All multimers present and uniformly decreased<br>▪ In type 1C (increased clearance), the VWF level at 4 hours post DDAVP trial shows rapid reduction in VWF | ▪ DDAVP* in most patients<br>▪ VWF concentrates in moderate, severe, and type 1C |
| **Type 2** (qualitative variant) | | | |
| *Type 2A* (selective deficiency of HMW multimers, reduced binding to platelet GPIb) | ▪ Accounts for approximately 10 to 20% of individuals with VWD<br>▪ Moderate to severe bleeding<br>▪ Mostly AD; occasional AR inheritance | ▪ VWF activity decreased out of proportion to VWF antigen<br>▪ Factor VIII activity normal or reduced<br>▪ RIPA decreased<br>▪ Multimer electrophoresis: Large multimers decreased | ▪ DDAVP*<br>▪ VWF concentrates in moderate and severe patients<br>▪ Follow VWF levels |
| *Type 2B* (enhanced binding of HMW VWF multimers to platelet GPIb; may have decrease in circulating HMW multimers) | ▪ Accounts for approximately 5% of individuals with VWD<br>▪ Moderate to severe bleeding<br>▪ Thrombocytopenia<br>▪ AD inheritance | ▪ VWF activity decreased out of proportion to VWF antigen<br>▪ Factor VIII activity normal or reduced<br>▪ Thrombocytopenia<br>▪ RIPA increased<br>▪ Multimer electrophoresis: Usually decreased large multimers | ▪ DDAVP** should be used with caution; it may be used to treat minor bleeding if a trial of DDAVP performed when the patient is not bleeding has demonstrated that the platelet count drop is temporary. Many experts will avoid DDAVP even for a temporary platelet count drop.<br>▪ VWF concentrates in moderate and severe patients |

| | | | |
|---|---|---|---|
| *Type 2M* (reduced binding of VWF to platelet GPIb) | ▪ Uncommon<br>▪ Moderate to severe bleeding<br>▪ AD or AR inheritance | ▪ VWF activity decreased out of proportion to VWF antigen<br>▪ Factor VIII activity normal or decreased<br>▪ RIPA decreased<br>▪ Multimer electrophoresis: All multimers present and uniformly decreased | ▪ DDAVP*<br>▪ VWF concentrates in moderate and severe patients |
| *Type 2N* (reduced binding of VWF to factor VIII) | ▪ Uncommon<br>▪ Clinically similar to hemophilia A with joint, soft tissue, and urinary bleeding<br>▪ AR inheritance | ▪ VWF activity and antigen normal<br>▪ Factor VIII levels low (5 to 15%)<br>▪ RIPA normal<br>▪ Multimer electrophoresis: Normal | ▪ DDAVP*<br>▪ VWF concentrates<br>▪ Monitor VWF and factor VIII levels |
| **Type 3** (severe quantitative deficiency/absent VWF) | ▪ Rare<br>▪ Clinically similar to hemophilia A with joint and soft tissue bleeding in addition to mucocutaneous bleeding<br>▪ AR inheritance | ▪ VWF activity and antigen absent or markedly decreased<br>▪ Factor VIII levels low (1 to 10%)<br>▪ RIPA absent or very low<br>▪ Multimer electrophoresis: Undetectable or too faint to visualize | ▪ VWF concentrates<br>▪ Factor VIII replacement<br>▪ **Do not** use DDAVP to treat bleeding (will not be effective) |

* DDAVP should only be used after a therapeutic trial (when not bleeding) shows efficacy in raising VWF levels (or factor VIII levels in type 2N disease) to >50%.
AD: autosomal dominant; AR: autosomal recessive; AVWS: acquired von Willebrand syndrome; DDAVP: desmopressin; GPIb: platelet glycoprotein Ib; HMW: high molecular weight; RIPA: ristocetin-induced platelet aggregation; VWD: von Willebrand disease; VWF: von Willebrand factor.

## Resources:

Advate [antihemophilic factor (recombinant)] product information, revised by Takeda Pharmaceuticals America, Inc. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 06, 2024.

Adynovate, (antihemophilic factor, recombinant, PEGylated) product information, revised by Takeda Pharmaceuticals America, Inc. 08-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Afstyla [antihemophilic factor (recombinant), single chain] product information, revised by CSL Behring Lengnau AG 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Alphanate (antihemophilic factor/von Willebrand factor complex [human]) product information, revised by Grifols USA, LLC 11-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Altuviiio [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl] product information, revised by Bioverativ Therapeutics Inc. 05-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 11, 2024.

Eloctate [antihemophilic factor (recombinant), Fc fusion protein] product information, revised by Bioverativ Therapeutics Inc. 05-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Esperoct (antihemophilic factor (recombinant), glycopegylated-exei product information, revised by Novo Nordisk 08-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Hemlibra (emicizumab-kxwh) product information, revised by Genentech, Inc. 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Hemofil M (antihemophilic factor (human), method M, monoclonal purified) product information, revised by Takeda Pharmaceuticals America, Inc. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Humate-P [antihemophilic factor/von Willebrand factor complex (human)] product information, revised by CSL Behring GmbH 06-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Jivi [antihemophilic factor (recombinant), PEGylated-aucl] product information, revised by Bayer HealthCare LLC 08-2018. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Koate [antihemophilic factor (human)] product information, revised by Kedrion Biopharma, Inc. 01-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Kogenate FS (antihemophilic factor [recombinant], formulated with sucrose) product information, revised by Bayer HealthCare LLC 12-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Kovaltry [antihemophilic factor (recombinant)] product information, revised by Bayer HealthCare LLC 12-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Novoeight (antihemophilic factor, recombinant) product information, revised by Novo Nordisk 07-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Nuwiq [(antihemophilic factor (recombinant)] product information, revised by Octapharma USA Inc 06-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Obizur [antihemophilic factor (recombinant), porcine sequence] product information, revised by Takeda Pharmaceuticals America, Inc. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Recombinate [antihemophilic factor (recombinant)] product information, revised by Takeda Pharmaceuticals America, Inc. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Wilate [von Willebrand Factor/Coagulation Factor VIII Complex (Human)] product information, revised by Octapharma USA Inc 11-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 13, 2024.

Xyntha Solofuse (antihemophilic factor [recombinant]) product information, revised by Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 07-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 04, 2024.

Hoots WK, Malec L. Clinical manifestations and diagnosis of hemophilia. In: UpToDate, Shapiro AD, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated June 04, 2024. Accessed June 08, 2024.

Hoots WK, Shapiro AD. Hemophilia A and B: Routine management including prophylaxis. In: UpToDate, Lueng LLK, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated April 16, 2023. Accessed June 08, 2024.

Hoots WK, Lewandowska M. Acute treatment of bleeding and surgery in hemophilia A and B. In: UpToDate, Shapiro AD, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated April 30, 2024. Accessed June 08, 2024.

Hoots WK, Shapiro AD. Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication. In: UpToDate, Leung LLK, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated May 20, 2024. Accessed June 10, 2024.

James P. Clinical presentation and diagnosis of von Willebrand disease. In: UpToDate, Leung LLK, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated May 14, 2024. Accessed June 12, 2024.

James P. von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care. In: UpToDate, Leung LLK, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated September 11, 2023. Accessed June 12, 2024.

James P. von Willebrand disease (VWD): Treatment of major bleeding and major surgery. In: UpToDate, Leung LLK, Tirnauer JS (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated May 22, 2024. Accessed June 12, 2024.

Konkle BA, Nakaya Fletcher S. Hemophilia B. 2000 Oct 2 [Updated 2024 Jun 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1495/. Accessed June 08, 2024.

Konkle BA, Nakaya Fletcher S. Hemophilia A. 2000 Sep 21 [Updated 2023 Jul 27]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1404/. Accessed June 08, 2024.

Goodeve A, James P. von Willebrand Disease. 2009 Jun 4 [Updated 2017 Oct 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7014/. Accessed June 08, 2024.