BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

VONVENDI® [von Willebrand factor (recombinant)] 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
- **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:** Vonvendi [von Willebrand factor (recombinant)] 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 is 18 years of age or older

  3. Individual has a confirmed diagnosis of von Willebrand disease (VWD) and the request is for **ONE** of the following:
     a. On-demand treatment and control of bleeding episodes given at the time of bleeding
     b. Perioperative management of bleeding to prevent bleeding for short periods of time

c. Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD receiving on-demand therapy (see Definitions section)

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. von Willebrand antigen (VWF:Ag)
   b. Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)
   c. Factor VIII activity level

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, 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)

6. 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):** Vonvendi [von Willebrand factor (recombinant)] 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 has a confirmed diagnosis of von Willebrand disease (VWD) and the request is for **ONE** of the following:
   a. On-demand treatment and control of bleeding episodes given at the time of bleeding
   b. Perioperative management of bleeding to prevent bleeding for short periods of time
   c. Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD receiving on-demand therapy (see Definitions section)

3. Individual's condition has responded while on therapy with response defined as the following:
   a. Factor VIII coagulation activity has reached 40 IU/dL (i.e., 40% of normal activity)
   b. Achieved and maintains hemostasis

4. Individual has been adherent with the medication

5. **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)

6. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
   a. Hypersensitivity reaction
   b. Thromboembolic reaction

7. 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**

Description:

Vonvendi [von Willebrand factor (recombinant) (rVWF)] is indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) as: 1) on-demand treatment and control of bleeding episodes; 2) perioperative management of bleeding; and 3) routine prophylaxis to reduce the frequency of bleeding episodes in individuals with severe Type 3 VWD receiving on-demand therapy. It can be given with or without an approved recombinant (non-von Willebrand factor containing) factor VIII (rFVIII). von Willebrand factor (VWF) plays key hemostatic roles in platelet adhesion and aggregation at sites of vascular injury, and acts as a chaperone for factor VIII (FVIII). Other factor products that may be used to treat VWD that combine VWF and FVIII include Alphanate® [(antihemophilic factor/von Willebrand factor complex (human)], Humate-P® [antihemophilic factor/von Willebrand factor complex (human)], and Wilate® [(von Willebrand factor/coagulation factor VIII complex (human)]. These three agents can be used to treat both hemophilia A and VWD. (See Hemophilia A coverage guideline).

VWD, is a congenital bleeding disorder caused by deficient or defective plasma VWF. VWD individuals may experience excessive mucocutaneous bleeding, heavy menstrual bleeding, epistaxis, easy bruising, prolonged bleeding from minor wounds, and gastrointestinal bleeding. They may also have bleeding after dental work, childbirth, and surgery, with musculoskeletal bleeding seen in the most severe cases.

There are three types of VWD with type 2 divided into several subtypes. Type 1 VWD is due to quantitative reduction of VWF where concentration and activity of factor are decreased. Type 1 usually manifests as mild mucocutaneous bleeding. Type 2 VWD is due to dysfunction of VWF. Type 2 subtypes include: Type 2A, which typically manifests as mild-to-moderate mucocutaneous bleeding; Type 2B manifests as mild-to-moderate mucocutaneous bleeding that can include thrombocytopenia that worsens in certain circumstances; Type 2M, typically manifests as mild-moderate mucocutaneous bleeding; Type 2N, can manifest as excessive bleeding with surgery and mimics mild hemophilia A. Type 3 VWD is due to absent or severely reduced VWF and manifests with severe mucocutaneous and musculoskeletal bleeding.

Recent guidelines on VWD have suggested VWF levels of 30 or 40 IU/dL as a cutoff for the diagnosis of the disorder. Individuals with VWF levels greater than 30 IU/dL and lower than 50 IU/dL can be labeled as having a risk factor for bleeding.

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Individuals benefit from care in a comprehensive bleeding disorders program. The main treatments for VWD are desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), clotting factor concentrates (recombinant and plasma-derived) containing both VWF and FVIII (VWF/FVIII concentrate), and recombinant von Willebrand factor (rVWF). Indirect hemostatic treatments that reduce symptoms include fibrinolytic inhibitors (tranexamic acid) and hormones for menorrhagia are also beneficial. Individuals with VWD should receive prompt treatment for severe bleeding episodes. Pregnant women with VWD are at increased risk for bleeding complications at or following childbirth.

Definitions:

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

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 ▪ Variable bleeding severity from mild to severe ▪ AD inheritance	▪ VWF activity and antigen decreased concordantly ▪ Factor VIII activity normal or reduced ▪ RIPA decreased (may be normal in mild disease) ▪ Multimer electrophoresis: All multimers present and uniformly decreased ▪ In type 1C (increased clearance), the VWF level at 4 hours post DDAVP trial shows rapid reduction in VWF	▪ DDAVP* in most patients ▪ 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 ▪ Moderate to severe bleeding ▪ Mostly AD; occasional AR inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or reduced ▪ RIPA decreased ▪ Multimer electrophoresis: Large multimers decreased	▪ DDAVP* ▪ VWF concentrates in moderate and severe patients ▪ 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 ▪ Moderate to severe bleeding ▪ Thrombocytopenia ▪ AD inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or reduced ▪ Thrombocytopenia ▪ RIPA increased ▪ 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. ▪ VWF concentrates in moderate and severe patients
Type 2M (reduced binding of VWF to platelet GPIb)	▪ Uncommon ▪ Moderate to severe bleeding ▪ AD or AR inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or decreased ▪ RIPA decreased ▪ Multimer electrophoresis: All multimers present and uniformly decreased	▪ DDAVP* ▪ VWF concentrates in moderate and severe patients
Type 2N (reduced binding of VWF to factor VIII)	▪ Uncommon ▪ Clinically similar to hemophilia A with joint, soft tissue, and urinary bleeding ▪ AR inheritance	▪ VWF activity and antigen normal ▪ Factor VIII levels low (5 to 15%) ▪ RIPA normal ▪ Multimer electrophoresis: Normal	▪ DDAVP* ▪ VWF concentrates ▪ Monitor VWF and factor VIII levels
Type 3 (severe quantitative deficiency/absent VWF)	▪ Rare ▪ Clinically similar to hemophilia A with joint and soft tissue bleeding in addition to mucocutaneous bleeding ▪ AR inheritance	▪ VWF activity and antigen absent or markedly decreased ▪ Factor VIII levels low (1 to 10%) ▪ RIPA absent or very low ▪ Multimer electrophoresis: Undetectable or too faint to visualize	▪ VWF concentrates ▪ Factor VIII replacement ▪ **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.

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Resources:

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

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Mannucci PM. Rare inherited coagulation disorders. In: UpToDate, Leung LLK, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated February 02, 2024. Accessed June 13, 2024.

James PD, Connell NT, Ameer B, et al.: ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Advances 2021 January 12;5(1): 280-300. Accessed June 13, 2024.

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