

Hemophilia Products – von Willebrand Factor: Vonvendi® (Intravenous)

Effective date: 01/01/2020

Review date: 10/02/2019, 12/13/2019, 1/22/2020, 7/15/2021, 12/02/2021, 4/14/2022, 7/7/2022, 6/22/2023, 12/07/2023, 01/04/2024, 05/15/2024, 08/14/2024

Scope: Medicaid, Commercial, Medicare-Medicaid Plan (MMP)

I. Length of Authorization

Unless otherwise specified*, the initial authorization will be provided for 3 months and may be renewed.

Note: The cumulative amount of medication the patient has on-hand will be taken into account for authorizations. Up to 5 'on-hand' doses for the treatment of acute bleeding episodes will be permitted at the time of the authorization request.

** Initial and renewal authorization periods may vary by specific covered indication*

II. Dosing Limits

A. Quantity Limit (max daily dose) [Pharmacy Benefit]:

- Vonvendi 450-850 units: 82 vials per 90-day supply
- Vonvendi 900-1700 units: 41 vials per 90-day supply

B. Max Units (per dose and over time) [Medical Benefit]:

- 36,800 billable units per 90-day supply

III. Summary of Evidence

Vonvendi is recombinant von Willebrand factor used in the adults diagnoses with VWD for on demand treatment and control of bleeding episodes, perioperative bleeding management and routine prophylaxis to reduce the amount of bleeding episodes. Testing for on-demand treatment and control of bleeding episodes was evaluated through a multicenter, open-label trial to assess dosing strategies with and without recombinant Factor VIII (rFVIII). All subjects requiring rFVIII received Advate. Bleeding episodes were initially treated with Vonvendi and Advate at a ratio of 1.3:1 respectively, and subsequently with Vonvendi with or without Advate, depending on FVIII levels. The primary efficacy endpoint was the number of subjects with treatment success for control of bleeding episodes. Treatment success was defined as a mean efficacy rating score of less than 2.5 for all bleeding episodes in a subject treated with Vonvendi (with or without Advate) and efficacy was measured using a 4-point rating scale comparing the predicted number of infusions versus the actual number of infusions administered to treat bleeding episodes. All bleeding episodes treated with Vonvendi and Advate or Vonvendi alone had an efficacy rating of excellent (96.6%) or good (3.1%). Adverse effects include arthralgia, joint injury, vertigo, ALT increase and pruritus.

IV. Initial Approval Criteria

Hemophilia Management Program
Requirements for inhibitor tests are a part of the hemophilia management program. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide.

A. Vonvendi

Coverage is provided in the following conditions:

- MMP members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

Von Willebrand Disease (vWD) †

- Patient is at least 18 years of age; **AND**
- Diagnosis of von Willebrand disease has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
 - Used as treatment in at least one of the following:
 - On demand treatment and control of bleeding episodes: **AND**
 - Patient has severe vWD; **OR**
 - Patient has mild or moderate vWD and the use of desmopressin is known or suspected to be ineffective or contraindicated; **OR**
 - Perioperative management of bleeding (*Note: Authorizations valid for 1 month*); **OR**
 - Routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
 - Patient has severe Type 3 vWD and is receiving on-demand therapy

Hemophilia Management Program
For minimally treated patients (< 50 exposure days to factor products) previously receiving a different factor product, inhibitor testing is required at baseline, then at every comprehensive care visit (yearly for the mild and moderate patients, semi-annually for the severe patients).

† FDA Approved Indication(s) ‡ Compendia recommended Indication(s); Ⓢ Orphan Drug

V. Dispensing Requirements for Rendering Providers (Hemophilia Management Program)

- Prescriptions cannot be filled without an expressed need from the patient, caregiver or prescribing practitioner. Auto-filling is not allowed.
- Monthly, rendering provider must submit for authorization of dispensing quantity before delivering factor product. Information submitted must include:

- Original prescription information, requested amount to be dispensed, vial sizes available to be ordered from the manufacturer, and patient clinical history (including patient product inventory and bleed history)
- Factor dose should not exceed +1% of the prescribed dose and a maximum of three vials may be dispensed per dose. If unable to provide factor dosing within the required threshold, below the required threshold, the lowest possible dose able to be achieved above +1% should be dispensed. Prescribed dose should not be increased to meet assay management requirements.
- The cumulative amount of medication(s) the patient has on-hand should be taken into account when dispensing factor product. Patients should not have more than 5 extra doses on-hand for the treatment of acute bleeding episodes.
- Dispensing requirements for renderings providers are a part of the hemophilia management program. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide.

VI. Renewal Criteria

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the indication specific relevant criteria identified in section IV; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include:
 - hypersensitivity reactions (including anaphylactic shock, generalized urticaria, angioedema, chest tightness, hypotension, shock, lethargy, nausea, vomiting, paresthesia, pruritus, restlessness, blurred vision, wheezing and/or acute respiratory distress), thromboembolic reactions (including disseminated intravascular coagulation [DIC], thromboembolism, venous thrombosis, pulmonary embolism, myocardial infarction, and stroke), development of neutralizing antibodies (inhibitors), etc.; **AND**
- Any increases in dose must be supported by an acceptable clinical rationale (i.e., weight gain, half-life study results, increase in breakthrough bleeding when patient is fully adherent to therapy, etc.); **AND**
- The cumulative amount of medication(s) the patient has on-hand will be taken into account when authorizing. The authorization will allow up to 5 doses on-hand for the treatment of acute bleeding episodes as needed for the duration of the authorization; **AND**

On-demand treatment and control of bleeding episodes

- Renewals will be approved for a 6 month authorization period

Perioperative management of surgical bleeding

- Coverage may NOT be renewed

Routine prophylaxis to reduce the frequency of bleeding episodes

- Renewals will be approved for a 6 month authorization period; **AND**
- Patient has demonstrated a beneficial response to therapy (i.e., the frequency of bleeding episodes has decreased from pre-treatment baseline)

VII. Dosage/Administration

Indication	Dose
On-demand treatment and control of bleeding episodes VWD	<ul style="list-style-type: none"> • For each bleeding episode, administer the first dose of VONVENDI with an approved recombinant (non-von Willebrand factor containing) factor VIII (rFVIII) if factor VIII baseline levels are below 40% or are unknown. • If recombinant factor VIII is required, the rFVIII dose should be calculated according to the difference between the patient’s baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an appropriate plasma FVIII:C level based on the approximate mean recovery of 2 (IU/dL)/(IU/kg). • Administer the complete dose of Vonvendi followed by rFVIII within 10 minutes. <p><u>Minor (e.g., readily managed epistaxis, oral bleeding, menorrhagia):</u> Loading dose: 40-50 IU/kg; Maintenance dose: 40-50 IU/kg every 8-24 hours as clinically required</p> <p><u>Major (e.g., severe or refractory epistaxis, menorrhagia, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage):</u> Loading dose: 50-80 IU/kg; Maintenance dose: 40-60 IU/kg every 8-24 hours for approximately 2 to 3 days (as clinically required)</p>
Perioperative management of bleeding VWD	<p><u>Elective Surgical Procedure</u></p> <p>A preoperative dose may be administered 12-24 hours prior to surgery to allow the endogenous factor VIII levels to increase to at least 30 IU/dL (minor surgery) or 60 IU/dL (major surgery) before the loading dose (1 hour preoperative dose) of rVWF, with or without recombinant factor VIII, is administered.</p>

Indication	Dose
	<ul style="list-style-type: none"> Ensure baseline FVIII:C level is available prior to determining the need for 12-24 hr preoperative dose. FVIII:C level should also be assessed within 3 hours prior to initiating the surgical procedure. If the level is at the recommended minimum target levels (30 IU/dL for minor surgery and 60 IU/dL for major surgery), administer a dose of Vonvendi alone (without factor VIII treatment) within 1 hour prior to the procedure. If the FVIII:C level is below the recommended minimum target level, administer complete dose of Vonvendi followed by recombinant factor VIII within 10 minutes to raise VWF:RCo and FVIII:C. Assess baseline VWF:RCo levels within 3 hours of administration of the 12- 24 hr preoperative dose. If the 12-24 hour preoperative dose is not administered, then assess baseline level VWF:RCo prior to surgery. When possible, measure incremental recovery (IR) for Vonvendi before surgery. For calculation of IR, measure baseline plasma VWF:RCo. Then infuse a dose of 50 IU/kg of Vonvendi. Measure VWF:RCo, 30 minutes after infusion of Vonvendi. <ul style="list-style-type: none"> Use the following formula to calculate IR: $IR = \frac{[\text{Plasma VWF:RCo at 30 minutes (IU/dL)} - \text{Plasma VWF:RCo at baseline (IU/dL)}]}{\text{Dose(IU/kg)}}$. <p><u>Emergency Surgery</u></p> <ul style="list-style-type: none"> A 12-24 hr preoperative dose may not be feasible in subjects requiring emergency surgery. Baseline VWF:RCo and FVIII:C levels should be assessed within 3 hours prior to initiating the surgical procedure if it is feasible. The loading dose (1 hour preoperative dose) can be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR. If the IR is not available, assume an IR of 2.0 IU/dL per IU/kg. If baseline VWF:RCo and FVIII:C is not available, as a general guidance a loading dose (1 hour preoperative dose) of Vonvendi, 40 to 60 IU/kg VWF:RCo, should be administered. Additionally, recombinant factor VIII at a dose of 30 to 45 IU/kg may be infused sequentially, preferably within 10 minutes after the Vonvendi infusion in patients whose factor VIII plasma levels already are (or are highly likely to be) less than 40 to 50 IU/dL for minor surgery or 80 to 100 IU/dL for major surgery. <p>Note: refer to the package insert for recommended VWF:RCo and FVIII:C target peak plasma levels and dosing guidelines for perioperative management of bleeding.</p>
<p>Routine prophylaxis to reduce the frequency of bleeding episodes in patients with sever Type 3 VWD</p>	<ul style="list-style-type: none"> For initiation of prophylactic treatment, administer 40 to 60 IU/kg twice weekly. <ul style="list-style-type: none"> Adjust prophylaxis dose up to 60 IU/kg twice weekly if breakthrough bleeding* occurs in joints or if severe bleeding occurs. <p><i>*Treat breakthrough bleeding as per the dosing guidelines for minor and major bleeding.</i></p>

Investigational use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed

published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

VIII. Billing Code/Availability Information

HCPCS & NDC:

Drug	Manufacturer	J-Code	1 Billable Unit Equiv.	Vial Size	NDC
Vonvendi	Takeda Pharmaceuticals USA	J7179	1 IU	450-850 units	00944-7551
				900-1700 units	00944-7553

IX. References

1. Vonvendi [package insert]. Lexington, MA; Baxalta US Inc.; March 2023. Accessed May 2024.
2. Guidelines for the Management of Hemophilia. 2nd Edition. World Federation of Hemophilia. 2013. available at: <https://www1.wfh.org/publications/files/pdf-1863.pdf>. Accessed May 2024.
3. Available at: <https://www1.wfh.org/publication/files/pdf-1472.pdf>. Accessed January 2019.
4. Annual Review of Factor Replacement Products. Oklahoma Health Care Authority Review Board. Updated April 2016. Access January 2019.
5. Graham A1, Jaworski K. Pharmacokinetic analysis of anti-hemophilic factor in the obese patient. Haemophilia. 2014 Mar;20(2):226-9.
6. Croteau SE1, Neufeld EJ. Transition considerations for extended half-life factor products. Haemophilia. 2015 May;21(3):285-8.
7. Mingot-Castellano, et al. Application of Pharmacokinetics Programs in Optimization of Haemostatic Treatment in Severe Hemophilia a Patients: Changes in Consumption, Clinical Outcomes and Quality of Life. Blood. 2014 December; 124 (21).
8. MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors. MASAC Document #267; April 2022. Available at: <https://www.bleeding.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-267-masac-recommendation-concerning-prophylaxis-for-hemophilia-a-and-b-with-and-without-inhibitors>. Accessed May 2024.
9. MASAC Recommendations Regarding the Treatment of von Willebrand Disease. MASAC Document #266; March 2021. Available at: <https://www.bleeding.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-266-masac-recommendations-regarding-the-treatment-of-von-willebrand-disease>. Accessed May 2024.
10. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Advances, Volume 5, Issue 1, 2021, Pages 301-325, <https://doi.org/10.1182/bloodadvances.2020003264>.
11. Franchini M, Seidzadeh, Mannucci P, et al. Prophylactic management of patients with von Willebrand disease. Ther Adv Hematol. 2021; 12: 20406207211064064. Published online 2021 Dec 22. doi: 10.1177/20406207211064064.

12. MASAC Recommendations Concerning Products Licensed For The Treatment Of Hemophilia And Selected Disorders of the Coagulation System. MASAC Document #284 (Replaces Document #280); April 2024. Available at <https://www.bleeding.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-284-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-selected-disorders-of-the-coagulation-system>. Accessed May 2024.
13. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv.* 2021 Jan 12;5(1):280-300. doi: 10.1182/bloodadvances.2020003265. PMID: 33570651; PMCID: PMC7805340.
14. James P. (2023). von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care. In Leung LLK, Tirnauer JS (Eds.), *UptoDate*. Last updated: Sept 11, 2023. Accessed on: May 8, 2024. Available from https://www.uptodate.com/contents/von-willebrand-disease-vwd-treatment-of-minor-bleeding-use-of-ddavp-and-routine-preventive-care?search=von%20willebrand%20disease&source=search_result&selectedTitle=4%7E150&usage_type=default&display_rank=4.
15. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Hemophilia Factor Products (A56482). Centers for Medicare & Medicaid Services Inc. Updated on 09/29/2023 with effective date 10/01/2023. Accessed May 2024.
16. Palmetto GBA. Local Coverage Article: Billing and Coding: Guidance for Anti-Inhibitor Coagulant Complex (AICC) National Coverage Determination (NCD) 110.3 (A56065). Centers for Medicare & Medicaid Services Inc. Updated on 11/14/2022 with effective date 11/24/2022. Accessed May 2024.
17. Novitas Solutions, Inc. Local Coverage Article: Billing and Coding: Hemophilia Factor Products (A56433). Centers for Medicare & Medicaid Services Inc. Updated on 09/29/2023 with effective date 10/01/2023. Accessed May 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D68.01	Von Willebrand disease, type 1
D68.020	Von Willebrand disease, type 2A
D68.021	Von Willebrand disease, type 2B
D68.022	Von Willebrand disease, type 2M
D68.023	Von Willebrand disease, type 2N
D68.03	Von Willebrand disease, type 3
D68.04	Acquired von Willebrand disease
D68.09	Other von Willebrand disease

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist

and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale: Vonvendi was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Vonvendi according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.