VONVENDI® [von Willebrand factor (Recombinant)] is indicated for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding in adult patients, with an option to be dosed independently of recombinant factor VIII, based on patient need as determined by monitoring levels and clinical judgment.[1]

vonvendi
[von Willebrand factor (Recombinant)]

Indications

VONVENDI [von Willebrand factor (recombinant)] is a recombinant von Willebrand factor (rVWF) indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Selected Important Risk Information

CONTRAINDICATIONS

Do not use in patients who have had life-threatening hypersensitivity reactions to VONVENDI or its components (tri-sodium citrate-dihydrate, glycine, mannitol, trehalose-dihydrate, polysorbate 80, and hamster or mouse proteins).

Please see VONVENDI full Detailed Important Risk Information on page 7.
Please click here for VONVENDI full Prescribing Information.

1 underlying cause of von Willebrand disease (VWD)[2,3]

The underlying cause of VWD is a deficiency or defect in functional von Willebrand factor (VWF).

- VWF plays two key roles in hemostasis: binding collagen and platelets to facilitate platelet plug formation, and binding factor VIII (FVIII) to protect it from clearance and stabilize plasma FVIII levels[3,4]
- VWD is a heterogeneous disease; neither bleeding frequency nor severity precisely correlate with the type of VWD[5]

Not every person with VWD, every bleed, or every surgery requires VWF/FVIII complex.[6]

- Across disease type and severity, patients with VWD have varying levels of endogenous FVIII[6]
- The low FVIII levels that are sometimes observed in patients with VWD can be attributed to VWF deficiency or defect[3]

Why replace only what is deficient or defective in VWD—VWF?

Frequent, repeated administration of VWF/FVIII complexes in patients with VWD can lead to an excessive rise in FVIII levels; such levels (>200%) have been associated with thromboembolic events in patients who have additional risk factors.[1,7-9,a]

[a]Additional risk factors include low ADAMTS13 levels, old age, previous thrombosis, obesity, immobility, cancer, orthopedic surgery, estrogen therapy, and the use of antifibrinolytics.[1,10]

Selected Important Risk Information
WARNINGS AND PRECAUTIONS
Embolism and Thrombosis
Thromboembolic reactions, including disseminated intravascular coagulation, venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, can occur, particularly in patients with known risk factors for thrombosis, including low ADAMTS13 levels. Monitor for early signs and symptoms of thrombosis such as pain, swelling, discoloration, dyspnea, cough, hemoptysis, and syncope, and institute prophylaxis measures against thromboembolism based on current recommendations.

In patients requiring frequent doses of VONVENDI in combination with recombinant factor VIII, monitor plasma levels for FVIII:C activity because sustained excessive factor VIII plasma levels can increase the risk of thromboembolic events.

One out of 80 subjects treated with VONVENDI in clinical trials developed proximal deep vein thrombosis in perioperative period after total hip replacement surgery.

Please see VONVENDI full Detailed Important Risk Information on page 7.
Please click here for VONVENDI full Prescribing Information.

1 factor may allow for independent dosing[1,b]

VONVENDI® [von Willebrand factor (Recombinant)] enables healthcare providers to manage VWF and FVIII levels separately and specifically, based on patient need.

- VONVENDI acts similarly to naturally occurring, functional VWF, allowing for binding to platelets and collagen and stabilization of endogenous FVIII

Administer recombinant factor VIII (rFVIII) only when needed.

- Dosing of VONVENDI, with or without rFVIII, should be based on patient need as determined by monitoring levels and clinical judgment

ON DEMAND

For treatment and control of bleeds[1]

VONVENDI may be administered alone if a patient's baseline plasma FVIII:C level is

≥40%

or

an immediate rise in FVIII levels is not necessary

SURGERY

For management of perioperative bleeding[1]

VONVENDI may be administered alone if a patient's presurgical plasma FVIII:C level is

≥30% for minor surgery

or

≥60% for major surgery

[b]VONVENDI contains only trace amounts of rFVIII.

vonvendi
[von Willebrand factor (Recombinant)]

- 100% (18/18; 95% CI, 81.5-100) of patients experienced treatment success

  Treatment success (the primary endpoint) was defined as a mean efficacy rating score of less than 2.5 for all bleeding episodes, assessed on a 4-point rating scale (Excellent=1, Good=2, Moderate=3, None=4)[1]

  Of the 22 participants, those with gastrointestinal bleeds (n=2) and those in whom the number of infusions to control a bleeding episode was estimated retrospectively (n=2) were excluded from the above primary analysis

1 infusion resolved the majority of bleeds regardless of bleed location or severity.[1]

- The study protocol stipulated that the first dose of VONVENDI [von Willebrand factor (Recombinant)] be administered together with recombinant factor VIII (rFVIII). However, according to dosing guidelines in the USPI, VONVENDI may be administered alone if an immediate rise in FVIII:C is not necessary, or if the baseline FVIII:C level is ≥40%[1,2]

81.8% (157/192) OF BLEEDS TREATED WERE RESOLVED WITH 1 INFUSION (MEDIAN 1, RANGE 1-4)[1]

Number of infusions per bleed	Minor n (%) (n=122)	Moderate n (%) (n=61)	Major/Severe n (%) (n=7)	Unknown n (%) (n=2)	All n (%) (n=192)
1	113 (92.6%)	41 (67.2%)	1 (14.3%)	2 (100%)	157 (81.8%)
2	8 (6.6%)	13 (21.3%)	4 (57.1%)	0 (0.0)	25 (13.0%)
3	1 (0.8%)	6 (9.8%)	2 (28.6%)	0 (0.0)	9 (4.7%)
4	0 (0.0)	1 (1.6%)	0 (0.0)	0 (0.0)	1 (0.5%)
Median	1	1	2	1	1
Range	1-3	1-4	1-3	1-1	1-4

Study design

A Phase 3 prospective, multicenter, open-label study assessed the efficacy and safety of on-demand use of VONVENDI, with and without rFVIII, in adult patients with severe von Willebrand disease (VWD). Bleeding episodes were treated with an initial infusion of 40 to 60 IU/kg of VONVENDI for minor to moderate bleeds and up to 80 IU/kg of VONVENDI for major bleeds.[1,2]

8/125 (6.4%) of adverse events (AEs) observed during the trial were considered to have a causal relationship to VONVENDI; they subsequently resolved.[2]

6/8 (75%) of AEs in 4 subjects were not serious (mild infusion site paresthesia, moderate dysgeusia, moderate tachycardia [n=1], mild electrocardiogram T wave inversion, mild generalized pruritus, mild hot flush [n=1 each]). One patient experienced 2 simultaneous serious AEs (chest discomfort and increased heart rate); symptoms improved after 10 minutes of oxygen therapy with a full recovery within 3 hours.

Selected Important Risk Information

WARNINGS AND PRECAUTIONS (continued)

Hypersensitivity Reactions

Hypersensitivity reactions have occurred with VONVENDI. These reactions can include anaphylactic shock, generalized urticaria, angioedema, chest tightness, hypotension, shock, lethargy, nausea, vomiting, paresthesia, pruritus, restlessness, blurred vision, wheezing and/or acute respiratory distress. Discontinue VONVENDI if hypersensitivity symptoms occur and administer appropriate emergency treatment.

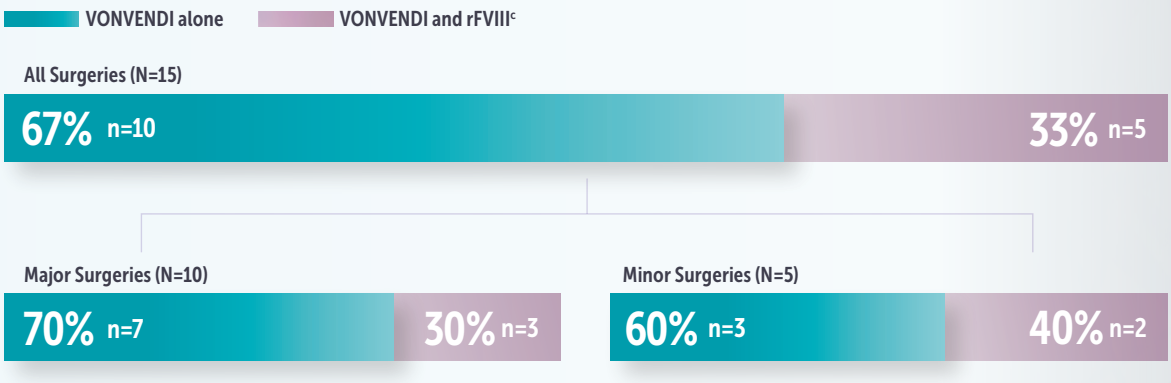
Please see VONVENDI full Detailed Important Risk Information on page 7.

Please click here for VONVENDI full Prescribing Information.

- 100% (15/15; 90% CI, 81.9-100) of patients had a mean overall hemostatic efficacy rating score of ≤2
- Overall hemostatic efficacy (the primary endpoint) was assessed using a 4-point scale (Excellent=1, Good=2, Moderate=3, None=4)[1]

1 factor was all most patients needed.[11,b]

PERIOPERATIVE BLEEDING IN 10/15 PATIENTS WAS MANAGED BY VONVENDI ALONE[11]



[b]VONVENDI contains only trace amounts of rFVIII.
[c]Of the 5 patients who did receive concomitant rFVIII, 2 patients received a preoperative infusion (1 infusion each), 2 patients received a postoperative infusion (1 infusion each), and 1 patient received both one preoperative and six postoperative infusions. Only 2 out of a total of 11 infusions in these 5 patients were performed when the FVIII:C level was actually below a protocol-defined target level.[1,11]

Study design

A Phase 3 prospective, multicenter, open-label study assessed the efficacy and safety of VONVENDI with or without rFVIII in adults (age 18 years and older) diagnosed with severe VWD of all types undergoing elective surgical procedures. Patients received 40 to 60 IU/kg of VONVENDI 12 to 24 hours before surgery, followed by VONVENDI with or without rFVIII within 1 hour of surgery, and postoperatively, as needed. Dosing of VONVENDI with or without rFVIII was based on monitoring of FVIII:C levels and clinical judgment.[11,12]

Treatment-emergent adverse events were reported in 6 patients.[11]

11 of 12 adverse events were considered unrelated to treatment: acne, anemia, deep vein thrombosis (DVT), diverticulitis, dizziness, dry skin, headache, joint swelling, nasopharyngitis, pelvic pain, and peripheral swelling.

1 DVT event, considered possibly related to VONVENDI, was managed throughout the postoperative period; it subsequently resolved.

vonvendi
[von Willebrand factor (Recombinant)]

VONVENDI® [von Willebrand factor (Recombinant)] may be stored at room temperature (≤30°C/86°F) for the life of the product[1]

- Store at room temperature not to exceed 30°C (86°F) or at refrigerated temperature 2°C to 8°C (36°F to 46°F)
- Do not freeze
- Store in the original box and protect from extreme exposure to light
- Do not use beyond the expiration date printed on the VONVENDI vial label or carton
- Use reconstituted product immediately or within 3 hours after reconstitution
- Discard any unused reconstituted product after 3 hours

VONVENDI is available in 2 vial sizes.

Up to 2 vials of VONVENDI may be pooled into a single syringe

- VONVENDI is available as a non-pyrogenic lyophilized powder for reconstitution in single-use vials containing nominally 650 or 1300 international units VWF:RCo per vial

PRODUCT STRENGTHS OF VONVENDI SINGLE-USE VIALS

Color Code	VWF:RCo Potency Range	Carton NDC	sWFI fill size
Green	450–850 IU per vial	0944-7551-02	5 mL
Dark Red	900–1700 IU per vial	0944-7553-02	10 mL

- Each package includes VONVENDI, Sterile Water for Injection (sWFI), one Mix2Vial® reconstitution device, one full prescribing physician insert, one patient insert, and one instructions for use
- The actual product strength will be printed on the vial label and on the box

Please see VONVENDI full Detailed Important Risk Information on the following page and click here for VONVENDI full Prescribing Information.

VONVENDI [von Willebrand factor (recombinant)] Important Information

Indications

VONVENDI [von Willebrand factor (recombinant)] is a recombinant von Willebrand factor (rVWF) indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Detailed Important Risk Information

CONTRAINDICATIONS

Do not use in patients who have had life-threatening hypersensitivity reactions to VONVENDI or its components (tri-sodium citrate-dihydrate, glycine, mannitol, trehalose-dihydrate, polysorbate 80, and hamster or mouse proteins).

WARNINGS AND PRECAUTIONS

Embolism and Thrombosis

Thromboembolic reactions, including disseminated intravascular coagulation, venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, can occur, particularly in patients with known risk factors for thrombosis, including low ADAMTS13 levels. Monitor for early signs and symptoms of thrombosis such as pain, swelling, discoloration, dyspnea, cough, hemoptysis, and syncope, and institute prophylaxis measures against thromboembolism based on current recommendations.

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One out of 80 subjects treated with VONVENDI in clinical trials developed proximal deep vein thrombosis in perioperative period after total hip replacement surgery.

Hypersensitivity Reactions

Hypersensitivity reactions have occurred with VONVENDI. These reactions can include anaphylactic shock, generalized urticaria, angioedema, chest tightness, hypotension, shock, lethargy, nausea, vomiting, paresthesia, pruritus, restlessness, blurred vision, wheezing and/or acute respiratory distress. Discontinue VONVENDI if hypersensitivity symptoms occur and administer appropriate emergency treatment.

Neutralizing Antibodies (Inhibitors)

Inhibitors to VWF and/or factor VIII can occur. If the expected plasma levels of VWF activity (VWF:RCo) are not attained, perform an appropriate assay to determine if anti-VWF or anti-factor VIII inhibitors are present. Consider other therapeutic options and direct the patient to a physician with experience in the care of either VWD or hemophilia A.

In patients with high levels of inhibitors to VWF or factor VIII, VONVENDI therapy may not be effective and infusion of this protein may lead to severe hypersensitivity reactions. Since inhibitor antibodies can occur concomitantly with anaphylactic reactions, evaluate patients experiencing an anaphylactic reaction for the presence of inhibitors.

ADVERSE REACTIONS

In clinical trials, the most common adverse reactions observed in ≥2% of subjects (n=80) were generalized pruritus, vomiting, nausea, dizziness, and vertigo.

One subject treated with VONVENDI in perioperative setting developed deep vein thrombosis after total hip replacement surgery.

Please click here for VONVENDI full Prescribing Information.

References: 1. VONVENDI [von Willebrand factor (recombinant)] Prescribing Information. **2.** Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood.* 2015;126(17):2038-2046. **3.** Nichols WL, Hultin MB, James AH, et al. Von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia.* 2008;14(2):171-232. **4.** Turecek PL, Mitterer A, Matthiessen HP. Development of a plasma- and albumin-free recombinant von Willebrand factor. *Hämostaseologie.* 2009;29(suppl 1):S32-S38. **5.** The Lewin Group. Strategic Summit on Von Willebrand Disease. National Hemophilia Foundation. March 2015. **6.** Favaloro EJ. Towards personalised therapy for von Willebrand disease: a future role for recombinant products. *Blood Transfus.* 2016;14(2):262-276. **7.** Franchini M, Mannucci PM. Von Willebrand factor (Vonvendi®): the first recombinant product licensed for the treatment of von Willebrand disease. *Expert Rev Hematol.* 2016;9(9):825-830. **8.** Mannucci PM. Venous thromboembolism in von Willebrand disease. *Thromb Haemost.* 2002;88(3):378-379. **9.** Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med.* 2004;351(7):683-694. **10.** Miesbach W, Berntorp E. Von Willebrand disease – the 'Dos' and 'Don'ts' in surgery. *Eur J Haematol.* 2017;98(2):121-127. **11.** Peyvandi F, Mamaev A, Wang JD, et al. Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery. *J Thromb Haemost.* 2019;17(1):52-62. **12.** Data on file, Takeda, Ltd.

vonvendi
[von Willebrand factor (Recombinant)]

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1 may be all your patients need[1]

- **1 and only recombinant von Willebrand factor (rVWF).** Addresses the underlying cause of von Willebrand disease (VWD)[1-5,7]
- **1 factor allows for independent dosing.**[a] Enables healthcare providers to manage von Willebrand factor and factor VIII (FVIII) levels separately and specifically, based on patient need[1]
- **1 factor can achieve hemostatic levels of endogenous FVIII.**[a] Normalized FVIII:C levels across all types of VWD over time[1,2]

  Dosing of VONVENDI® [von Willebrand factor (Recombinant)], with or without rFVIII, should be based on patient need as determined by monitoring levels and clinical judgment.
- **1 infusion was all most patients needed.** Treated and controlled the majority of bleeding episodes, regardless of bleed location or severity, with a single infusion[1]

  The study protocol stipulated that the first dose of VONVENDI be administered together with rFVIII. However, according to dosing guidelines in the USPI, VONVENDI may be administered alone if an immediate rise in FVIII:C is not necessary, or if the baseline FVIII:C level is ≥40%.
- **1 factor was all most patients needed.**[a] Managed perioperative bleeding without concomitant recombinant factor VIII (rFVIII) in the majority of patients[1,11]

[a]VONVENDI contains only trace amounts of rFVIII.

Selected Important Risk Information
CONTRAINDICATIONS
Do not use in patients who have had life-threatening hypersensitivity reactions to VONVENDI or its components (tri-sodium citrate-dihydrate, glycine, mannitol, trehalose-dihydrate, polysorbate 80, and hamster or mouse proteins).

Please see VONVENDI Indications and full Detailed Important Risk Information on page 7.
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