# Clinical Policy: Factor VIII/von Willebrand Factor Complex (Human - Alphanate, Humate-P, Wilate); von Willebrand Factor (Recombinant – Vonvendi)

Reference Number: ERX.SPA.185
Effective Date: 01.11.17
Last Review Date: 11.21 Revision Log
Line of Business: Commercial, Medicaid

**See Important Reminder at the end of this policy for important regulatory and legal information.**

**Description**
The following are factor VIII/von Willebrand factor complexes (human) or recombinant von Willebrand factor requiring prior authorization: Alphanate®, Humate®-P, Vonvendi®, and Wilate®.

**FDA Approved Indication(s)**
Factor VIII/von Willebrand factor complexes are indicated for:
- Hemophilia A
  - Alphanate: Control and prevention of bleeding episodes and perioperative management in adult and pediatric patients with factor VIII deficiency due to hemophilia A
  - Humate-P: Treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia)
  - Wilate:
    - Control and prevention of bleeding episodes
    - Routine prophylaxis to reduce the frequency of bleeding episodes
- Von Willebrand disease (VWD) in children and adults:
  - Alphanate: Surgical and/or invasive procedures in patients in whom desmopressin (DDAVP) is either ineffective or contraindicated
  - Humate-P:
    - Treatment of spontaneous and trauma-induced bleeding episodes
    - Prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of DDAVP is known or suspected to be inadequate
  - Wilate:
    - On-demand treatment and control of bleeding episodes
    - Perioperative management of bleeding

Vonvendi is indicated in adults with VWD for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Limitation(s) of use: Alphanate is not indicated for patients with severe VWD (type 3) undergoing major surgery.

**Policy/Criteria**
*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Alphanate, Humate-P, Vonvendi, and Wilate are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**
**A. Congenital Hemophilia A** (must meet all)**:**

1. Diagnosis of congenital hemophilia A (factor VIII deficiency);
2. Request is for Alphanate, Humate-P, or Wilate;
3. Prescribed by or in consultation with a hematologist;
4. Request is for one of the following uses (a, b, or c):
   a. Control or prevention of bleeding episodes;
   b. Perioperative management (Alphanate only);
   c. Routine prophylaxis to reduce the frequency of bleeding episodes (Wilate only);
5. For routine prophylaxis requests (Wilate only), member meets one of the following (a or b):
   a. Member has severe hemophilia (defined as factor VIII level of < 1%);
   b. Member has experienced at least one life-threatening or serious spontaneous bleed (*see Appendix D*);
6. If factor VIII coagulant activity levels are > 5%, failure of desmopressin acetate, unless contraindicated, clinically significant adverse effects are experienced, or an appropriate formulation of desmopressin acetate is unavailable;
7. For routine prophylaxis requests (Wilate only), if the member has used a dosage that exceeds the maximum recommended dose for at least 4 of the last 6 months, then member must use Hemlibra® unless contraindicated or clinically significant adverse effects are experienced;
8. Documentation of member's current body weight (in kg);
9. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

**Approval duration: 3 months**

**B. Von Willebrand Disease** (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. VWD type 1 or 2 (except 2B), and member has had a failure of desmopressin acetate, unless contraindicated, clinically significant adverse effects are experienced, or an appropriate formulation of desmopressin acetate is unavailable;
   b. VWD type 2B or 3;
2. Prescribed by or in consultation with a hematologist;
3. Request is for one of the following uses (a or b):
   a. Treatment of bleeding episodes (Humate-P, Vonvendi, and Wilate only);
   b. Perioperative management;
4. For Vonvendi only: Age ≥ 18 years;
5. Documentation of member's current body weight (in kg);
6. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

**Approval duration: 3 months**

**C. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. All Indications in Section I** (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. For routine prophylaxis requests (Wilate only), if the member has used a dosage that exceeds the maximum recommended dose for at least 4 of the last 6 months, then member must use Hemlibra unless contraindicated or clinically significant adverse effects are experienced;
3. Documentation of member's current body weight (in kg);
4. If request is for a dose increase, new dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

**Approval duration: 3 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 3 months (whichever is less)**; or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*
DDAVP: desmopressin acetate
FDA: Food and Drug Administration
VWD: von Willebrand disease
vWF: von Willebrand factor

*Appendix B: Therapeutic Alternatives*
*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| desmopressin acetate (Stimate® nasal spray; generic injection solution) | When factor VIII coagulant activity levels are > 5% and for VWD type 1 or 2 (except 2B):<br><br>Injection: 0.3 mcg/kg IV every 48 hours<br><br>Nasal spray:<br>< 50 kg: 1 spray intranasally in one nostril only; may repeat based on laboratory response and clinical condition<br>≥ 50 kg: 1 spray intranasally in each nostril; may repeat based on laboratory response and clinical condition | Injection: 0.3 mcg/kg IV every 48 hours<br><br>Nasal spray: 1 spray intranasally in each nostril |
| Hemlibra (emicizumab-kxwh) | 3 mg/kg per week IV during the first four weeks of therapy, followed by either 1.5 mg/kg per week, 3 mg/kg once every two weeks, or 6 mg/kg once every four weeks thereafter | 6 mg/kg/month |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*
- Contraindication(s): factor VIII/vWF complex: patients with known hypersensitivity reactions, including anaphylactic or severe systemic reaction, to human plasma-derived products, any ingredient in the formulation, or components of the container; Vonvendi: history of life-threatening hypersensitivity reactions to Vonvendi or its components
- Boxed warning(s): none reported

*Appendix D: General Information*
- Life-threatening bleeding episodes include, but are not limited to, bleeds in the following sites: intracranial, neck/throat, or gastrointestinal.
- Serious bleeding episodes include bleeds in the following site: joints (hemarthrosis).
- Spontaneous bleed is defined as a bleeding episode that occurs without apparent cause and is not the result of trauma.

## V. Dosage and Administration

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| Factor VIII/von Willebrand factor complex (Alphanate) | Hemophilia A - control and prevention of bleeding episodes | Minor episodes: 15 IU/kg IV every 12 hours<br><br>Moderate episodes: 25 IU/kg IV every 12 hours<br><br>Major episodes: 40-50 IU/kg IV initially followed by 25 IU/kg IV every 12 hours | 100 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Humate-P) | Hemophilia A - control and prevention of bleeding episodes | Minor episodes: 15 IU/kg IV loading dose followed by half of the loading dose given once or twice daily if needed<br><br>Moderate episodes: 25 IU/kg IV loading dose followed by 15 IU/kg IV every 8-12 hours<br><br>Major episodes: 40-50 IU/kg IV initially followed by 20-25 IU/kg IV every 8 hours | 75 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Alphanate) | Hemophilia A – perioperative management | Pre-operative: 40-50 IU/kg IV once as a single dose<br><br>Post-operative: 30-50 IU/kg IV every 12 hours | 100 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Humate-P) | VWD – control and prevention of bleeding episodes | Type 1 VWD, mild disease<br>Minor or major episodes: 40-60 IU/kg IV loading dose followed by 40-50 IU/kg IV every 8-12 hours<br><br>Type 1 VWD, moderate or severe disease<br>Minor episodes: 40-50 IU/kg IV as one or two doses<br><br>Major episodes: 50-75 IU/kg loading dose followed by 40-60 IU/kg every 8-12 hours<br><br>Type 2 or 3 VWD<br>Minor episodes: 40-50 IU/kg IV as one or two doses<br><br>Major episodes: 60-80 IU/kg IV loading dose followed by 40-60 IU/kg every 8-12 hours | 240 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Wilate) | VWD – control and prevention of bleeding episodes | All VWD types<br>Minor episodes: 20-40 IU/kg IV loading dose followed by 20-30 IU/kg IV every 12-24 hours | 80 IU/kg/day |

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| | | Major episodes: 40-60 IU/kg IV loading dose followed by 20-40 IU/kg every 12-24 hours | |
| Factor VIII/von Willebrand factor complex (Alphanate) | VWD – perioperative management **(except Type 3 patients undergoing major surgery)** | Pre-operative: (adults) 60 IU/kg IV once as a single dose; (pediatrics) 75 IU/kg IV once as a single dose<br><br>Maintenance: (adults) 40-60 IU/kg IV every 8-12 hours; (pediatrics) 50-75 IU/kg IV every 8-12 hours | 225 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Humate-P) | VWD – perioperative management | Minor or major surgery:<br>IU required = (Plasma VWF:RCo$_{time+30\ min}$ – Plasma VWF:RCo$_{baseline}$ ) x body weight (kg) / IVR<br><br>For major surgeries, if the IVR is not available, assume an IVR of 2.0 IU/dL per IU/kg and calculate the<br>loading dose as follows:<br>(100 – baseline plasma VWF:RCo) x body weight(kg) / 2.0<br><br>Emergency surgery: 50-60 IU/kg IV one time | Varies |
| Factor VIII/von Willebrand factor complex (Wilate) | Hemophilia A - control and prevention of bleeding episodes | Minor or moderate episodes: 30-40 IU/kg IV every 12-24 hours<br><br>Major episodes: 35-50 IU/kg IV every 12-24 hours<br><br>Life-threatening episodes: 35-50 IU/kg IV every 8-24 hours | 150 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Wilate) | Hemophilia A – routine prophylaxis | 20-40 IU/kg IV every 2 to 3 days | 40 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Wilate) | VWD – control and prevention of bleeding episodes | Minor episodes: 20-40 IU/kg IV loading dose followed by 20-30 IU/kg every 12-24 hours<br><br>Major episodes: 40-60 IU/kg IV loading dose followed by 20-40 IU/kg every 12-24 hours | 60 IU/kg/day |
| Factor VIII/von Willebrand factor complex (Wilate) | VWD – perioperative management | Minor surgeries (including tooth extraction): 30-60 IU/kg IV loading dose followed by 15-30 IU/kg every 12-24 hours<br><br>Major surgeries: 40-60 IU/kg IV loading dose followed by 20-40 IU/kg every 12-24 hours | 60 IU/kg/day |

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| von Willebrand factor (Vonvendi) | VWD – treatment and control of bleeding episodes | Minor episodes: 40-50 IU/kg IV loading dose followed by 40-50 IU/kg every 8-24 hours<br><br>Major episodes: 50-80 IU/kg IV loading dose followed by 40-60 IU/kg every 8-24 hours for approximately 2 to 3 days | Minor episodes: 150 IU/kg/day<br><br>Major episodes: 180 IU/kg/day |
| von Willebrand factor (Vonvendi) | VWD – perioperative management | Minor surgeries: 25-30 IU/kg IV every 12-48 hours<br><br>Major surgeries: 40-60 IU/kg IV every 12-48 hours | Minor surgeries: 60 IU/kg/day<br><br>Major surgeries: 120 IU/kg/day |

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Factor VIII/von Willebrand factor complex (Alphanate) | Vial: 250, 500, 1,000, 1,500 IU and 2,000 IU FVIII |
| Factor VIII/von Willebrand factor complex (Humate-P) | Vial: 250/600, 500/1,200, 1,000/2,400 IU FVIII/VWF:RCo |
| von Willebrand factor (Vonvendi) | Vial: 450-850 IU (5 mL), 900-1,700 IU (10 mL) |
| Factor VIII/von Willebrand factor complex (Wilate) | Vial: 500/500, 1,000/1,000 IU FVIII/VWF:RCo |

## VII. References

1. Alphanate Prescribing Information. Los Angeles, CA: Grifols Biologicals Inc.; June 2018. Available at www.alphanate.com. Accessed December 1, 2020.
2. Humate-P Prescribing Information. Kankakee, IL: CSL Behring, LLC; September 2017. Available at www.humate-p.com. Accessed December 1, 2020.
3. Vonvendi Prescribing Information. Lexington, MA: Baxalta US Inc.; February 2019. Available at: https://www.shirecontent.com/PI/PDFs/VONVENDI_USA_ENG.pdf. Accessed December 1, 2020.
4. Wilate Prescribing Information. Hoboken, NJ: Octapharma USA Inc.; September 2019. Available at www.wilateusa.com. Accessed December 1, 2020.
5. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. Jan 2013; 19(1): e1-47.
6. Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF): Database of treatment guidelines. Available at https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed December 1, 2020.
7. MASAC of the NHF: Recommendations regarding the treatment of Von Willebrand disease. Available at: https://www.hemophilia.org/sites/default/files/document/files/244.pdf. Accessed December 1, 2020.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created | 12.16 | 01.17 |
| 4Q17 Annual Review<br>No significant changes. References reviewed and updated. | 10.10.17 | 11.17 |
| 1Q18 annual review: removed major surgery restriction for Alphanate, per previous specialist feedback. Added efficacy statement to renewal criteria. | 11.27.17 | 02.18 |
| 1Q 2019 annual review: hemophilia – clarified that disease must be congenital; VWD – removed trial of desmopressin per Wilate's FDA labeling; references reviewed and updated. | 09.26.18 | 02.19 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q 2020 annual review: no significant changes; RT4 policy update addition of hemophilia A indication for Wilate, mirroring previously approved hemophilia A coverage policies for other FVIII products; references reviewed and updated. | 11.27.19 | 02.20 |
| Added 1 month approval duration for use post-valoctocogene gene therapy administration in hemophilia A for Wilate only. | 04.17.20 | 05.20 |
| Added Vonvendi to the policy; added routine prophylaxis-specific requirement for severe hemophilia classification or at least one life-threatening or serious spontaneous bleed for classification of non-severe hemophilia; added requirement for prescriber attestation of not partaking in contact sports. | 05.12.20 | 08.20 |
| Removed requirement for prescriber attestation of not partaking in contact sports. | 10.01.20 | 11.20 |
| 1Q 2021 annual review: added requirement for documentation of member's body weight for calculation of appropriate dosage; removed references to valoctocogene, as it was not FDA-approved and likely will not face FDA review again until at least late 2022; for VWD type 1 or 2 (except 2B), added requirement for a prior trial of desmopressin; references reviewed and updated. | 12.01.20 | 02.21 |
| Added a requirement for high utilizers of factor VIII products for routine prophylaxis to use Hemlibra. | 10.12.21 | 11.21 |

**Important Reminder**
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.