Clinical Policy: Factor VIII/von Willebrand Factor Complex (Human – Alphanate, Humate-P, Wilate); von Willebrand Factor (Recombinant – Vonvendi)
Reference Number: CP.PHAR.216
Effective Date: 05.01.16
Last Review Date: 08.20
Line of Business: Commercial, HIM, 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 for 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.

It is the policy of health plans affiliated with Centene Corporation® 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. Prescriber attestation that member is not taking part in high contact or collision sports (e.g., soccer, boxing, skiing);
      8. For Wilate only: member meets one of the following (a or b):
         a. Member has not received treatment with valoctocogene roxaparvovec;
         b. Request is for prophylaxis post-valoctocogene roxaparvovec gene therapy administration;
      9. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

Approval duration: 1 month (if immediately following valoctocogene roxaparvovec gene therapy administration) or 3 months (congenital hemophilia A with no valoctocogene roxaparvovec administration)

B. Von Willebrand Disease (must meet all):
   1. Diagnosis of VWD (types 1, 2, 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. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.
CLINICAL POLICY  
Factor VIII/von Willebrand Factor Complex; von Willebrand Factor

Approval duration: 3 months

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy
A. All Indications in Section I (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. For Wilate only: member meets one of the following (a or b):
   a. Member is responding positively to therapy and has not received treatment with valoctocogene roxaparvovec;
   b. Member is responding positively to therapy and request is for prophylaxis post-valoctocogene roxaparvovec gene therapy administration;
3. Prescriber attestation that member is not taking part in high contact or collision sports (e.g., soccer, boxing, skiing);
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: 1 month (if immediately following valoctocogene roxaparvovec gene therapy administration) or 3 months (other indications)

B. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 3 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   DDAVP: desmopressin acetate                     VWD: von Willebrand disease
   FDA: Food and Drug Administration               vWF: von Willebrand factor

   Appendix B: Therapeutic Alternatives
CLINICAL POLICY
Factor VIII/von Willebrand Factor Complex; von Willebrand Factor

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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>desmopressin acetate (Stimate® nasal spray; generic injection solution)</td>
<td>When Factor VIII coagulant activity levels are &gt; 5%</td>
<td>Injection: 0.3 mcg/kg IV every 48 hours</td>
</tr>
<tr>
<td></td>
<td>Injection: 0.3 mcg/kg IV every 48 hours</td>
<td>Nasal spray: 1 spray intranasally in each nostril</td>
</tr>
<tr>
<td></td>
<td>Nasal spray: &lt; 50 kg: 1 spray intranasally in one nostril only; may repeat based on laboratory response and clinical condition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 50 kg: 1 spray intranasally in each nostril; may repeat based on laboratory response and clinical condition</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII/von Willebrand factor complex (Alphanate)</td>
<td>Hemophilia A - control and prevention of bleeding episodes</td>
<td>Minor episodes: 15 IU/kg IV every 12 hours</td>
<td>100 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate episodes: 25 IU/kg IV every 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

Page 4 of 11
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII/von Willebrand factor complex</td>
<td>Hemophilia A - control and prevention of bleeding episodes</td>
<td>Major episodes: 40-50 IU/kg IV initially followed by 25 IU/kg IV every 12 hours</td>
<td>75 IU/kg/day</td>
</tr>
<tr>
<td>(Humate-P)</td>
<td></td>
<td>Minor episodes: 15 IU/kg IV loading dose followed by half of the loading dose given once or twice daily if needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate episodes: 25 IU/kg IV loading dose followed by 15 IU/kg IV every 8-12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major episodes: 40-50 IU/kg IV initially followed by 20-25 IU/kg IV every 8 hours</td>
<td></td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex</td>
<td>Hemophilia A – perioperative management</td>
<td>Pre-operative: 40-50 IU/kg IV once as a single dose</td>
<td>100 IU/kg/day</td>
</tr>
<tr>
<td>(Alphanate)</td>
<td></td>
<td>Post-operative: 30-50 IU/kg IV every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex</td>
<td>VWD – control and prevention of bleeding episodes</td>
<td>Type 1 VWD, mild disease Minor or major episodes: 40-60 IU/kg IV loading dose followed by 40-50 IU/kg IV every 8-12 hours</td>
<td>240 IU/kg/day</td>
</tr>
<tr>
<td>(Humate-P)</td>
<td></td>
<td>Type 1 VWD, moderate or severe disease</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Indication</td>
<td>Dosing Regimen</td>
<td>Maximum Dose</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex (Wilate)</td>
<td>Hemophilia A - control and prevention of bleeding episodes</td>
<td>Minor episodes: 40-50 IU/kg IV as one or two doses</td>
<td>150 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major episodes: 50-75 IU/kg loading dose followed by 40-60 IU/kg every 8-12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2 or 3 VWD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor episodes: 40-50 IU/kg IV as one or two doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major episodes: 60-80 IU/kg IV loading dose followed by 40-60 IU/kg every 8-12 hours</td>
<td></td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex (Wilate)</td>
<td>Hemophilia A – routine prophylaxis</td>
<td>20-40 IU/kg IV every 2 to 3 days</td>
<td>40 IU/kg/day</td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex (Wilate)</td>
<td>VWD – control and prevention of bleeding episodes</td>
<td>Minor episodes: 20-40 IU/kg IV loading dose followed by 20-30 IU/kg every 12-24 hours</td>
<td>60 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major episodes: 40-60 IU/kg IV loading</td>
<td></td>
</tr>
</tbody>
</table>
### CLINICAL POLICY
Factor VIII/von Willebrand Factor Complex; von Willebrand Factor

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII/von Willebrand factor complex (Wilate)</td>
<td>VWD – perioperative management</td>
<td>Minor surgeries (including tooth extraction): 30-60 IU/kg IV loading dose followed by 15-30 IU/kg every 12-24 hours</td>
<td>60 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major surgeries: 40-60 IU/kg IV loading dose followed by 20-40 IU/kg every 12-24 hours</td>
<td></td>
</tr>
<tr>
<td>von Willebrand factor (Vonvendi)</td>
<td>VWD – treatment and control of bleeding episodes</td>
<td>Minor episodes: 40-50 IU/kg IV loading dose followed by 40-50 IU/kg every 8-24 hours</td>
<td>Minor episodes: 150 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>Major episodes: 180 IU/kg/day</td>
</tr>
<tr>
<td>von Willebrand factor (Vonvendi)</td>
<td>VWD – perioperative management</td>
<td>Minor surgeries: 25-30 IU/kg IV every 12-48 hours</td>
<td>Minor surgeries: 60 IU/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major surgeries: 40-60 IU/kg IV every 12-48 hours</td>
<td>Major surgeries: 120 IU/kg/day</td>
</tr>
</tbody>
</table>

### VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII/von Willebrand factor complex (Alphanate)</td>
<td>Vial: 250, 500, 1,000, 1,500 IU and 2,000 IU FVIII</td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex (Humate-P)</td>
<td>Vial: 250/600, 500/1,200, 1,000/2,400 IU FVIII/VWF:RCo</td>
</tr>
</tbody>
</table>
CLINICAL POLICY
Factor VIII/von Willebrand Factor Complex; von Willebrand Factor

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Willebrand factor (Vonvendi)</td>
<td>Vial: 450-850 IU (5 mL), 900-1,700 IU (10 mL)</td>
</tr>
<tr>
<td>Factor VIII/von Willebrand factor complex (Wilate)</td>
<td>Vial: 500/500, 1,000/1,000 IU FVIII/VWF:RCo</td>
</tr>
</tbody>
</table>

VII. References

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7183</td>
<td>Injection, von Willebrand factor complex (human), Wilate, 1 IU vWF:RCo</td>
</tr>
<tr>
<td>J7186</td>
<td>Injection, antihemophilic factor VIII/von Willebrand factor complex (human), per factor VIII i.u. (Alphanate)</td>
</tr>
<tr>
<td>J7187</td>
<td>Injection, von Willebrand factor complex (Humate-P), per IU VWF:RCo</td>
</tr>
<tr>
<td>J7179</td>
<td>Injection, von Willebrand factor (recombinant), (Vonvendi), per 1 IU vWF:Rco</td>
</tr>
</tbody>
</table>
**Clinical Policy**

Factor VIII/von Willebrand Factor Complex; von Willebrand Factor

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy split from CP.PHAR.12.Blood Factors and converted to new template. Removed requests for documentation. Removed indication for prophylaxis after 2 joint bleeds/approval period 6 months as there is no FDA approved indication for long-term prophylaxis. Approval period is edited to be 3 months initial and one 3-month re-auth as, in some circumstances, treatment could be necessary for up to six months (e.g., intracranial hemorrhage per Alphanate PI). Reviewed by specialist.</td>
<td>04.01.16</td>
<td>05.16</td>
</tr>
<tr>
<td>Removed “major surgery” restriction for Alphanate. Required trial of desmopressin is edited to avoid necessity of testing for coagulation factors. Safety information removed. Uses and approval periods across all blood factor policies worded consistently. Efficacy statement added to renewal criteria. Hemophilies are specified as “congenital” versus “acquired” across blood factor policies where indicated. Reviewed by specialist- hematology/internal medicine</td>
<td>04.01.17</td>
<td>05.17</td>
</tr>
</tbody>
</table>
| 1Q18 annual review:  
- Converted to new template  
- No significant changes  
- References reviewed and updated. | 11.27.17   | 02.18            |
| 1Q 2019 annual review: added HIM-Medical Benefit; no significant changes; references reviewed and updated. | 09.26.18   | 02.19            |
| 1Q 2020 annual review: no significant changes; added HIM line of business; 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 Commercial line of business. | 03.13.20   |                   |
| 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. | 05.27.20   | 08.20            |

**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. The Health Plan makes no representations and
accepts no liability with respect to the content of any external information used or relied upon in
developing this clinical policy. This clinical policy is consistent with standards of medical
practice current at the time that this clinical policy was approved. “Health Plan” means a health
plan that has adopted this clinical policy and that is operated or administered, in whole or in part,
by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a
component of the guidelines used to assist in making coverage decisions and administering
benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage
decisions and the administration of benefits are subject to all terms, conditions, exclusions and
limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,
contract of insurance, etc.), as well as to state and federal requirements and applicable Health
Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting
may not be the effective date of this clinical policy. This clinical policy may be subject to
applicable legal and regulatory requirements relating to provider notification. If there is a
discrepancy between the effective date of this clinical policy and any applicable legal or
regulatory requirement, the requirements of law and regulation shall govern. The Health Plan
retains the right to change, amend or withdraw this clinical policy, and additional clinical
policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is
not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to
recommend treatment for members. Members should consult with their treating physician in
connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent
judgment and over whom the Health Plan has no control or right of control. Providers are not
agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and
distribution of this clinical policy or any information contained herein are strictly prohibited.
Providers, members and their representatives are bound to the terms and conditions expressed
herein through the terms of their contracts. Where no such contract exists, providers, members
and their representatives agree to be bound by such terms and conditions by providing services to
members and/or submitting claims for payment for such services.

**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the
coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence.
Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical
policy.