MEDICA®

Hemophilia Products – Factor VIII/VWF Complex: Alphanate, Humate-P, Wilate
(Intravenous)

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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) [NDC Unit]:

- N/A

B. Max Units (per dose and over time) [HCPCS Unit]:

- Alphanate: 55,200 billable units per 28 day supply
- Humate-P: 55,200 billable units per 28 day supply
- Wilate: 55,200 billable units per 28 day supply

III. Initial Approval Criteria [1-5,10]

Hemophilia Management Program
Requirements for half-life study and 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.

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Coverage is provided in the following conditions:

A. Alphanate, Humate-P ONLY

Hemophilia A (congenital factor VIII deficiency) †

- Diagnosis of congenital factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
- Used as treatment in one of the following:
  - Control and prevention of bleeding episodes (episodic treatment of acute hemorrhage); **OR**
  - Perioperative management *(*Authorization is valid for 1 month)*; **OR**
  - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes; **AND**
    - Patient must have severe hemophilia A (factor VIII level of <1%); **OR**
    - Patient has at least two documented episodes of spontaneous bleeding into joints

Hemophilia Management Program
• If the request is for routine prophylaxis and the requested dose exceeds dosing limits under part II, a half-life study should be performed to determine the appropriate dose and dosing interval. • For members with a BMI ≥ 30, a half-life study should be performed to determine the appropriate dose and dosing interval. • 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)

von Willebrand disease (vWD) † Φ

- Diagnosis of von Willebrand disease has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
- Used as treatment in one of the following:
  - Spontaneous and trauma-induced bleeding episodes; **OR**
  - Surgical bleeding prophylaxis during major or minor procedures in patients with vWD in whom desmopressin is either ineffective or contraindicated *(*Authorization valid for 1 month)*; **AND**
- Alphanate is not indicated for patients with severe (type 3) vWD undergoing major surgery OR treatment of spontaneous/trauma-induced bleeding episodes

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)

B. Wilate

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Hemophilia A (congenital factor VIII deficiency) †

- Diagnosis of congenital factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
- Used as treatment in one of the following:
    - Control and prevention of bleeding episodes (episodic treatment of acute hemorrhage); **OR**
    - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes; **AND**
        - Patient must have severe hemophilia A (factor VIII level of <1%); **OR**
        - Patient has at least two documented episodes of spontaneous bleeding into joints

von Willebrand disease (vWD) † Φ

- Diagnosis of von Willebrand disease has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
- Used as treatment in one of the following;
    - Perioperative management of bleeding *(*Authorization valid for 1 month)*; **OR**
    - Used as treatment of spontaneous and trauma-induced bleeding episodes in at least one of the following:
        - Patients with severe vWD; **OR**
        - Patients with mild or moderate vWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated

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

† FDA Approved Indication(s); Φ Orphan Drug

IV. 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

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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.

V. Renewal Criteria [1-3,4,5,10]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet indication-specific relevant criteria identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: symptoms of allergic-anaphylactic reactions (anaphylaxis, dyspnea, rash, etc.), thromboembolic events (thromboembolism, pulmonary embolism), 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**

Treatment of acute bleeding episodes/Treatment of Spontaneous and trauma-induced bleeding episodes/On-demand treatment of bleeding episodes

- Renewals will be approved for a 6 month authorization period

Prevention of acute bleeding episodes/Routine prophylaxis to prevent or reduce the frequency of bleeding episode

- Renewals will be approved for a 12 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)

VI. Dosage/Administration [1-5]

Alphanate

Indication	Dose
Control and prevention of bleeding Congenital Hemophilia A	The expected in vivo peak increase in FVIII level expressed as IU/dL (or % normal) can be estimated using the following formulas: Dosage (units) = body weight (kg) x desired FVIII rise (IU/dL or % normal) x 0.5 (IU/kg per IU/dL) **OR** IU/dL (or %of normal) = [Total Dose (IU)/body weight (kg)] x 2

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Indication	Dose
	Minor FVIII:C levels should be brought to 30% of normal (15 IU FVIII/kg twice daily) until hemorrhage stops and healing has been achieved (1-2 days). Moderate FVIII:C levels should be brought to 50% (25 IU FVIII/kg twice daily) until healing has been achieved (2-7 days, on average). Major FVIII:C levels should be brought to 80-100% for at least 3-5 days (40-50 IU FVIII/kg twice daily). Following this treatment period, FVIII levels should be maintained at 50% (25 IU FVIII/kg twice daily) until healing has been achieved. Major hemorrhages may require treatment for up to 10 days. Intracranial hemorrhages may require prophylaxis therapy for up to 6 months.
Perioperative management Congenital Hemophilia A	Prior to surgery, the levels of FVIII:C should be brought to 80-100% of normal (40-50 IU FVIII/kg). For the next 7-10 days after surgery, or until healing has been achieved, the patient should be maintained at 60-100% FVIII levels (30-50 IU FVIII/kg twice daily).
Control and prevention of bleeding and perioperative management von Willebrand Disease (VWD)	The ratio of VWF:RCo to FVIII in Alphanate varies by lot, so with each new lot, check the IU VWF:RCo/Vial to ensure accurate dosing. Minor *Pre-operative/pre-procedure dose (Target FVIII:C Activity – 40-50 IU/dL):* Adults: 60 IU VWF:RCo/kg body weight. Pediatrics: 75 IU VWF:RCo/kg body weight. *Maintenance dose (Target FVIII:C Activity – 40-50 IU/dL):* Adults: 40 to 60 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for 1-3 days. Pediatrics: 50 to 75 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for 1-3 days. Major *Pre-operative/pre-procedure dose (Target FVIII:C Activity – 100 IU/dL):* Adults: 60 IU VWF:RCo/kg body weight. Pediatrics: 75 IU VWF:RCo/kg body weight. *Maintenance dose (Target FVIII:C Activity – 100 IU/dL):* Adults: 40 to 60 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for at least 3-7 days. Pediatrics: 50 to 75 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for at least 3-7 days.

Humate-P

Indication	Dose
Control and prevention of	One International Unit (IU) of Factor VIII (FVIII) activity per kg body weight will increase the circulating FVIII level by approximately 2.0 International Units (IU)/dL.

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Indication	Dose
bleeding Congenital Hemophilia A	Minor Loading dose 15 IU FVIII:C/kg to achieve a FVIII:C plasma level of approximately 30% of normal; one infusion may be sufficient. If needed, half of the loading dose may be given once or twice daily for 1-2 days. Moderate Loading dose 25 IU FVIII:C/kg to achieve a FVIII:C plasma level of approximately 50% of normal, followed by 15 IU FVIII:C/kg every 8-12 hours for the first 1-2 days to maintain the FVIII:C plasma level at 30% of normal. Continue the same dose once or twice daily for up to 7 days or until adequate wound healing is achieved. Major Initially 40-50 IU FVIII:C/kg, followed by 20-25 IU FVIII:C/kg every 8 hours to maintain the FVIII:C plasma level at 80-100% of normal for 7 days. Continue the same dose once or twice daily for another 7 days to maintain the FVIII:C level at 30-50% of normal.
Control and prevention of bleeding von Willebrand Disease (VWD)	Administer 40 to 80 International Units (IU) VWF:RCo (corresponding to 17 to 33 International Units (IU) FVIII in Humate-P) per kg body weight every 8 to 12 hours. Adjust the dosage based on the extent and location of bleeding. Administer repeat doses as long as needed based on monitoring of appropriate clinical and laboratory measures.
Perioperative management von Willebrand Disease (VWD)	**Loading Doses** Major *VWF:Rco Target Peak Plasma Level – 100 IU/dL* *Target FVIII:C Activity – 80-100 IU/dL* ((Target peak plasma VWF:RCo level – baseline plasma VWF:RCo level) x Body wt (kg)) /IVR (in vivo recovery) If the IVR is not available, assume an IVR of 2.0 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma VWF:RCo) x BW (kg)/2.0 Minor *VWF:Rco Target Peak Plasma Level – 50-60 IU/dL* *Target FVIII:C Activity – 40-50 IU/dL* ((Target peak plasma VWF:RCo level – baseline plasma VWF:RCo level) x Body wt (kg)) /IVR (in vivo recovery) Emergency *VWF:Rco Target Peak Plasma Level – 100 IU/dL* *Target FVIII:C Activity – 80-100 IU/dL* Administer a dose of 50-60 IU VWF:RCo/kg body weight. **Maintenance Doses** The initial maintenance dose of Humate-P for the prevention of excessive bleeding during and after surgery should be half of the loading dose, irrespective of additional dosing required to meet FVIII:C targets. Subsequent maintenance doses should be based on the patient's VWF:RCo and FVIII levels.

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Wilate

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>Control of bleeding episodes VWD</td><td>The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1. The dosage should be adjusted according to the extent and location of the bleeding.
<u>Minor and Moderate</u>
Loading dose: 20-40 IU/kg; Maintenance dose: 20-30 IU/kg every 12-24 hours until VWF:Rco and FVIII activity trough levels > 30%, for up to 3 days.
<u>Major</u>
Loading dose: 40-60 IU/kg; Maintenance dose: 20-40 IU/kg every 12-24 hours until VWF:Rco and FVIII activity trough levels > 50%, for up to 5-7 days.</td></tr>
<tr><td>Perioperative management of bleeding vWD</td><td><u>Minor</u>
Loading dose: 30-60 IU/kg; Maintenance dose: 15-30 IU/kg or half of the loading dose every 12-24 hours until wound healing achieved, up to 3 days. VWF:Rco trough levels > 30% and peak levels 50%.
<u>Major</u>
Loading dose: 40-60 IU/kg; Maintenance dose: 20-40 IU/kg or half the loading dose every 12-24 hours (at least 2 doses within the first 24 hours after the start of surgery) until wound healing achieved, up to 6 days or more. VWF:Rco trough levels > 50% and peak levels 100%.</td></tr>
<tr><td>Control and prevention of bleeding/ Routine Prophylaxis Congenital Hemophilia A</td><td>Calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by approximately 2% of normal activity or 2 IU/dL when assessed using the one stage clotting assay. Use the following formula to determine the required dose:
– Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)
– Expected Factor VIII rise (% of normal) = 2 x administered IU / body weight (kg)
Dose and duration of therapy depend on the patient's weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors. Titrate dose and frequency to the patient's clinical response, individual needs, severity of deficiency, severity of hemorrhage, desired FVIII level, and presence of inhibitor, and the patient's clinical condition. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to Wilate.
<u>Routine Prophylaxis</u>
A guide for dosing as routine prophylaxis to reduce the frequency of bleeding is provided below. Exact dosing should be defined by the patient's clinical status and response.
<table>
<tr><th>Patients</th><th>Recommended Dose (IU/kg)</th><th>Frequency</th></tr>
<tr><td>Adolescents and adults</td><td>20-40 IU/kg</td><td>Every 2-3 days</td></tr>
</table>
<u>Dosing for Hemorrhages</u>
A guide for dosing in the treatment of major and minor hemorrhages is provided below. Exact dosing should be defined by the patient's clinical status and response.
<table>
<tr><th>Hemorrhage Type</th><th>Recommended Dose (IU/kg)</th><th>Frequency</th><th>Frequency</th></tr>
<tr><td>Minor</td><td>30-40</td><td>Repeat every 12-24 hours</td><td>At least 1 day, until bleed stops</td></tr>
<tr><td>Moderate</td><td>30-40</td><td>Repeat every 12-24 hours</td><td>3+ days, until bleed stops</td></tr>
</table></td></tr>
</table>

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Indication	Dose			
	Major	35-50	Repeat every 12-24 hours	3+ days, until bleed stops
	Life-Threatening	35-50	Repeat every 8-24 hours	Until threat has resolved

VII. Billing Code/Availability Information

HCPCS Code & NDC:

Drug	Manufacturer	J-Code	1 Billable Unit Equiv.	Vial Size	NDC
Alphanate	Grifols Biologicals Inc	J7186	1 IU	250 units	68516-4601 68516-4611
				500 units	68516-4602 68516-4612
				1000 units	68516-4603 68516-4613
				1500 units	68516-4604 68516-4614
				2000 units	68516-4609 68516-4615
Humate-P	CSL Behring LLC	J7187	1 IU	600 units	63833-0615 63833-0625
				1200 units	63833-0616 63833-0626
				2400 units	63833-0617 63833-0627
Wilate	Octapharma USA	J7183	1 IU VWF:RCO	500 units	68982-0182
				1000 units	

VIII. References

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D66	Hereditary factor VIII deficiency
D68.0	Von Willebrand's disease

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

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 Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

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Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): N	NCD/LCD Document (s): A56482
https://www.cms.gov/medicare-coverage-database/new-search/search-results.aspx?keyword=a56482&areaId=all&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP	

Jurisdiction(s): J,M	NCD/LCD Document (s): A56065
https://www.cms.gov/medicare-coverage-database/new-search/search-results.aspx?keyword=a56065&areaId=all&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP	

Jurisdiction(s): H,L	NCD/LCD Document (s): A56433
https://www.cms.gov/medicare-coverage-database/new-search/search-results.aspx?keyword=a56433&areaId=all&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP	

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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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

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