Factor VIII/VWF Complex (Alphanate®, Humate-P®, Wilate®)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: OHP020

Description
Alphanate, Humate-P, and Wilate are factor VIII concentrates containing von Willebrand factor (VWF) for the treatment of von Willebrand disease (vWD) and/or hemophilia A.

Length of Authorization
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Alphanate, antihemophilic factor/von Willebrand factor complex (human)	250, 500, 1000, 1500, 2000 IU FVIII	**Control and prevention of bleeding – hemophilia A** δ: Up to 50 IU factor VIII/kg twice daily for at least three to five days. Following this, factor VIII levels should be maintained at 25 IU factor VIII/kg twice daily until healing has been achieved. Major hemorrhages may require treatment for up to ten days. Intracranial hemorrhages may require prophylaxis therapy for up to six months.	**Control and prevention of bleeding in hemophilia A:** Up to the number of doses requested every 28 days
		Perioperative management – hemophilia A: Up to 50 IU factor VIII/kg prior to surgery, then up to 50 IU factor VIII/kg twice daily for the next seven to ten days, or until healing has been achieved	**Perioperative management in hemophilia A:** Up to the number of doses requested for 28 days
		Control and prevention of bleeding and perioperative management – vWDγ: Pre-operative/pre-procedure dose: • Adults: Up to 60 IU VWF:RCo/kg body weight • Pediatrics: Up to 75 IU VWF:RCo/kg body weight Maintenance: • Adults: Up to 60 IU VWF:RCo/kg body weight at eight to 12 hour intervals as	**Control and prevention of bleeding and perioperative management in vWD:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		clinically needed for at least three to seven days • Pediatrics: Up to 75 IU VWF:RCo/kg body weight at eight to 12 hour intervals as clinically needed for at least three to seven days	
Humate-P, antihemophilic factor/von Willebrand factor complex (human)	600, 1200, 2400 IU vWF:RCo	**Control and prevention of bleeding – hemophilia A*:** • Minor: Up to 15 IU factor VIII:C/kg to achieve a factor VIII: C plasma level of approximately 30% of normal. One infusion may be sufficient. If needed, half of the loading dose may be given one or twice daily for one to two days • Moderate: Up to 25 15 IU factor VIII:C/kg to achieve a factor VIII: C plasma level of approximately 50% of normal, followed by 15 IU factor VIII:C/kg every eight to 12 hours for the first one to two days to maintain the factor VIII:C plasma level at 30% of normal. Continue the same dose one or twice for up to seven days or until adequate wound healing is achieved • Major: Initially up to 50 IU factor VIII:C/kg, followed by up to 25 IU factor VIII:C/kg every eight hours to maintain the factor VIII:C plasma level at 80-100% of normal for seven days. Continue the same dose one or twice daily for another seven days to maintain the factor VIII:C level at 30-50% of normal **Control and prevention of bleeding – vWD:** Up to 80 IU vWF:RCo (corresponding to 17 to 33 IU factor VIII in Humate-P) per kg body weight every eight to 12 hours. Adjust as needed based on the extent and location of bleeding. Repeat doses as long as necessary.	**Control and prevention of bleeding – hemophilia A:** Up to the number of doses requested every 28 days **Control and prevention of bleeding – vWD:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		Perioperative management – vWD: Loading: • Major: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL • Minor: vWF:RCo target peak plasma level – 50-60 IU/dL; Target factor VIII:C activity – 40-50 IU/dL • Emergency: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL. Administer a dose of 50-60 IU vWF:RCo/kg body weight Maintenance: Initial maintenance dose should be half the loading dose, irrespective of additional dosing required to meet factor VIII:C targets. Subsequent doses should be based on the patient's vWF:RCo and factor VIII levels	**Perioperative management – vWD:** Up to the number of doses requested for 28 days
Wilate, von Willebrand factor/coagulation factor VIII complex (human)		**Control of bleeding episodes – vWD**€: Up to 60 IU/kg initially, followed by up to 40 IU/kg every 12 to 24 hours until vWF:Rco and factor VIII activity trough levels > 50%, for up to five to seven days **Perioperative management of bleeding – vWD**: Up to 60 IU/kg initially, followed by up to 40 IU/kg every 12 to 24 hours until wound healing achieved, up to six days or more. vWF:Rco and factor VIII activity trough levels > 50% and peak levels 100% until wound healing is achieved, up to six days or more	**Control of bleeding episodes – vWD:** Up to the number of doses requested every 28 days **Perioperative management of bleeding – vWD:** Up to the number of doses requested for 28 days

‡Allows for +5% to account for assay and vial availability

δ Dose (IU) = body weight (kg) x desired factor VIII rise (IU/dL or % normal) x 0.5 (IU/kg per IU/dL)

ɣ The ratio of VWF:RCo to factor VIII varies by lot, so with each new lot, check the IU vWF:RCo/Vial to ensure accurate dosing

* One IU of factor VIII activity per kg body weight will increase the circulating factor VIII level by approximately 2 IU/dL

ψ Target peak plasma vWF:RCo level – baseline plasma vWF:RCo level) – body weight (kg)/in vivo recovery. If the in vivo recovery is not available, assume an in vivo recovery of 2 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma vWF:RCo) x body weight (kg)/2

€ The ratio between vWF:RCo and factor VIII activities is approximately 1:1. The dosage should be adjusted according to the extent and location of the bleeding.

Initial Evaluation

<u>von Willebrand Disease</u>

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. Treatment of spontaneous and trauma-induced bleeding episodes; **OR**
      2. Used as surgical bleeding prophylaxis during major or minor procedures when desmopressin (DDAVP) is either ineffective or contraindicated; **AND**
      3. **Alphanate** will <u>not</u> be used for severe (type 3) vWD undergoing major surgery

II. **Wilate** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. Perioperative management of bleeding; **OR**
      2. For the treatment of spontaneous and trauma-induced bleeding episodes when one of the following is met:
         i. Member has severe vWD; **OR**
         ii. Member has mild or moderate vWD and the use of desmopressin (DDAVP) is known or suspected to be ineffective or contraindicated; **AND**
   D. Wilate will not be used for the routine prophylactic treatment of spontaneous bleeding episodes; **AND**
   E. Wilate is not being used for hemophilia A

<u>Hemophilia A (congenital factor VIII deficiency)</u>

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**

B. A diagnosis of hemophilia A has been confirmed by blood coagulation testing; **AND**
C. Use is planned for one of the following indications:
    1. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII/VWF units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
    2. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
        i. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
        ii. Member has had more than one documented episode of spontaneous bleeding; **OR**
    3. Perioperative management of bleeding; **AND**
D. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**
E. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Alphanate, Humate-P, and Wilate are considered investigational when used for any other condition.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

von Willebrand Disease

I. Von Willebrand disease (vWD) is the most common of the inherited bleeding disorders. Although vWD is common, only a fraction of patients seek medical attention due to bleeding symptoms due to the mild nature of the disease in many patients, and to the lack of bleeding challenges.
II. There are three types of inherited vWD:
    - Type 1 – The most common type that accounts for about 70% of cases. It reflects a quantitative deficiency of von Willebrand factor (vWF). The clinical presentation varies from mild to moderately severe.
    - Type 2 – Accounts for 25-30% of cases and is characterized by several qualitative abnormalities of vWF (e.g. altered size rations or biologic properties).

- Type 3 – The most severe type of disease with very low or undetectable levels of vWF. Patients typically present with severe bleeding involving both the skin and mucous membrane surfaces and soft tissues and joints. Replacement therapy with vWF is usually required.

III. Choice of therapy begins with an accurate and complete diagnosis of vWD, plus patient-specific factors must be taken to account (e.g. history of bleeding, response to prior therapies).

IV. A trial of desmopressin (DDAVP) should be considered in all patients with type 1 and most with type 2, but not in patients with type 3 vWD. Typically, minor bleeding episodes can be treated with DDAVP without further therapeutic intervention. Major surgery typically requires replacement with vWF. However, Alphanate is not indicated for patients with severe vWD undergoing major surgery.

V. Patients with type 3 vWD, those with more severe type 1, and many of those with certain subtypes of type 2 disease often require replacement therapy with a vWF-containing product to control bleeding. However, vWF is not generally given as long-term prophylaxis like is done in patients with hemophilia A.

VI. The safety and efficacy of factor VIII/vWF complex products were established based on open-label, non-randomized trails. All replacement are effective in restoring hemostasis.

<u>Hemophilia A</u>

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia A.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:

i. **Severe**: <1% factor activity (<0.01 IU/mL)
ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia A:

i. Episodic (“on demand”) treatment that is given at the time of clinically evident bleeding
ii. Perioperative management of bleeding for those undergoing elective surgery/procedures
iii. Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic (“on demand”) treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment

of choice for hemophilia A as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of factor VIII/vWF complex products in any other condition.

References

1. Alphanate® [Prescribing Information]. Los Angeles, CA: Grifols; June 2018
2. Humate-P® [Prescribing Information]. Kankakee, IL; CSL Behring LLC; September 2017
3. Wilate® [Prescribing Information]. Hoboken, NJ; Octapharm USA; September 2016
4. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
5. UpToDate, Inc. Treatment of von Willebrand disease. UpToDate [database online]. Last updated July 19, 2019.
6. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
7. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
8. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date

New policy created for factor VIII/vWF complex products	08/2019