

POLICY: Hemophilia – Factor VIII Products

Extended Half-Life Products

- Adynovate[®] (Antihemophilic Factor PEGylated injection – Baxalta)
- Eloctate[®] (Antihemophilic Factor Fc fusion protein injection – Bioverativ)
- Esperoct[®] (Antihemophilic factor glycopegylated injection – Novo Nordisk)
- Jivi[®] (Antihemophilic Factor PEGylated-aucl injection – Bayer HealthCare)

Standard Half-Life Products

- Advate[®] (Antihemophilic Factor injection – Baxalta)
- Afstyla[®] (Antihemophilic Factor single chain injection – CSL Behring)
- Helixate[®] FS (Antihemophilic Factor injection – Bayer HealthCare/CSL Behring)
- Kogenate[®] FS (Antihemophilic Factor injection – Bayer HealthCare)
- Kovaltry[®] (Antihemophilic Factor injection – Bayer HealthCare)
- Novoeight[®] (Antihemophilic Factor injection – Novo Nordisk)
- Nuwiq[®] (Antihemophilic Factor injection – Octapharma)
- Recombinate[®] (Antihemophilic Factor injection – Baxalta)
- Xyntha[®]/Xyntha[®] Solofuse[™] (Antihemophilic Factor injection, plasma/albumin-free – Wyeth/Pfizer)

Plasma-Derived Standard Half-Life Products without Von Willebrand Factor

- Hemofil[®] M (Antihemophilic Factor injection – Baxalta)
- Monoclate-P[®] (Antihemophilic Factor injection – CSL Behring)

Plasma-Derived Standard Half-Life Products with Von Willebrand Factor

- Alphanate[®] (Antihemophilic Factor/von Willebrand Factor Complex [human] injection – Grifols)
- Humate-P[®] (Antihemophilic Factor/von Willebrand Factor Complex injection – CSL Behring)
- Koate[®] (Antihemophilic Factor injection – Grifols/Kedrion Biopharma)
- Wilate[®] (von Willebrand Factor/Coagulation Factor VIII Complex for intravenous use – Octapharma)

APPROVAL DATE: 02/27/2019

OVERVIEW

For the management of hemophilia A, many recombinant Factor VIII products are available, including extended half-life products¹⁻⁴ (Adynovate, Eloctate, Esperoct, and Jivi) as well as standard half-life products (Advate, Afstyla, Helixate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha).⁵⁻¹⁶ In general, such products are used for the on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and for routine prophylaxis to reduce the frequency of bleeding episodes. Several standard half-life Factor VIII plasma-derived products are available. Hemofil M and Monoclate P are plasma-derived standard half-life products that do not contain substantial amounts of von Willebrand Factor which are indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.^{17,18} Plasma-derived Factor VIII products that contain von Willebrand Factor include Alphanate, Humate P, Koate, and Wilate.¹⁹⁻²² Alphanate is indicated for the control and prevention of bleeding in adult and pediatric patients with hemophilia A.¹ Alphanate is also indicated for surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin is either ineffective or contraindicated. The agent is not indicated for patients with severe von Willebrand Disease (type 3) undergoing major

surgery.¹⁹ Humate-P is indicated for the treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia).²⁰ Humate P is also indicated in adult and pediatric patients with von Willebrand disease for the treatment of spontaneous and trauma-induced bleeding episodes and for the prevention of excessive bleeding during and after surgery. The indication in von Willebrand Disease applies to patients with severe von Willebrand disease, as well as in patients with mild to moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate. Koate is indicated for the control and prevention of bleeding episodes or in order to perform emergency elective surgery in patients with hemophilia A.²¹ Wilate is indicated in children and adults with von Willebrand disease for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding.²² Wilate is not indicated for the treatment of hemophilia A but may be an option for some patients as it does contain Factor VIII, as well as Von Willebrand Factor.

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in Factor VIII.²³⁻²⁵ In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. Sometimes the disorder is caused by a spontaneous genetic mutation. Males primarily have the disorder and most times females are asymptomatic carriers. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas (e.g., muscles, central nervous system, gastrointestinal). Hemarthrosis is the main sign of hemophilia in older children and adults. In newborns and toddlers, bleeding in the head (intracranial hemorrhage and extracranial hemorrhage), bleeding from circumcision, and in the oral cavity are more common. The bleeding manifestations can lead to substantial morbidity, as well as mortality, if not properly treated. Disease severity is usually defined by the plasma levels of Factor VIII and have been classified as follows: severe (levels less than 1% of normal [normal plasma levels are 50 to 100 U/dL]), moderate (levels 1% to 5% of normal), and mild (levels > 5%); phenotypic expression may also vary. Approximately 25% to 30% of patients with hemophilia A have severe deficiency whereas 3% to 13% of patients have moderate to mild deficiency. Diagnoses can be substantially delayed, especially in patients with mild disease, as bleeding may not clinically occur. Higher doses than that typically used for these uses of standard half-life products can be given if the patient develops an inhibitor, which develop in approximately 25% of patients.²⁶

VWD is a group of inherited bleeding disorders related to defects of von Willebrand Factor (vWF), which is needed to achieve hemostasis.²⁷⁻²⁹ It occurs equally in males and females. The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of factor VIII. Mucous membrane and skin bleeding symptoms, as well as bleeding with surgical or other hemostatic challenges, may occur. The prevalence of the disease is approximately 1.3%. Pregnancy can increase vWF levels and confound diagnosis. The three major subtypes of VWD include: partial quantitative vWF deficiency (type 1, 75% of patients); qualitative vWF deficiency (type 2, 25% of patients); and complete vWF deficiency (type 3, rare). Type 2 disease is further divided into four variants (2A, 2B, 2M, 2N) on the basis of the phenotype. In type 3 VWD, Factor VIII levels are usually very low. Acquired von Willebrand syndrome may result but is rare, occurring in fewer than one in 100,000 adults. The bleeding risk varies between modest increases in bleeding which occur only with procedures to a major risk of spontaneous hemorrhage. Approaches to the management of VWD involve increasing plasma concentrations of vWF through stimulation with desmopressin; replacing VWF by using human plasma-derived viral inactivated concentrates; and promoting hemostasis by use of hemostatic agents with mechanisms other than increasing VWF; and Vonvendi® (von Willebrand factor [recombinant] injection for intravenous use). Regular prophylaxis is not frequently required.

Guidelines

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia and other bleeding disorders.²³ It is noted that recombinant Factor VIII products are the recommended treatment of choice for patients with hemophilia A. The MASAC recommendations regarding plasma-derived Factor VIII products state that improved viral-depleting processes and donor screening practices have greatly reduced the risk of transmission and human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV).

MASAC recommendations also discuss VWD and vWF-containing Factor VIII products.²³ Most patients with VWD type 1 may be treated with either desmopressin (either parenterally [DDAVP injection] or by a highly concentrated nasal spray [Stimate nasal spray]). For surgery, trauma, or other serious bleeding episodes, if hemostasis is not achieved using DDAVP, a Factor VIII concentrate that contains high molecular weight multimers of vWF should be used. Patients with type 2B and type 3 VWD, and those with type 1, 2A, 2M, and 2N who have not responded adequately to DDAVP should be treated with a Factor VIII concentrate that contains higher molecular weight multimers of vWF. Products FDA-approved for this use include Alphanate, Humate P, and Wilate. Koate may be effective but it not FDA-approved for this use.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of the following Factor VIII products: Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha, Hemofil M, Monoclate P, Alphanate, Humate-P, Koate, and Wilate. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor VIII products, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

- I. Coverage of Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha is recommended in those who meet one of the following criteria.

FDA-Approved Indications

-
1. **Hemophilia A.** Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve one of the following dosing regimens (A or B):

- A) For Adynovate, Eloctate, Esperoct, and Jivi approve the following dosing regimens (i, ii, iii, and/or iv):
 - i. Routine prophylaxis: approve up to 100 IU per kg intravenously no more frequently than twice weekly; AND/OR

- ii. On-demand treatment and control of bleeding episodes: approve up to 65 IU per kg intravenously no more frequently than once every 8 hours for up to 10 days per episode; AND/OR
 - iii. Perioperative management: approve up to 65 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per procedure; OR
- B) For Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha approve the following dosing regimens (i, ii, iii, and/or iv):
- i. Routine prophylaxis: approve up to 60 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR
 - ii. On-demand treatment and control of bleeding episodes: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode; AND/OR
 - iii. Perioperative management: approve up to 60 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per procedure; AND/OR
 - iv. Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.
- II. Coverage of Hemofil M, Monoclote-P, Alphanate, Humate-P, Koate, and Wilate is recommended in those who meet one of the following criteria:

FDA-Approved Indications

-
1. **Hemophilia A.** Approve Hemofil M, Monoclote-P, Koate, Alphanate, Humate P, and Wilate for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens:

- A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR
 - B) On-demand treatment and control of bleeding episodes and perioperative management: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode or procedure; AND/OR
 - C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.
2. **Von Willebrand Disease.** Approve Alphanate, Humate P, and Wilate for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. On-demand treatment and control of bleeding episodes and perioperative management: approve up to 80 IU VWF:RCo per kg intravenously no more frequently than once every 8 hours for up to 10 days per episodes or procedure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

1. **Other Indications.** Coverage is not recommended for circumstances not listed in the Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Adynovate® lyophilized powder for solution for intravenous injection [prescribing information]. Lexington, MA: Baxalta; May 2018.
2. Elocate® lyophilized powder for solution for intravenous injection [prescribing information]. Waltham, MA: Bioverativ; December 2017.
3. Jivi® lyophilized powder for solution for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; August 2018.
4. Esperoct® lyophilized powder for solution for intravenous use [prescribing information]. Plainsboro, NJ: Novo Nordisk; February 2019.
5. Advate® lyophilized powder for reconstitution for intravenous injection [prescribing information]. Westlake Village, CA: Baxalta/Shire; December 2018
6. Kovaltry® lyophilized powder for solution for intravenous injection [prescribing information]. Whippany, NJ: Bayer HealthCare; March 2016.
7. Afstyla® lyophilized powder for solution for intravenous injection [prescribing information]. Kankakee, IL: CSL Behring; September 2017.
8. Helixate® FS lyophilized powder for reconstitution for intravenous use [prescribing information]. Kankakee, IL and Whippany, NJ: CSL Behring and Bayer HealthCare; May 2016.
9. Kogenate® FS lyophilized powder for reconstitution for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; May 2016.
10. Kogenate® FS lyophilized powder for reconstitution with vial adapter for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; May 2016.
11. Kogenate® FS lyophilized powder for reconstitution with BIO-SET® for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; May 2016.
12. Novoeight® lyophilized powder for solution for intravenous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; November 2018.
13. Nuwiiq® lyophilized powder solution for intravenous injection [prescribing information]. Hoboken, NJ: Octapharma; July 2017.
14. Recombinate™ lyophilized powder for reconstitution for injection [prescribing information]. Lexington, MA: Baxalta; June 2018.
15. Xyntha® lyophilized powder for solution intravenous injection [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals (a subsidiary of Pfizer); October 2014.
16. Xyntha® Solofuse™ lyophilized powder for solution in prefilled dual chamber syringe for intravenous injection [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals (a subsidiary of Pfizer); October 2014.
17. Hemofil® M for intravenous use [prescribing information]. Lexington, MA: Baxalta; June 2018.
18. Monoclate-P® for intravenous use [prescribing information]. Kankakee, IL: Aventis Behring; February 2014.
19. Alphanate® for intravenous injection [prescribing information]. Los Angeles, CA: Grifols; March 2017.
20. Humate-P® lyophilized powder for reconstitution for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; September 2017.
21. Koate for intravenous injection [prescribing information]. Fort Lee, NJ and Research Triangle Park, NC: Kedrion Biopharma and Grifols; June 2018.
22. Wilate® lyophilized powder for solution for intravenous injection [prescribing information]. Hoboken, NJ: Octapharma; August 2015.
23. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #253. Adopted on April 19, 2018. Available at: <https://www.hemophilia.org/node/3675>. Accessed on February 11, 2019.
24. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments and its complications. *Lancet*. 2016;388(10040):187-197.
25. Berntorp E, Shapiro. Modern haemophilia care. *Lancet*. 2012;379:1447-1456.
26. Valentino LA, Kempton CL, Kruse-Jarres R, et al, on behalf of the International Immune Tolerance Induction Study Investigators. US guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia*. 2015;21(5):559-567.
27. Neff AT, Sidonio RF. Management of VWD. *Hematology Am Soc Hematol Educ Program*. 2014;(1):536-541.
28. 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.
29. Favaloro EJ, Bodo I, Israels SJ, Brown SA. Von Willebrand disease and platelet disorders. *Hemophilia*. 2014;20(Suppl 4):59-64.

HISTORY

| Type of Revision | Summary of Changes* | Approval Date |
|-------------------------|----------------------------|----------------------|
| New policy | -- | 02/27/2019 |