| Reference number(s) |
|---|
| 4932-A |

# STANDARD MEDICARE PART B MANAGEMENT

## FACTOR VIII CONCENTRATES

### POLICY

### I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

**Table: Factor VIII Concentrates and Covered Uses**

| Brand | Generic | FDA-Approved Indication(s)[1-19,35,37] | Compendial Indication(s)[20-24] |
|---|---|---|---|
| ***Recombinant Factor VIII Concentrates*** | | | |
| **Advate** | antihemophilic factor [recombinant] | Hemophilia A | Acquired Hemophilia A |
| **Afstyla** | antihemophilic factor [recombinant], single chain | Hemophilia A | |
| **Kogenate FS** | antihemophilic factor [recombinant] | Hemophilia A | Acquired Hemophilia A |
| **Kovaltry** | antihemophilic factor [recombinant] | Hemophilia A | |
| **Novoeight** | antihemophilic factor [recombinant] | Hemophilia A | Acquired Hemophilia A |
| **Nuwiq** | antihemophilic factor [recombinant] | Hemophilia A | |
| **Recombinate** | antihemophilic factor [recombinant] | Hemophilia A | Acquired Hemophilia A |
| **Xyntha** | antihemophilic factor [recombinant] | Hemophilia A | Acquired Hemophilia A |
| ***Extended Half-life Recombinant Factor VIII Concentrates*** | | | |
| **Adynovate** | antihemophilic factor [recombinant], PEGylated | Hemophilia A | |
| **Altuviiio** | antihemophilic factor [recombinant], Fc-VWF-XTEN fusion protein-ehtl | Hemophilia A | |
| **Eloctate** | antihemophilic factor [recombinant], Fc fusion protein | Hemophilia A | |
| **Jivi** | antihemophilic factor [recombinant], PEGylated-aucl | Hemophilia A | |
| **Esperoct** | antihemophilic factor [recombinant], Glycopegylated-exei | Hemophilia A | |
| ***Human Plasma-Derived Factor VIII Concentrate*** | | | |
| **Hemofil M** | antihemophilic factor [human] monoclonal antibody purified | Hemophilia A | Acquired Hemophilia A |
| ***Human Plasma-Derived Factor VIII Concentrates That Contain Von Willebrand Factor*** | | | |

| | | | |
| --- | --- | --- | --- |
| **Alphanate**<br><br>**Humate-P** | antihemophilic factor/von Willebrand factor complex [human] | Hemophilia A, von Willebrand Disease | Acquired Hemophilia A, Acquired von Willebrand Syndrome |
| **Koate** | antihemophilic factor [human] | Hemophilia A | Acquired Hemophilia A, von Willebrand Disease |

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

## II. CRITERIA FOR INITIAL APPROVAL

### A. Hemophilia A

Authorization of 12 months of Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, or Xyntha may be granted for treatment of hemophilia A when either of the following criteria is met:

1. Member has mild disease (see Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
2. Member has moderate or severe disease (see Appendix A).

Authorization of 12 months of Jivi may be granted for treatment of hemophilia A when BOTH of the following criteria are met:

1. Member has previously received treatment for hemophilia A with a factor VIII product.
2. Member is ≥ 12 years of age.

### B. Von Willebrand Disease (VWD)

Authorization of 12 months of Alphanate, Humate-P, or Koate may be granted for treatment of VWD when any of the following criteria is met:

1. Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
2. Member has type 2B or type 3 VWD.

### C. Acquired Hemophilia A

Authorization of 12 months of Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, or Xyntha may be granted for treatment of acquired hemophilia A.

### D. Acquired von Willebrand Syndrome

Authorization of 12 months of Alphanate or Humate-P may be granted for treatment of acquired von Willebrand syndrome.

## III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

A. The member is currently receiving therapy with the requested medication.

B. The requested medication is being used to treat an indication enumerated in Section II.
C. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

**Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes**

| Severity | Clotting Factor Level % activity* | Bleeding Episodes |
| --- | --- | --- |
| Severe | <1% | Spontaneous bleeding episodes, predominantly into joints and muscles<br>Severe bleeding with trauma, injury or surgery |
| Moderate | 1% to 5% | Occasional spontaneous bleeding episodes<br>Severe bleeding with trauma, injury or surgery |
| Mild | 6% to 40% | Severe bleeding with serious injury, trauma or surgery |

*Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

**Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A and Type 1, 2A, 2M and 2N VWD**

B. Age < 2 years
C. Pregnancy
D. Fluid/electrolyte imbalance
E. High risk for cardiovascular or cerebrovascular disease (especially the elderly)
F. Predisposition to thrombus formation
G. Trauma requiring surgery
H. Life-threatening bleed
I. Contraindication or intolerance to desmopressin
J. Severe type 1 von Willebrand disease
K. Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

## IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for the factor VIII agents listed in section I.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007
4. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update.
5. WFH Guidelines for the Management of Hemophilia, 3rd edition.

6. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders
7. MASAC recommendations regarding the treatment of von Willebrand disease. Revised February 2021.
8. Acquired hemophilia. World Federation of Hemophilia.
9. International recommendations on the diagnosis and treatment of acquired hemophilia A.
10. Acquired haemophilia A: a 2013 update.
11. National Hemophilia Foundation. Hemophilia A (Factor VIII Deficiency).
12. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the factor VIII agents listed in section I are covered in addition to the following:

A. Acquired hemophilia A for Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, Xyntha
B. Acquired von Willebrand syndrome for Alphanate and Humate-P
C. Von Willebrand disease for Koate

## V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate and Xyntha to treat mild hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Mild disease is defined as having a clotting factor level of 6 to 40% of normal. The patient generally experiences severe bleeding with major trauma or surgery. It is rare these patients will bleed spontaneously. Desmopressin may be the treatment of choice for patients with mild hemophilia A when factor VIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using clotting factor concentrates. Desmopressin is not appropriate in all situations. Patients under 2 years of age, pregnant patients, patients with electrolytes or fluid imbalance, patients at high risk for cerebrovascular disease, predisposition to thrombus formation, patients who experienced trauma severe enough to require surgery, and patients experiencing a life-threatening bleed are not ideal candidates for desmopressin therapy.

Support for using Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate and Xyntha to treat moderate to severe hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Patients with moderate to severe hemophilia A should be started on prophylaxis with factor VIII or a non-factor therapy like Hemlibra to prevent a recurring life-threatening bleed. Desmopressin is not appropriate in these patients.

Support for using Alphanate, Humate-P, and Koate to treat von Willebrand syndrome can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Humate-P and Alphanate are approved by the FDA to treat von Willebrand syndrome. Koate has been used off-label for this use as well. Regarding the use of desmopressin, Type 2B and type 3 VWD does not respond consistently to desmopressin therapy and therefore desmopressin is not considered clinically useful in these patients.

Support for using Advate, Kogenate FS, Novoeight, Recombinate, and Xyntha to treat acquired hemophilia A can be found in the AHFS-DI database maintained by the American Society of Health System Pharmacists. Antihemophilic factor (recombinant) has been used in the management of bleeding episodes in some patients

with acquired hemophilia A who have low levels of inhibitors. Although antihemophilic factor therapy may be effective in some patients with low levels of acquired antihemophilic factor inhibitors when given in high doses current evidence indicates that bypassing agents are substantially more effective in achieving hemostatic control and are considered the treatment of choice in patients with this condition.

Support for using Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, and Xyntha to treat acquired hemophilia A can be found in the international recommendations on the diagnosis and treatment of acquired hemophilia A (Tiede et al, 2020). Human (plasma-derived or recombinant) factor VIII is recommended if recombinant factor VIIa, activated prothrombin complex concentrate and recombinant porcine factor VIII is unavailable, and the inhibitor titer is low.

Support for using Alphanate and Humate-P to treat acquired von Willebrand syndrome can be found in the National Institutes of Health publication called the “Diagnosis, Evaluation, and Management of von Willebrand Disease”. The guideline indicates DDAVP and VWF/FVIII concentrates are first line therapy. If a patient has an inadequate response to DDAVP and VWF/FVIII concentrates, intravenous immunoglobulin given alone was effective in controlling bleeding and raising VWF:RCo activity.

## IV. REFERENCES

1. Advate [package insert]. Lexington, MA: Baxalta US Inc.; December 2018.
2. Jivi [package insert]. Whippany, NJ: Bayer HealthCare LLC; August 2018.
3. Kogenate FS [package insert]. Whippany, NJ: Bayer HealthCare LLC; May 2016.
4. Kogenate FS with BIO-SET [package insert]. Whippany, NJ: Bayer HealthCare LLC; May 2016.
5. Kogenate FS with Vial Adapter [package insert]. Whippany, NJ: Bayer HealthCare LLC; December 2019.
6. Kovaltry [package insert]. Whippany, NJ: Bayer Healthcare LLC; December 2022.
7. Novoeight [package insert]. Plainsboro, NJ: Novo Nordisk Inc., July 2020.
8. Nuwiq [package insert]. Hoboken, NJ: Octapharma USA, Inc., June 2021.
9. Recombinate with 5 mL Sterile Water for Injection using BAXAJECT II [package insert]. Lexington, MA: Baxalta US Inc.; June 2018.
10. Xyntha [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; July 2022.
11. Xyntha Solufuse [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; July 2022.
12. Adynovate [package insert]. Lexington, MA: Baxalta US Inc.; July 2021.
13. Afstyla [package insert]. Marburg, Germany: CSL Behring GmbH. April 2021.
14. Eloctate [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; December 2020.
15. Hemofil M [package insert]. Lexington, MA: Baxalta US Inc.; June 2018.
16. Alphanate [package insert]. Los Angeles, CA: Grifols Biologicals Inc.; March 2021.
17. Humate-P [package insert]. Marburg, Germany: CSL Behring GmbH; June 2020.
18. Koate [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; June 2018.
19. Koate-DVI [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; August 2012.
20. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed December 1, 2022.
21. National Institutes of Health. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007. NIH publication No. 08-5832.
22. Tiede A, Rand J, Budde U, et al. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117(25):6777-85.
23. Federici A, Budde U, Castaman G, Rand J, Tiede A. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update. *Semin Thromb Hemost*. 2013;39(2):191-201.

24. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
25. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised March 2022. MASAC Document #272. https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed December 1, 2022.
**26.** National Hemophilia Foundation. MASAC recommendations regarding the treatment of von Willebrand disease. Revised February 2021. MASAC Document #266. https://www.hemophilia.org/sites/default/files/document/files/266.pdf. Accessed December 1, 2022.
27. Acquired hemophilia. World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1186.pdf. Accessed December 1, 2022.
28. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. *Haematologica.* 2020;105(7):1791-1801. doi:10.3324/haematol.2019.230771.
29. Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. *Thromb Haemost*. 2013;110(6):1114-20.
30. National Hemophilia Foundation. Hemophilia A (Factor VIII Deficiency). Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=180&contentid=45&rptname=bleeding. Accessed December 1, 2022.
31. Stimate [package insert]. King of Prussia, PA: CSL Behring LLC; June 2021.
32. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. *Haemophilia*. 2014;20:158-167.
33. Reding MT, NG HJ, Poulsen LH, et al. Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. *Journal of thrombosis and Haemostasis*. 2017; 15: 411-9.
34. Esperoct [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; August 2022.
35. Altuviiio [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; February 2023.