Standard Half-Life Factor VIII Products – Hemophilia A
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO062

Description
Advate, Afstyla, Hemofil M, Kogenate FS, Koate DVI, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha are standard half-life factor VIII products for the treatment and prevention of bleeding in patients with 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‡
Advate, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000, 3000, 4000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • Up to 40 IU/kg every other day (3 to 4 times weekly) or every third day **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat every 12 to 24 hours as needed until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 60 IU/kg preoperative to achieve 100% activity; Repeat every 8 to 24 (every 6 to 24 hours for patients under the age of six) hours to keep factor VIII activity in desired range until healing is complete	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** Up to 672 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Afstyla, antihemophilic factor (recombinant), single chain	250, 500, 1000, 1500, 2000, 2500, 3000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg two to three times per week • <12 years: Up to 50 IU/kg two to three times per week. More frequent or higher dosing may be required to account for the higher clearance in this age group. **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg every 24 hours for at least one day until healing is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg every 8 to 24 hours until adequate wound healing, then continue therapy for at least another seven days	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 630 IU/kg every 28 days • <12 years: Up to 630 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Hemofil M, antihemophilic factor (human)	250, 500, 1000, 1700 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL; Repeat every 8 to 24 hours until the bleeding threat is resolved **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): A single infusion of up to 80 IU/dL plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases	**On-demand Treatment:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat dose every 8 to 24 hours depending on state of healing	
Koate DVI, antihemophilic factor (human)	250, 500, 1000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 12 hours until bleeding threat is resolved **Perioperative Management** δ**:** For major surgical procedures, the factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. Repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of factor replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate homeostasis.	**On-demand Treatment:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Kogenate FS, antihemophilic factor (recombinant), formulated with sucrose	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 50 IU/kg every 8 to 12 hours until bleeding is resolved **Routine Prophylaxis:** • Adults: Up to 25 IU/kg three times per week • Children: Up to 25 IU/kg every other day **Perioperative Management** δ**:**	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • Adults: Up to 315 IU/kg every 28 days • Children: Up to 368 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• *Minor* (e.g. tooth extraction): Up to 30 IU/kg every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg preoperative to achieve 100% activity; Repeat every 6 to 12 hours to keep factor VIII activity in desired range until healing is complete	
Kovaltry, antihemophilic factor (recombinant)	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg two or three times per week • ≤ 12 years: Up to 50 IU/kg twice weekly, three times weekly, or every other day **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 24 hours until healing is achieved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 504 IU/kg every 28 days • ≤12 years: Up to 735 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Novoeight, antihemophilic	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 24 hours until	**On-demand Treatment:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
factor (recombinant)		resolution of bleed (approximately seven to ten days) **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg three times per week or up to 40 IU/kg every other day • ≤ 12 years: Up to 60 IU/kg three times weekly or up to 50 IU/kg every other day **Perioperative Management**δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**Routine Prophylaxis:** • ≥12 years: Up to 630 IU/kg every 28 days • ≤12 years: Up to 756 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Nuwiq, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000, 2500, 3000, 4000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding risk is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg every other day • ≤ 12 years: Up to 50 IU/kg every other day or three times per week **Perioperative Management**δ**:**	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 588 IU/kg every 28 days • ≤12 years: Up to 735 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• *Minor* (e.g. tooth extraction): Up to 40 IU/dL every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	
Recombinate, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved **Perioperative Management**δ**:** • *Minor* (e.g. tooth extraction): Up to 80 IU/dL as a single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours depending on state of healing	**On-demand Treatment:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Xyntha, antihemophilic factor (recombinant)	250, 500, 1000, 2000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved **Perioperative Management**δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL for 3 to 4 days or until adequate hemostasis is achieved. For tooth extraction,	**On-demand Treatment:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved	

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

δ Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL); *Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg)*

Initial Evaluation

I. Standard half-life factor VIII products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia A (congenital factor VIII deficiency)** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of standard half-life factor VIII is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. 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**

4. 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. Standard half-life factor VIII products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For **on-demand treatment** and **routine prophylaxis**:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; **AND**
   ii. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; **AND**
   iii. *For **on-demand treatment only***, the dose and frequency is not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

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:
   - Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - 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 standard half-life factor VIII products in any other condition.

References

1. Advate [package insert]. Westlake Village, CA; Baxalta US Inc. May 2018.
2. Afstyla [package insert]. Kankakee, IL; CSL Behring, LLC; April 2017.
3. Hemofil M [package insert]. Westlake Village, CA; Baxalta US Inc. June 2018.
4. Koate DVI [package insert]. Research Triangle Park, NC; Grifols Therapeutics Inc.; August 2012.
5. Kogenate FS [package insert]. Whippany, NJ. Bayer HealthCare LLC; May 2016.
6. Novoeight [package insert]. Bagsvaerd, Denmark; Novo Nordisk; November 2018.
7. NUWIQ [package insert]. Elersvagen, Sweden; Octapharma AB; July 2017.
8. Recombinate [package insert]. Westlake Village, CA; Baxalta US Inc. June 2018.
9. Kovaltry [package insert]. Whippany, NJ; Bayer HealthCare LLC; March 2016
10. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
11. 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.
12. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 1500 strength of Nuwiq	02/2021
New policy created for standard half-life factor products	08/2019