Clinical Policy: Factor VIII (Human - Hemofil M, Koate-DVI; Recombinant - Advate, Adynovate, Afstyla, Eloctate, Esperoct, Helixate FS, Jivi, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Xyntha)

Reference Number: ERX.SPA.184
Effective Date: 01.11.17
Last Review Date: 11.21 Revision Log
Line of Business: Commercial, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following are factor VIII products requiring prior authorization: human – Hemofil M®, Koate-DVI®; recombinant – Advate®, Adynovate®, Afstyla®, Eloctate®, Esperoct®, Helixate® FS, Jivi®, Kogenate® FS, Kovaltry®, Novoeight®, Nuwiq®, Obizur®, Recombinate®, Xyntha®, and Xyntha® Solofuse®.

FDA Approved Indication(s)
Factor VIII products are indicated for patients with hemophilia A for the following uses:
- Control and prevention of bleeding episodes:
  - Children and adults: Advate, Adynovate, Afstyla, Eloctate, Esperoct, Helixate FS, Hemofil M, Jivi (in previously treated patients ≥ 12 years of age only), Koate-DVI, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha
- Perioperative management:
  - Children and adults: Advate, Adynovate, Afstyla, Eloctate, Esperoct, Helixate FS, Hemofil M, Jivi (in previously treated patients ≥ 12 years of age only), Koate-DVI, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes:
  - Adults only: Kogenate FS
  - Children and adults: Advate, Adynovate, Afstyla, Eloctate, Esperoct, Helixate FS, Jivi (in previously treated patients ≥ 12 years of age only), Kovaltry, Novoeight, Nuwiq, Xyntha
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes and to reduce the risk of joint damage in children without pre-existing joint damage:
  - Children: Helixate FS, Kogenate FS
- On-demand treatment and control of bleeding episodes in acquired hemophilia A:
  - Adults: Obizur

Limitation(s) of use:
- Factor VIII products are not indicated for treatment of von Willebrand disease.
- Obizur is not indicated for the treatment of congenital hemophilia A.
- Safety and efficacy of Obizur have not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of > 20 Bethesda units (BU).
- Jivi is not indicated for use in children < 12 years of age due to a greater risk for hypersensitivity reactions.
- Jivi is not indicated for use in previously untreated patients.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that factor VIII products are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hemophilia A (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. Congenital hemophilia A (factor VIII deficiency) (all products except Obizur);
   b. Acquired hemophilia A (Obizur only);
2. Prescribed by or in consultation with a hematologist;
3. Request is for one of the following uses (a, b, or c):
   a. Control and prevention of bleeding episodes;
   b. Perioperative management (all products except Obizur);
   c. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes;
4. For routine prophylaxis requests: Request is for Advate, Adynovate, Eloctate, Esperoct, Helixate FS, Jivi, Kogenate FS, Kovaltry, Novoeight, Nuwiq, or Xyntha, and member meets one of the following (a or b):
   a. Member has severe hemophilia (defined as factor VIII level of < 1%);
   b. Member has experienced at least one life-threatening or serious spontaneous bleed (*see Appendix D*);
5. If the request is for routine prophylaxis and the member has used a dosage that exceeds the maximum recommended dose for at least 4 of the last 6 months, then member must use Hemlibra® unless contraindicated or clinically significant adverse effects are experienced;
6. For all products except Obizur: If factor VIII coagulant activity levels are > 5%, failure of desmopressin acetate, unless contraindicated, clinically significant adverse effects are experienced, or an appropriate formulation of desmopressin acetate is unavailable;
7. For Jivi: Member meets both of the following (a and b):
   a. Age ≥ 12 years;
   b. Has previously been treated for hemophilia A;
8. If request is for a non-preferred product, failure of 2 preferred products, unless contraindicated or clinically significant adverse effects are experienced;
9. Documentation of member's body weight (in kg);
10. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

Approval duration: 3 months (surgical/acute bleeding) or 6 months (prophylaxis)

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Hemophilia A (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. If the request is for routine prophylaxis and the member has used a dosage that exceeds the maximum recommended dose for at least 4 of the last 6 months, then member must use Hemlibra unless contraindicated or clinically significant adverse effects are experienced;
3. Member is responding positively to therapy;
4. Documentation of member's body weight (in kg);
5. If request is for a dose increase, new dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

Approval duration: 3 months (surgical/acute bleeding) or 6 months (prophylaxis)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

B. Von Willebrand disease.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BU: Bethesda unit
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
desmopressin acetate (Stimate® nasal spray; generic injection solution)	When Factor VIII coagulant activity levels are > 5% Injection: 0.3 mcg/kg IV every 48 hours Nasal spray: < 50 kg: 1 spray intranasally in one nostril only; may repeat based on laboratory response and clinical condition ≥ 50 kg: 1 spray intranasally in each nostril; may repeat based on laboratory response and clinical condition	Injection: 0.3 mcg/kg IV every 48 hours Nasal spray: 1 spray intranasally in each nostril
Hemlibra (emicizumab-kxwh)	3 mg/kg per week IV during the first four weeks of therapy, followed by either 1.5 mg/kg per week, 3 mg/kg once every two weeks, or 6 mg/kg once every four weeks thereafter	6 mg/kg/month

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): life-threatening hypersensitivity reactions, including anaphylaxis, to the product and its constituents*
  **Including bovine, mouse, or hamster protein for Advate, Adynovate, Afstyla, Helixate FS, Hemofil M, Jivi, Kogenate FS, Kovaltry, Novoeight, Obizur, Recombinate, and Xyntha*
- Boxed warning(s): none reported

Appendix D: General Information

- Life-threatening bleeding episodes include, but are not limited to, bleeds in the following sites: intracranial, neck/throat, or gastrointestinal.
- Serious bleeding episodes include bleeds in the following site: joints (hemarthrosis).
- Spontaneous bleed is defined as a bleeding episode that occurs without apparent cause and is not the result of trauma.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Antihemophilic factor – recombinant (Advate, Adynovate, Afstyla, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha)	Control and prevention of bleeding episodes	Minor episodes: 10-20 IU/kg IV every 12-24 hours (Advate: 8-24 hours for age < 6 years) Moderate episodes: 15-30 IU/kg IV every 12-24 hours (Advate: 8-24 hours for age < 6 years)	50 IU/kg every 6 hours until the bleeding episode is resolved

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Major episodes: 30-50 IU/kg IV every 8-24 hours (Advate: 6-12 hours for age < 6 years)	
Antihemophilic factor – recombinant (Eloctate)	Control and prevention of bleeding episodes	Minor and moderate episodes: 20-30 IU/kg every 24-48 hours (12-24 hours for age < 6 years) Major episodes: 40-50 IU/kg every 12-24 hours (8 to 24 hours for age < 6 years)	50 IU/kg every 8 hours until the bleeding episode is resolved
Antihemophilic factor – recombinant, glycopegylated (Esperoct)	Control and prevention of bleeding episodes	Minor to moderate episodes: 40-65 IU/kg IV; one dose should be sufficient for minor episodes; additional dose may be administered after 24 hours for moderate episodes. Major episodes: 50-65 IU/kg IV; additional doses may be administered approximately every 24 hours.	At least 12 years old: 40 IU/kg < 12 years old: 65 IU/kg
Antihemophilic factor – recombinant (Helixate FS, Kogenate FS)	Control and prevention of bleeding episodes	Minor episodes: 10-20 IU/kg IV; repeat dose if there is evidence of further bleeding Moderate episodes: 15-30 IU/kg IV every 12-24 hours Major episodes: initial 40-50 IU/kg IV followed by 20-25 IU/kg IV every 8-24 hours (Kogenate FS: every 8-12 hours)	50 IU/kg single dose or 30 IU/kg/repeated dose
Antihemophilic factor – recombinant (Advate, Adynovate)	Perioperative management	Minor surgery: 30-50 IU/kg IV as a single dose within 1 hour of the operation and every 12-24 hours (Adynovate: 24 hours) thereafter as needed to control bleeding Major surgery: 40-60 IU/kg IV as a single dose preoperatively to achieve 100% activity and every 8-24 hours thereafter to keep factor VIII activity in desired range (Advate: every 6-24 hours for age < 6 years; Adynovate: every 6-24 hours if age < 12 years)	Minor surgery: 50 IU/kg/dose Major surgery: 60 IU/kg/dose
Antihemophilic factor – recombinant (Eloctate)	Perioperative management	Minor surgery: 25-40 IU/kg every 24 hours (12-24 hours age < 6 years) Major surgery: pre-operative dose of 40-60 IU/kg followed by a repeat dose of 40-50 IU/kg after 8-24 hours (6-24 hours for age < 6 years) and then every 24 hours to	Minor surgery: 40 IU/kg/dose Major surgery: 60 IU/kg/dose

Drug Name	Indication	Dosing Regimen	Maximum Dose
		maintain Factor VIII activity within the target range	
Antihemophilic factor – recombinant, glycopegylated (Esperoct)	Perioperative management	Minor and major surgery: 50-65 IU/kg IV; additional doses can be administered after 24 hours if necessary for minor surgeries; additional doses can be administered approximately every 24 hours for the first week and then approximately every 48 hours until wound healing has occurred for major surgeries	At least 12 years old: 50 IU/kg < 12 years old: 65 IU/kg
Antihemophilic factor – recombinant (Helixate FS, Kogenate FS)	Perioperative management	Minor surgery: 15-30 IU/kg IV every 12-24 hours Major surgery: pre-operative dose of 50 IU/kg followed by a repeat dose every 6-12 hours to maintain Factor VIII activity within the target range	Minor surgery: 30 IU/kg/dose Major surgery: 50 IU/kg/dose
Antihemophilic factor – recombinant (Afstyla, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha)	Perioperative management	Minor surgery: 15-30 IU/kg IV every 24 hours (Xyntha: every 12-24 hours) (Recombinate: 30-40 IU/kg as a single infusion) Major surgery: 40-50 IU/kg IV every 8-24 hours (Xyntha: 30-50 IU/kg)	Minor surgery: 30 IU/kg/dose (Recombinate: 40 IU/kg/dose) Major surgery: 50 IU/kg every 8 hours
Antihemophilic factor – recombinant (Xyntha)	Routine prophylaxis	30 IU/kg IV 3 times weekly < 12 years of age: 25 IU/kg every other day.	30 IU/kg/dose
Antihemophilic factor – recombinant (Advate)	Routine prophylaxis	20-40 IU/kg IV every other day (3 to 4 times weekly) OR Use every third day dosing regimen targeted to maintain Factor VIII trough levels ≥ 1%	40 IU/kg every other day
Antihemophilic factor – recombinant (Adynovate)	Routine prophylaxis	≥ 12 years of age: 40-50 IU/kg IV 2 times per week < 12 years of age: 55 IU/kg IV 2 times per week	70 IU/kg/dose
Antihemophilic factor – recombinant (Afstyla)	Routine prophylaxis	≥ 12 years of age: 20-50 IU/kg IV 2-3 times per week < 12 years of age: 30-50 IU/kg IV 2-3 times per week	50 IU/kg/dose
Antihemophilic factor – recombinant (Eloctate)	Routine prophylaxis	50 IU/kg IV every 4 days For children < 6 years of age: 50 IU/kg IV twice weekly	65 IU/kg/dose

Drug Name	Indication	Dosing Regimen	Maximum Dose
Antihemophilic factor – recombinant, glycopegylated (Esperoct)	Routine prophylaxis	At least 12 years old: 50 IU/kg IV every 4 days < 12 years old: 65 IU/kg IV twice weekly	At least 12 years old: 50 IU/kg < 12 years old: 65 IU/kg
Antihemophilic factor – recombinant (Helixate FS, Kogenate FS)	Routine prophylaxis	Adults: 25 IU/kg IV three times per week Children: 25 IU/kg every other day	25 IU/kg/dose
Antihemophilic factor – recombinant (Novoeight)	Routine prophylaxis	≥ 12 years of age: 20-50 IU/kg IV 3 times per week OR 20-40 IU/kg IV every other day < 12 years of age: 25-60 IU/kg IV 3 times per week OR 25-50 IU every other day	60 IU/kg/dose
Antihemophilic factor – recombinant (Nuwiq)	Routine prophylaxis	≥ 12 years of age: 30-40 IU/kg IV every other day < 12 years of age: 30-50 IU/kg IV every other day or 3 times/week	50 IU/kg/dose
Antihemophilic factor – recombinant (Kovaltry)	Routine prophylaxis	> 12 years of age: 20-40 IU/kg IV 2-3 times per week ≤ 12 years of age: 25-50 IU/kg twice or three times weekly or every other day according to individual requirements	50 IU/kg every other day
Antihemophilic factor – recombinant, porcine sequence (Obizur)	Treatment of bleeding episodes in acquired hemophilia A	200 IU/kg every 4-12 hours	200 IU every 4 hours
Antihemophilic factor – human (Hemofil M)	Control and prevention of bleeding episodes	Minor episodes: 10-20 IU/kg IV every 12-24 hours Moderate episodes: 15-30 IU/kg IV every 12-24 hours Major episodes: 30-50 IU/kg IV every 8-24 hours	100 IU/kg every 8 hours
Antihemophilic factor – human (Koate-DVI)	Control and prevention of bleeding episodes	Minor episodes: 10 IU/kg IV as a single dose; repeat only if there is evidence of further bleeding Moderate episodes: 15-25 IU/kg IV as a single dose followed by 10-15 IU/kg every 8-12 hours if needed Major episodes: 40-50 IU/kg IV as a single dose followed by 20-25 IU/kg IV every 8-12 hours	25 IU/kg every 8 hours until the bleeding episode is resolved
Antihemophilic factor – human (Hemofil M)	Perioperative management	Minor surgery: 30-40 IU/kg as a single infusion	Minor surgery: 80 IU/kg/dose

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Major surgery: 40-50 IU/kg every 8-24 hours	Major surgery: 100 IU/kg every 8 hours
Antihemophilic factor – human (Koate-DVI)	Perioperative management	Major surgery: 50 IU/kg pre-operative dose followed by 50 IU/kg every 6-12 hours as needed Minor surgery: less intensive schedules may be adequate	Major surgery: 50 IU/kg every 6 hours
Antihemophilic factor – recombinant, PEGylated-aucl (Jivi)	Control and prevention of bleeding episodes	Minor episodes: 10-20 IU/kg every 24-48 hours Moderate episodes: 15-30 IU/kg every 24-48 hours Major episodes: 30-50 IU/kg every 8-24 hours	50 IU/kg every 8 hours
	Perioperative management	Minor surgery: 15-30 IU/kg every 24 hours Major surgery: 40-50 IU/kg every 12-24 hours	Minor surgery: 30 IU/kg/dose Major surgery: 50 IU/kg/dose
	Routine prophylaxis	30-40 IU/kg twice weekly; may be adjusted to 45-60 IU/kg every 5 days with further individual adjustment to less or more frequent dosing	60 IU/kg/dose; frequency varies based on bleeding episodes

VI. Product Availability

Drug Name	Availability
Antihemophilic factor – recombinant (Advate)	Vial: 250, 500, 1,000, 1,500, 2,000, 3,000, 4,000 IU
Antihemophilic factor – recombinant (Adynovate)	Vial: 250, 500, 750, 1,000, 1,500, 2,000, 3,000 IU
Antihemophilic factor – recombinant (Afstyla)	Vial: 250, 500, 1,000, 1,500, 2,000, 2,500, 3,000 IU
Antihemophilic factor – recombinant (Eloctate)	Vial: 250, 500, 750, 1,000, 1,500, 2,000, 3,000 4,000, 5,000, 6,000 IU
Antihemophilic factor – recombinant, glycopegylated-exei (Esperoct)	Vial: 500, 1,000, 1,500, 2,000, 3,000 IU
Antihemophilic factor – recombinant (Helixate FS, Kogenate FS, Kovaltry)	Vial: 250, 500, 1,000, 2,000, 3,000 IU
Antihemophilic factor – recombinant (Novoeight)	Vial: 250, 500, 1,000, 1,500, 2,000, 3,000 IU
Antihemophilic factor – recombinant (Nuwiq)	Vial: 250, 500, 1,000, 2,000, 2,500, 3,000, 4,000 IU
Antihemophilic factor – recombinant (Recombinate)	Vial: 220-400, 401-800, 801-1240, 1241-1800, 1801-2400 IU
Antihemophilic factor – recombinant (Xyntha)	Vial: 250, 500, 1,000, 2,000 IU
Antihemophilic factor – recombinant (Xyntha Solofuse)	Prefilled syringe: 250, 500, 1,000, 2,000, 3,000 IU
Antihemophilic factor – recombinant (Obizur)	Vial: 500 IU

Drug Name	Availability
Antihemophilic factor – human (Hemofil M)	Vial: 250, 500, 1,000, 1,700 IU
Antihemophilic factor – human (Koate-DVI)	Vial: 250, 500, 1,000 IU
Antihemophilic factor – recombinant, PEGylated-aucl (Jivi)	Vial: 500, 1,000, 2,000, 3,000 IU

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.16	01.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q17 Annual Review Converted to new template. Updated FDA-approved indications based on package labeling for individual products. Removed age restriction from Adynovate as package labeling supports use in children < 12 years of age.	10.09.17	11.17
1Q18 annual review: - Added Afstyla to the policy under the same coverage guidelines as the other recombinant factor VIII products. - Removed age limit from Obizur based on specialist feedback gained during previous revision of the Medicaid policy. - Removed "short-term" from ReFacto. - Added requirement for positive response to therapy.	11.27.17	02.18
1Q 2019 annual review: added Jivi; removed Monoclate-P since it is no longer available on market; removed requirement for failure of Advate for Xyntha requests per formulary status (both NF); allowed use of Kovaltry for routine prophylaxis per FDA indication; added requirement for failure of 2 preferred products for non-preferred products; clarified that disease must be congenital for all products except Obizur; moved criterion that member does not have VWD to Section III Diagnoses/Indications Not Covered; decreased continued approval duration for prophylaxis from 12 to 6 months to align with other blood factor policies; references reviewed and updated.	10.29.18	02.19
1Q 2020 annual review: no significant changes; added Esperoct as an RT4 policy update; references reviewed and updated.	11.27.19	02.20
Added 1 month approval duration for use post-valoctocogene gene therapy administration in hemophilia A.	04.17.20	05.20
Added routine prophylaxis-specific requirement for severe hemophilia classification or at least one life-threatening or serious spontaneous bleed for classification of non-severe hemophilia; added requirement for prescriber attestation of not partaking in contact sports.	05.27.20	08.20
RT4: Added newly FDA-approved indication for Xyntha - routine prophylaxis of bleeding episodes.	08.31.20	
Removed requirement for prescriber attestation of not partaking in contact sports.	10.01.20	11.20
1Q 2021 annual review: added requirement for documentation of member's body weight for calculation of appropriate dosage; removed ReFacto from the policy as it is no longer available; removed references to valoctocogene roxaparvovec as it did not receive FDA approval and likely will not face FDA review again until at least late 2022; references reviewed and updated.	12.01.20	02.21
Added a requirement for high utilizers of factor VIII products for routine prophylaxis to use Hemlibra.	10.12.21	11.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional

medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.