Clinical Policy: Factor IX (Human - AlphaNine SD, Mononine; Recombinant - Alprolix, BeneFIX, Idelvion, Ixinity, Rebinyn, Rixubis)

Reference Number: ERX.SPA.187
Effective Date: 01.11.17
Last Review Date: 02.21 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 IX products requiring prior authorization: human – AlphaNine SD®, Mononine®; recombinant – Alprolix®, BeneFIX®, Idelvion®, Ixinity®, Rebinyn®, and Rixubis®.

FDA Approved Indication(s)
Factor IX products are indicated for patients with hemophilia B (congenital factor IX deficiency or Christmas disease) for the following uses:

- Prevention and control of bleeding (on-demand treatment)
  - Adults and children: AlphaNine SD (≥ 17 years), Alprolix, BeneFIX, Idelvion, Ixinity (≥ 12 years), Mononine, Rebinyn, and Rixubis
- Perioperative management of bleeding
  - Adults and children: Alprolix, BeneFIX, Idelvion, Ixinity (≥ 12 years), Rebinyn, and Rixubis
- Routine prophylaxis to reduce the frequency of bleeding episodes
  - Adults and children: Alprolix, Benefix (≥ 16 years), Idelvion, Ixinity (≥ 18 years), and Rixubis

Limitation(s) of use:

- AlphaNine SD and Mononine contain low, non-therapeutic levels of factors II, VII, and X, and, therefore, are not indicated for the treatment of factor II, VII or X deficiencies. They are also not indicated for the reversal of coumarin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to factor VIII.
  Mononine is also not indicated in a hemorrhagic state caused by hepatitis-induced lack of production of liver dependent coagulation factors.
- Alprolix, Benefix, Idelvion, Ixinity, Rebinyn, and Rixubis are not indicated for induction of immune tolerance in patients with hemophilia B.
- Rebinyn is not indicated for routine prophylaxis in the treatment of patients with hemophilia B.

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 AlphaNine SD, Mononine, Alprolix, BeneFIX, Idelvion, Ixinity, Rebinyn, and Rixubis are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of congenital hemophilia B (factor IX deficiency);
2. Prescribed by or in consultation with a hematologist;
3. For AlphaNine requests only: age ≥ 17 years;
4. For Benefix requests only: age ≥ 16 years if request is for routine prophylaxis;
5. For Ixinity requests only: age ≥ 18 years if request is for routine prophylaxis or ≥ 12 years for non-routine prophylaxis indications;

6. Request is for one of the following uses (a, b, or c):
   a. Control and prevention of bleeding episodes;
   b. Perioperative management;
   c. Routine prophylaxis to reduce the frequency of bleeding episodes;
7. For routine prophylaxis requests: Request is for Alprolix, Benefix, Idelvion, Ixinity, or Rixubis, and member meets one of the following (a or b):
   a. Member has severe hemophilia (defined as factor level of < 1%);
   b. Member has experienced at least one life-threatening or serious spontaneous bleed (*see Appendix D*);
8. Documentation of member's current body weight (in kg);
9. 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. Congenital Hemophilia B (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. Member is responding positively to therapy;
3. Documentation of member's current body weight (in kg);
4. 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.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - All products except AlphaNine SD: known history of hypersensitivity reactions, including anaphylaxis, to the product or its excipients*
    **Including mouse or hamster protein for BeneFix, Idelvion, Ixinity, Mononine, Rebinyn, and Rixubis*
  - Rixubis: disseminated intravascular coagulation, signs of fibrinolysis
- 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
Factor IX, human (AlphaNine SD)	Control and prevention of bleeding episodes	Minor episodes: 20-30 IU/kg IV twice daily Moderate episodes: 25-50 IU/kg IV twice daily Major episodes: 30-50 IU/kg IV twice daily for at least 3-5 days, followed by 20 IU/kg IV twice daily Surgery: 50-100 IU/kg IV twice daily before surgery, followed by the same regimen for 7-10 days thereafter	Bleeding episodes: 100 IU/kg/day Surgery: 200 IU/kg/day
Factor IX, human (Mononine)	Control and prevention of bleeding episodes	Minor episodes: 20-30 IU/kg IV every 24 hours Major trauma or surgery: 75 IU/kg IV every 18-30 hours	Minor episodes: 30 IU/kg/day Major trauma or surgery: 750 IU/kg/18 hours
Factor IX, recombinant (Alprolix)	Control and prevention of bleeding episodes, perioperative management	Minor and moderate episodes: 30-60 IU/dL/kg IV every 48 hours if there is further evidence of bleeding after the first dose Major episodes: 80-100 IU/dL/kg IV initially; consider a repeat dose after 6-10 hours and then every 24 hours for the first 3 days. May extend to dosing every 48 hours or longer after the first 3 days Minor surgery: 50-80 IU/dL/kg IV initially followed by every 24-48 hours until bleeding stops and healing is achieved Major surgery: 60-80 IU/dL/kg IV initially; consider a repeat dose after 6-10 hours and then every 24 hours for the first 3 days. May extend to dosing every 48 hours or longer after the first 3 days	Bleeding episodes: 100 IU/dL/kg/dose Surgery: 80 IU/dL/kg/dose
	Routine prophylaxis	50 IU/dL/kg IV once weekly or 100 IU/dL/kg IV once every 10 days (start with 60 IU/kg once weekly for < 12 years)	100 IU/dL/kg/dose
Factor IX, recombinant (BeneFIX)	Control and prevention of bleeding	Minor episodes: 20-30 IU/dL/kg IV every 12-24 hours	200 IU/dL/kg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
	episodes, perioperative management	Moderate episodes: 25-50 IU/dL/kg IV every 12-24 hours Major episodes: 50-100 IU/dL/kg IV every 12-24 hours Surgery: 50-100 IU/dL/kg IV every 12-24 hours	
	Routine prophylaxis	100 IU/kg once weekly	100 IU/kg/dose
Factor IX, recombinant (Idelvion)	Control and prevention of bleeding episodes, perioperative management	Minor and moderate episodes: 30-60 IU/dL/kg IV every 48-72 hours Major episodes: 60-100 IU/dL/kg IV every 48-72 hours until bleeding stops and healing is achieved; maintenance dose is weekly Minor surgery: 50-80 IU/dL/kg IV every 48-72 hours until healing is achieved Major surgery: 60-100 IU/dL/kg IV every 48-72 hours until bleeding stops and healing is achieved; maintenance dose is 1-2 times per week	Bleeding episodes: 100 IU/dL/kg/48 hours Surgery: 80 IU/dL/kg/48 hours
	Routine prophylaxis	≥ 12 years of age: 25-40 IU/kg IV every 7 days followed by 50-75 IU/kg IV every 14 days once well-controlled < 12 years of age: 40-55 IU/kg IV every 7 days	55 IU/dL/kg/week
Factor IX, recombinant (Ixinity)	Control and prevention of bleeding episodes, perioperative management	Minor episodes: 30-60 IU/dL/kg IV every 24 hours Moderate episodes: 40-60 IU/dL/kg IV every 24 hours Major episodes: 60-100 IU/dL/kg IV every 12-24 hours Minor surgery: 50-80 IU/dL/kg IV pre-operatively followed by 30-80 IU/dL/kg every 24 hours Major surgery: 60-80 IU/dL/kg IV pre-operatively followed by 40-60 IU/dL/kg IV every 8-24 hours for 1-3 days or 30-50 IU/dL/kg IV every 8-24 hours for 4-6 days or 20-40 IU/dL/kg IV every 8-24 hours for 7-14 days	Bleeding episodes: 102 IU/dL/kg/dose Surgery: 81.6 IU/dL/kg/dose
	Routine prophylaxis	40 to 70 IU/kg IV twice weekly	140 IU/kg/week
Factor IX, recombinant (Rixubis)	Control and prevention of bleeding	Minor episodes: 20-30 IU/dL/kg IV every 12-24 hours until healing is achieved	100 IU/dL/kg/dose

Drug Name	Indication	Dosing Regimen	Maximum Dose
	episodes, perioperative management	Moderate episodes: 25-50 IU/dL/kg IV every 12-24 hours until bleeding stops and healing is achieved Major episodes: 50-100 IU/dL/kg IV every 12-24 hours until bleeding stops and healing is achieved Minor surgery: 30-60 IU/dL/kg IV every 24 hours until healing is achieved Major surgery: 80-100 IU/dL/kg IV every 8-24 hours until bleeding stops and healing is achieved	
	Routine prophylaxis	≥ 12 years of age: 40-60 IU/kg IV twice weekly < 12 years of age: 60-80 IU/kg IV twice weekly	80 IU/kg/dose
Factor IX, recombinant, glycopegylated (Rebinyn)	On-demand treatment and control of bleeding episodes	40 IU/kg body weight for minor and moderate bleeds, and 80 IU/kg body weight for major bleeds. Additional doses of 40 IU/kg can be given	80 IU/kg/dose
	Perioperative management of bleeding	Pre-operative dose of 40 IU/kg body weight for minor surgery, and 80 IU/kg body weight for major surgery. As clinically needed for the perioperative management of bleeding, repeated doses of 40 IU/kg (in 1-3 day intervals) within the first week after major surgery may be administered. Frequency may be extended to once weekly after the first week until bleeding stops and healing is achieved.	80 IU/kg pre-operatively; 40 IU/kg/dose after surgery

VI. Product Availability

Drug Name	Availability
Factor IX, human (AlphaNine SD)	Vial: 500, 1,000, 1,500 IU
Factor IX, human (Mononine)	Vial: 500, 1,000 IU
Factor IX, recombinant (Alprolix)	Vial: 250, 500, 1,000, 2,000, 3,000, 4,000 IU
Factor IX, recombinant (BeneFIX)	Vial: 250, 500, 1,000, 2,000, 3,000 IU
Factor IX, recombinant (Idelvion)	Vial: 250, 500, 1,000, 2,000, 3,500 IU
Factor IX, recombinant (Ixinity)	Vial: 250, 500, 1,000, 1,500, 2,000, 3,000 IU
Factor IX, recombinant (Rixubis)	Vial: 250, 500, 1,000, 2,000, 3,000 IU
Factor IX, recombinant, glycopegylated (Rebinyn)	Vial: 500, 1,000, 2,000 IU

VII. References

1. Alphanine SD Prescribing Information. Los Angeles, CA: Grifols Biologicals, Inc.; June 2018. Available at: www.alphaninesd.com. Accessed November 30, 2020.
2. Alprolix Prescribing Information. Cambridge, MA: Biogen Idec, Inc.; August 2020. Available at: www.alprolix.com. Accessed November 30, 2020.
3. BeneFix Prescribing Information. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; April 2021. Available at: www.benefix.com. Accessed May 12, 2021.

4. Idelvion Prescribing Information. Kankakee, IL: CSL Behring LLC; July 2020. Available at: www.idelvion.com. Accessed November 30, 2020.
5. Ixinity Prescribing Information. Berwyn, PA: Aptevo BioTherapeutics LLC; February 2021. Available at: www.ixinity.com. Accessed May 12, 2021.
6. Mononine Prescribing Information. Kankakee, IL: ZLB Behring, LLC; December 2018. Available at: www. http://labeling.cslbehring.com/PI/US/Mononine/EN/Mononine-Prescribing-Information.pdf. Accessed November 30, 2020.
7. Rebinyn Prescribing Information. Plainsboro, NJ: Novo Nordisk; June 2020. Available at: www.rebinyn.com. Accessed November 30, 2020.
8. Rixubis Prescribing Information. Westlake Village, CA: Baxalta US Inc.; June 2020. Available at: http://www.rixubis.com. Accessed November 30, 2020.
9. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. Jan 2013; 19(1): e1-47.
10. Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF): Database of treatment guidelines. Available at https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed November 30, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.01.16	01.17
4Q17 Annual Review - Converted to new template. - Added age limits for AlphaNine and Ixinity only, per their respective PIs.	10.11.17	11.17
1Q18 annual review: Added efficacy statement to renewal criteria.	11.28.17	02.18
No significant changes: added Rebinyn (new dosage form).	03.19.18	
1Q 2019 annual review: no significant changes; clarified that disease must be congenital; references reviewed and updated.	11.08.18	02.19
RT4: added new strength of Idelvion 3,500 IU.	06.21.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.27.19	02.20
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; RT4: updated Benefix indication of routine prophylaxis.	07.21.20	08.20
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 body weight, for calculation of appropriate dosage; RT4: added newly approved indication for Ixinity for routine prophylaxis; references reviewed and updated.	11.30.20	02.21
RT4: revised routine prophylaxis indications for Benefix and Ixinity to limit use to patients aged 16 and older or 18 and older, respectively, in accordance with FDA removal of use for younger patients from the Benefix and Ixinity labels.	05.12.21	

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.