Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO028

Description

Alprolix, Idelvion, and Rebinyn are extended half-life factor IX products for the treatment and prevention of bleeding in patients with hemophilia B.

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‡
Alprolix, coagulation factor IX (recombinant, Fc fusion protein	250, 500, 1000, 2000, 3000, 4000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL for the first dose, then again every 6 to 10 hours for another dose. Dosing is then every 24 hours for three days, then every 48 hours until healing is achieved **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg once weekly or 100 IU/kg once every ten days • <12 years: Up to 60 IU/kg once weekly. More frequent or higher doses may be required **Perioperative Management**δ**:** • *Minor surgery*: Up to 80 IU/dL as a single infusion, then every 24 to 48 hours if needed until bleeding stops • *Major surgery*: Up to 100 IU/dL as the initial dose, then repeat dose after 6 to 10 hours and then every 24 hours for the first three days. After day three, the dosing may be extended to	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 315 IU/kg every 28 days • <12 years: Up to 255 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‡
		every 48 hours until healing is achieved	
Idelvion, coagulation factor IX (recombinant, albumin fusion protein	250, 500, 1000, 2000, 3500 IU	**On-demand Treatment*:** Up to 100 IU/dL every 48-72 hours for seven to 14 days until bleeding stops **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg once weekly. Patients who are well controlled may be changed to 50-75 IU/kg every 14 days • <12 years: Up to 55 IU/kg every seven days **Perioperative Management*:** • *Minor*: Up to 80 IU/dL every 48 to 72 hours for at least one day until healing is achieved • *Major*: Up to 100 IU/dL every 48 to 72 hours for 7 to 14 days, or until bleeding stops and healing is achieved	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 170 IU/kg every 28 days • <12 years: Up to 230 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Rebinyn, coagulation factor IX (recombinant, GlycoPEGylated	500, 1000, 2000, 3000 IU	**On-demand Treatment:** Up to 80 IU/kg for the initial dose. Additional doses of 40 IU/kg can be given. **Routine Prophylaxis:** • 40 IU/kg once weekly **Perioperative Management:** • *Minor*: Preoperative dose of up to 40 IU/kg. Additional doses can be given if needed. • *Major*: Preoperative dose of up to 80 IU/kg. Repeated doses of 40 IU/kg (in one to three day intervals) within the first week after surgery may be administered.	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** Up to 170 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

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

δ One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Estimate the required dose or the expected in vivo peak increase in Factor IX level expressed as IU/dL (or % of normal) using the following: IU/dL (or % of normal) = [Total dose (IU)/Body Weight (kg)] x Recovery (IU/dL per IU/kg)

* One IU of Idelvion per kg body weight is expected to increase the circulating activity of factor IX as follows: adolescents and adults: 1.3 IU/dL per IU/kg; pediatrics (<12 years): 1 IU/dL per IU/kg. Determine the initial dose using the following: Required dose (IU) = body weight (kg) x desired factor IX rise (%of normal or IU/dL) x (reciprocal of recovery (IU/kg per IU/dL))

Initial Evaluation

I. Extended half-life factor IX products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia B (congenital factor IX deficiency)** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of extended half-life factor IX is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor IX 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 B (defined as factor IX level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. Prior treatment with a standard half-life factor IX product administered at the FDA approved dose for at least 50 exposure days was ineffective for the treatment or prevention of bleeding episodes; **OR**
      4. There is clinical documentation that all available standard half-life factor IX products are inappropriate; **AND**
      5. 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**
      6. Dose and frequency do 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. Extended half-life factor IX 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 B (factor IX 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 B.
II. There are varying severities of hemophilia B depending on the level of factor produced by the patient. Hemophilia B 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 B:
   - 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 B 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 IX products are the treatment of choice for hemophilia B 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 B. Therapy should be initiated early with the goal of keeping the trough factor IX 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 extended half-life products were established based on open-label, non-randomized trails. Alprolix and Idelvion demonstrated effectiveness in reducing annualized bleeding rates when used prophylactically compared to on-demand treatment.

VI. Rebinyn has been shown to stop or prevent bleeding in on-demand, perioperative settings, and prophylaxis. Prophylaxis use was approved based on two, phase 3 studies. Paradigm 2 was a multinational, randomized, single-blind trial using 2 prophylaxis groups (10 and 40 IU/kg once weekly) and a single on-demand group. Patients chose either prophylaxis or on-demand treatment and patients choosing prophylaxis were randomized 1:1 to either 10 or 40 IU/kg once weekly. The primary efficacy endpoint was hemostatic effect when treating a bleeding episode (patient reported) and assessing prophylactic effect via annualized bleeding rates (ABRs). The primary safety efficacy was development of FIX inhibitors. A total of 74 patients were enrolled with 67 completing the study. None of the withdrawal patients were due to adverse effects. No patients developed inhibitors. The median ABR was 2.93 and 1.04 for the 10 IU/kg and 40 IU/kg groups, respectively.

VII. Paradigm 4 was an open-label, non-randomized, multi-center extension trial. In addition to the 3 previous treatment arms, a fourth was added as 80 IU/kg every 2 weeks. Patients were able to change treatment arms based on clinical changes to disease. Length of treatment was equivalent to at least 50 exposure days. Primary endpoint was evaluation of factor inhibitors and secondary endpoint of treatment efficacy and prophylaxis. A total of 71 patients completed the extension, no patients developed inhibitors and no safety concerns were raised. There was 94.6% success rate in treated bleeds. Median ABR was similar for the 40 IU/kg group across paradigm 2 and paradigm 4 with little difference in ABR between the 10 IU/kg and 40 IU/kg group.

VIII. Extended half-life factor IX products were developed to extend the half-life and allow for longer infusion intervals. The majority of published clinical trial evidence evaluating extended half-life products have included previously treated patients with a minimum of 50 exposure days and no history of inhibitors.

IX. There is no evidence that extended half-life factor replacement products are safer or more effective than standard half-life products. There are no head-to-head trials comparing extended half-life products and standard half-life products to definitively establish superior safety or efficacy.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of extended half-life factor IX products in any other condition.

References

1. Alprolix® [Prescribing Information]. Waltham, MA: Bioverativ; July 2019
2. Idelvion® [Prescribing Information]. Kankakee, IL: CSL Behring; May 2018
3. Rebinyn® [Prescribing Information]. Plainsboro, NJ: Novo Nordisk; August 2022
4. Collins PW, Young G, Knobe K, et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial (paradigm 2). Blood. 2014; 124(26):3880-6. doi:10.1182/blood-2014-05-573055.
5. Young G, Collins PW, Colberg T, et al.Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase III safety and efficacy extension trial (paradigm 4). Thromb Res. 2016; 141:69-76. doi:10.1016/j.thromres.2016.02.030.
6. National Hemophilia Foundation. Hemophilia B. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-B. Accessed July 8, 2019.
7. 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.
8. 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
Updated policy and supportive evidence of Rebinyn for use in routine prophylaxis	06/2023
New policy created for extended half-life factor products	08/2019