FREQUENTLY ASKED QUESTIONS

Indications and Usage

Rebinyn®, Coagulation Factor IX (Recombinant), GlycoPEGylated, is a recombinant DNA derived coagulation Factor IX concentrate indicated for use in adults and children with hemophilia B (congenital Factor IX deficiency) for on demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes.

Limitations of Use: Rebinyn® is not indicated for immune tolerance induction in patients with hemophilia B.

Important Safety Information

Contraindications

- Rebinyn® is contraindicated in patients with a known hypersensitivity to Rebinyn® or its components, including hamster proteins.

Frequently Asked Questions

Q. What is the difference between hemophilia A and hemophilia B?

A. There are 2 main subtypes of hemophilia: hemophilia A, which is a deficiency of coagulation Factor VIII, and hemophilia B, which is a deficiency of coagulation Factor IX.[1] In both cases, bleeding is prolonged due to inability to make a strong blood clot.[1] The principal differences between hemophilia A and B are as follows[1]:

1. Hemophilia A is more common than B with an incidence of 1 in 5000 vs 1 in 30,000 male births. There are ~22,000 patients with hemophilia A in the United States vs ~7000 with hemophilia B.[1,2]
2. According to the Centers for Disease Control and Prevention (CDC), hemophilia A has a greater percentage of patients with severe deficiency or less than 1% Factor VIII activity. Hemophilia B has more patients that have only mild-moderate deficiency of Factor IX.[1,2]
3. Newly treated children with hemophilia A tend to have a higher risk of developing antibodies to their factor replacement called inhibitors; the risk is much lower in hemophilia B.[3]

Q. What is Rebinyn®?

A. Rebinyn®, Coagulation Factor IX (Recombinant), GlycoPEGylated, is a recombinant DNA derived coagulation Factor IX concentrate indicated for use in adults and children with hemophilia B (congenital Factor IX deficiency) for on demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes.[4]

Limitations of Use: Rebinyn® is not indicated for immune tolerance induction in patients with hemophilia B.

Q. How is Rebinyn® obtained?

A. Rebinyn® can be accessed and acquired through specialty distributors, hemophilia home care agencies, and hemophilia treatment center 340B programs.

Important Safety Information (cont'd)

Warnings and Precautions

- **Hypersensitivity Reactions:** Allergic-type hypersensitivity reactions, including anaphylaxis, have occurred with Rebinyn®. Signs may include angioedema, chest tightness, difficulty breathing, wheezing, urticaria, and itching. Discontinue Rebinyn® if allergic- or anaphylactic-type reactions occur and initiate appropriate treatment.

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Q. What is the mechanism of action of Rebinyn®?

A. Rebinyn® works by temporarily replacing the missing coagulation Factor IX protein that is needed for effective hemostasis. The Factor IX in Rebinyn® is conjugated to a 40-kDa polyethylene glycol (PEG) molecule, which slows down its removal from the blood circulation.[4]

Q. Does Rebinyn® contain any animal or human components?

A. No additives of human or animal origin are used in the cell culture, purification, conjugation, or formulation of Rebinyn®.[4]

Q. When did Rebinyn® receive FDA approval?

A. Rebinyn® was FDA approved on May 31, 2017.[5] The expanded indication to include routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia B was FDA approved on July 29, 2022.[6]

Q. How is Rebinyn® supplied?

A. Rebinyn® is supplied as white to off-white lyophilized powder in single-dose vials, one vial per carton. Rebinyn® is supplied in packages comprised of a single-dose vial, containing nominally 500, 1000, 2000, or 3000 IU of Factor IX potency; a MixPro® pre-filled diluent syringe containing 10 mM histidine solution (1.6 mg/mL), and a sterile vial adapter with 25 micrometer filter, which serves as a needleless reconstitution device. The actual Factor IX potency in international units (IU) is stated on each Rebinyn® carton and vial.[4]

Q. How is Rebinyn® administered?

A. Rebinyn® is administered by intravenous injection only. Each carton and vial label for Rebinyn® states the actual Factor IX potency in IU. Recommended dose for routine prophylaxis is 40 IU/kg body weight once weekly. Dosing regimen can be adjusted based on the individual patient's bleeding pattern and physical activity. Recommended dose for 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. Recommended dose for perioperative management: Preoperative dose of

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

- **Inhibitors:** The formation of inhibitors (neutralizing antibodies) to Factor IX has occurred following Rebinyn®. If expected plasma factor IX activity levels are not attained, or if bleeding is not controlled as expected with the administered dose, perform an assay that measures Factor IX inhibitor concentration. Monitor all patients using clinical observations and laboratory tests for the development of inhibitors. Factor IX activity assay results may vary with the type of activated partial thromboplastin time reagent used.

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How is Rebinyn® administered? (cont'd)

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- to 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.[4]

Q. Who can administer Rebinyn®?

A. Rebinyn® is administered by intravenous injection only.[4] Patients should be trained to infuse by their health care provider prior to self-infusing.

Q. What are the inactive ingredients in Rebinyn®?

A. Rebinyn® is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution with the provided histidine diluent for intravenous infusion. After reconstitution, the solution appears as a clear and colorless liquid, free from visible particles and contains the following excipients per mL: sodium chloride, 2.34 mg; histidine, 3.10 mg; sucrose, 10 mg; mannitol, 25 mg; polysorbate 80, 0.05 mg. Rebinyn® contains no preservatives.[4]

Q. What are the most frequently reported adverse reactions with Rebinyn®?

A. The most common adverse reactions for previously treated patients reported in clinical trials (incidence ≥1%) were itching and injection site reactions.[4]

The most common adverse reactions for previously untreated patients reported in clinical trials (incidence ≥1%) were rash, factor IX inhibitors, hypersensitivity, itching, injection site reaction, and anaphylactic reaction.[4]

The following adverse reactions have been identified during post-approval use of Rebinyn®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Blood and lymphatic system disorders: Factor IX inhibitor development.[4]

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

- **Thrombotic Events:** The use of Factor IX-containing products has been associated with thromboembolic complications. Monitor for thrombotic and consumptive coagulopathy when administering Rebinyn® to patients with liver disease, post-operatively, to newborn infants, or to patients at risk of thrombosis or disseminated intravascular coagulation (DIC).
- **Nephrotic Syndrome:** Nephrotic syndrome has been reported following immune tolerance induction therapy with Factor IX products in hemophilia B patients with Factor IX inhibitors, often with a history of allergic reactions to Factor IX. The safety and efficacy of using Rebinyn® for immune tolerance induction have not been established.

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Q. Who should not use Rebinyn®?

A. Rebinyn® is contraindicated in patients with a known hypersensitivity to Rebinyn® or its components, including hamster proteins.[4]

Q. Is the use of Rebinyn® associated with the development of inhibitors?

A. The formation of neutralizing antibodies (inhibitors) to Factor IX has occurred following Rebinyn®. If expected plasma Factor IX activity levels are not attained, or if bleeding is not controlled as expected with the administered dose, perform an assay that measures Factor IX inhibitor concentration. Monitor all patients using clinical observations and laboratory tests for the development of inhibitors.[4]

An association between the development of Factor IX inhibitors and allergic reactions has been reported. Evaluate patients experiencing allergic reactions for the presence of an inhibitor. Patients with Factor IX inhibitors may be at an increased risk of severe allergic reactions with subsequent exposure to Factor IX.[4]

Subjects treated with Rebinyn® were monitored for inhibitory antibodies to Factor IX prior to dosing, on a monthly basis for the first three months, every two months up to one year, every three months for an additional year, and then every 6 months until end of trial. No inhibitors were reported in the clinical trials in previously treated patients.[4]

The most common adverse reactions for previously untreated patients reported in clinical trials include Factor IX inhibitors. Of 50 previously untreated patients, 4 developed FIX inhibition (8%).

Allergic-type hypersensitivity reactions, including anaphylaxis, have occurred with Rebinyn®. Signs may include angioedema, chest tightness, difficulty breathing, wheezing, urticaria, and itching. Discontinue Rebinyn® if allergic- or anaphylactic-type reactions occur and initiate appropriate treatment. Inhibitor development and anaphylactic reactions are more likely to occur during the early phases of Factor IX replacement therapy.[4]

Important Safety Information (cont'd)

Adverse Reactions

- The most common adverse reactions reported in previously treated patients in clinical trials (≥1%) were itching and injection site reactions. The most common adverse reactions (≥1%) in previously untreated patients reported in clinical trials were rash, FIX inhibitors, hypersensitivity, itching, injection site reaction, and anaphylactic reaction.
- Animals administered Rebinyn® showed accumulation of PEG in the choroid plexus, pituitary, circumventricular organs, and cranial motor neurons. The potential clinical implications of these animal findings are unknown. Consider whether the patient is vulnerable to cognitive impairment, such as infants and children who have developing brains, and patients who are cognitively impaired.

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Q. What effect does PEGylation have on the safety of Rebinyn®?

A. In clinical trials, previously untreated and previously treated pediatric patients receiving routine prophylaxis with once-weekly Rebinyn® were followed for central nervous system-related ADRs for 6 and 8 years, respectively. Neurological examinations and neurocognitive assessments were prospectively performed in previously untreated and previously treated pediatric patients. Although no clear clinical implications of the animal findings are known and no clear clinical neurologic or neurocognitive safety signal has emerged, the physician should consider whether the patient is vulnerable to cognitive impairment, such as infants and children who have developing brains, and patients who are cognitively impaired. Factors such as duration of use, cumulative dose, age of the patient and co-morbidities that may increase risk of adverse neurologic and/or neurocognitive events should be considered when prescribing Rebinyn®. Report adverse neurocognitive and neurologic reactions.[4]

Animals administered repeat doses of Rebinyn® showed accumulation of PEG in the choroid plexus, pituitary, circumventricular organs, and cranial motor neurons. The potential clinical implications of these animal findings are unknown.[4]

Q. How should Rebinyn® be stored?

A. Store Rebinyn® in the original package in order to protect from light. Rebinyn® should be stored under refrigeration at a temperature of 36°F-46°F (2°C-8°C) for up to 24 months from the date of manufacture until the expiration date stated on the label.[4]

Rebinyn® may be stored at room temperature not to exceed 86°F (30°C) for up to 6 months within the 24-month time period. Record the date when the product was removed from the refrigerator in the space provided on the outer carton. The total time of storage at room temperature should not exceed 6 months. Do not return the product to the refrigerator.[4]

Do not use Rebinyn® after the end of the 6-month period at room temperature storage, or after the expiration date stated on the vial, whichever occurs earlier. Do not freeze Rebinyn®.[4]

Use Rebinyn® within 4 hours after reconstitution when stored at room temperature. Store the reconstituted product in the vial. Discard any unused reconstituted product stored at room temperature for more than 4 hours.[4]

Q. Who manufactures Rebinyn®?

A. Rebinyn® is manufactured by Novo Nordisk A/S. Rebinyn® is distributed by Novo Nordisk Inc.[4]

Q. Where can I get more information about Rebinyn®?

A. If you would like additional information about Rebinyn®, please visit **https://www.novomedlink.com/rare-bleeding-disorders/products/treatments/rebinyn.html**

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References: 1. Sharathkumar A, Pipe S. Congenital bleeding disorders. In: Schmaier AH, Lazarus HM, eds. *Concise Guide to Hematology.* Blackwell Publishing; 2011:112-130. **2.** The HTC population profile. Centers for Disease Control and Prevention. Accessed August 15, 2022. https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2022-03/table-2-factor.html **3.** 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. **4.** Rebinyn. Prescribing information. Novo Nordisk Inc.; 2022. **5.** US Food and Drug Administration. BLA approval letter for Rebinyn®. Updated May 31, 2017. Accessed August 10, 2022. https://www.fda.gov/media/105612/download **6.** Data on file. US Food and Drug Administration. BLA approval letter for Rebinyn®. Updated July 29, 2022. Novo Nordisk Inc.; Plainsboro, NJ.

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