PRODUCT INFORMATION FORM FOR HOSPITALS

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.

Please see additional Important Safety Information on page 14.

Please click here for Prescribing Information.

novo nordisk®

rebinyn®
Coagulation Factor IX (Recombinant), GlycoPEGylated

Product Information Form for Hospitals

1 AHFS CLASSIFICATION NUMBER

20:28.16.00: Blood Formation, Coagulation, and Thrombosis Agents: Antihemorrhagic Agents, Hemostatics

2 GENERIC NAME

Coagulation Factor IX (Recombinant), GlycoPEGylated

3 SOURCE OF SUPPLY

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

4 BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

BL 125611, May 31, 2017
BL 125611/223, July 29, 2022

5 PHYSICAL PROPERTIES

a. Macroscopic appearance

Rebinyn® is available as a white to off-white lyophilized powder in single-dose vials containing nominally 500, 1000, 2000, or 3000 international units (IU) per vial. Each carton and vial label for Rebinyn® states the actual Factor IX potency in IU.

After reconstitution with 4 mL of histidine diluent, the reconstituted solution contains approximately 125, 250, 500, or 750 IU per mL of Rebinyn®, respectively.

b. Solubility

Rebinyn® is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous infusion after reconstitution with the provided histidine diluent.

6 CHEMICAL PROPERTIES

a. Structural similarities to other available compounds or groups of compounds

Rebinyn® is a purified recombinant human Factor IX (rFIX) with a 40 kDa polyethylene glycol (PEG) conjugated to the protein. The 40 kDa PEG group is selectively attached to specific -N-linked glycans in the rFIX activation peptide, with mono-PEGylated rFIX as the predominant form of Rebinyn®. The rFIX protein in Rebinyn® consists of a gamma-carboxylated (Gla) domain, two EGF-like (epidermal growth factor) domains, an activation peptide (which is cleaved off upon activation), and a protease domain. Once Rebinyn® is activated, the resulting rFIX has structural and functional properties similar to those of endogenous activated Factor IX. The primary amino acid sequence in Rebinyn® is identical to the Thr148 allelic form of human plasma-derived Factor IX and consists of 415 amino acids. The average molecular weight of Rebinyn® is approximately 98 kDa and the molecular weight of the protein moiety alone is 56 kDa. The nominal specific activity of Rebinyn® is 152 IU/mg protein.

b. Recommended storage conditions for Rebinyn®

Store Rebinyn® in the original package in order to protect from light.

Store Rebinyn® 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.

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.

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®.

Use Rebinyn® within 4 hours after reconstitution when stored at room temperature. Store the reconstituted product in the vial.

Discard any unused reconstituted product.

c. Excipients contained in the commercially available product

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® is available in single-use vials containing the labeled amount of Factor IX activity, expressed in IU. Each vial contains nominally 500 IU, 1000 IU, 2000 IU, or 3000 IU.

Rebinyn® contains no preservatives.

7 PHARMACOLOGIC CLASSIFICATION

a. Pharmacologic class

Rebinyn® is a hemostatic.

b. Mechanism of action

Patients with hemophilia B are deficient in coagulation Factor IX, which is required for effective hemostasis. Treatment with Rebinyn® temporarily replaces the missing coagulation Factor IX.

The Factor IX in Rebinyn® is conjugated to a 40-kDa polyethylene glycol molecule, which slows down its removal from the blood circulation.

c. Pharmacokinetic data

Pharmacokinetic (PK) parameters of Rebinyn® were evaluated in previously treated subjects, including a subset of subjects in the adult/adolescent trial and all subjects in the main phase of the pediatric trial. PK samples were collected prior to dosing and at multiple time points up to 168 hours after dosing. The analysis of plasma samples was conducted using the one-stage clotting assay.

Steady-state PK parameters for adolescents and adults following once-weekly prophylactic treatment of Rebinyn® 40 IU/kg are shown in the following table.

Steady-state pharmacokinetic parameters of Rebinyn® (40 IU/kg) in adolescents and adults (geometric mean (CV))

PK Parameter	13-17 years N = 3	≥18 years N = 6
Half-life (hours)	103.1 (14.2)	114.9 (9.7)
Incremental Recovery$_{30min}$ (IU/dL per IU/kg)	1.82 (28.2)	1.92 (19.6)
AUC$_{0-168}$ (IU*hours/dL)	9072 (22)	9280 (15)
Clearance (mL/hour/kg)	0.4 (16.7)	0.4 (11.4)
Mean residence time (hours)	144.4 (15.3)	158.1 (9.6)
Vss (mL/kg)	60.5 (31.1)	65.8 (11.9)
Factor IX activity 168 h after dosing (%)	28.9 (18.6)	32.4 (17.1)

Abbreviations: AUC = area under plasma concentration-time curve; CV = coefficient of variation; Vss = volume of distribution at steady state.

7 PHARMACOLOGIC CLASSIFICATION (cont'd)

The mean steady-state pre-dose trough levels and post-dose peak levels across the clinical trials for all previously treated subjects are shown in the following table.

Factor IX peak and trough levels of Rebinyn® (40 IU/kg) by age at steady state

	≤6 years N = 12	7-12 years N = 13	13-17 years N = 9	≥18 years N = 20
Mean Factor IX peak level (%) (95% CI)	65.5 (60.6; 70.7)	71.4 (66.3; 77.0)	82.8 (70.7; 96.9)	97.9 (87.7; 109.3)
Mean Factor IX trough level* (%) (95% CI) Min, Max **	15.4 (13.2; 17.9) 9.2; 24.5	18.7 (16.2; 21.6) 8.3; 28.3	23.7 (19.9; 28.2) 18.6; 34.6	29.3 (26.0; 33.0) 21.3; 42.2

*Factor IX activity from samples collected at clinical site visits just prior to administration of next weekly dose

**Individual geometric mean trough values

Single-dose PK parameters of Rebinyn® in children, adolescents, and adults are listed in the following table.

Single-Dose pharmacokinetic parameters of Rebinyn® (40 IU/kg) in children, adolescents, and adults (geometric mean (CV))

PK parameter	≤6 years N = 12	7-12 years N = 13	13-17 years N = 3	≥18 years N = 6
Half-life (hours)	69.6 (15.8)	76.3 (25.5)	89.4 (24.1)	83.0 (22.5)
Incremental Recovery$_{30min}$ (IU/dL per IU/kg)	1.51 (7.31)	1.59 (16.2)	1.96 (14.7)	2.34 (11.3)
AUC$_{inf}$ (IU*h/dL)	4617 (14)	5618 (19)	7986 (35)	9063 (16)
Clearance (mL/hour/kg)	0.8 (13.0)	0.6 (21.9)	0.5 (30.4)	0.4 (14.7)
Mean residence time (hours)	95.4 (15.3)	105.1 (24.2)	124.2 (24.4)	115.5 (21.8)
Vss (mL/kg)	72.3 (14.8)	68.3 (21.7)	58.6 (7.8)	47.0 (15.9)
Factor IX activity 168 h after dosing (%)	8.4 (16.3)	10.9 (18.9)	14.6 (59.6)	16.8 (30.6)

Abbreviations: AUC = area under plasma concentration-time curve; Vss = volume of distribution at steady state; CV = coefficient of variation.

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7 PHARMACOLOGIC CLASSIFICATION (cont'd)

Pharmacokinetics were investigated in 9 subjects in the adult/adolescent trial, of which 5 were normal weight (body mass index [BMI] 18.5 to 24.9 kg/m^2) and 4 were overweight (BMI 25 to <29.9 kg/m^2). The PK parameters were not affected by BMI.

The Factor IX activity following 80 IU/kg infusion in major surgery is shown in the following table.

Factor IX activity following 80 IU/kg bolus for major surgery

	30 minutes N = 13	8 hours[1] N = 12	24 hours[1] N = 12	48 hours[2] N = 7
Factor IX activity (%) Median (Range)	143 (123-224)	138 (101-175)	112 (62-146)	73 (40-110)

[1]Excludes one subject with no Factor IX activity measurement obtained.

[2]Excludes two subjects with no Factor IX activity measurement obtained and additionally 4 subjects re-dosed prior to the second day after surgery for whom the Factor IX activity at 24 hours were 84%, 112%, 131%, and 134%. The 48 hours measurement reflects a measurement on the second day after surgery (range, 47-57 hours).

8 DOSAGE RANGE

a. Dosage range and route of administration

Rebinyn® is for intravenous infusion after reconstitution only.

- Dose and duration of treatment depend on the location and extent of bleeding, and the patient's clinical condition.
- If monitoring of Factor IX activity is performed, use a chromogenic assay or selected one-stage clotting assay validated for use with Rebinyn®.
- Each carton and vial label for Rebinyn® states the actual Factor IX potency in IU.

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8 DOSAGE RANGE (cont'd)

On-demand Treatment and Control of Bleeding Episodes

Rebinyn® dosing for on-demand treatment and control of bleeding episodes is provided in the following table.

Dosing for on-demand treatment and control of bleeding episodes

Type of bleeding	Recommended dose IU/kg body weight	Additional information
Minor and moderate For example: Uncomplicated joint bleeds, minor muscular bleeds, mucosal, or subcutaneous bleeds	40	A single dose should be sufficient for minor and moderate bleeds. Additional doses of 40 IU/kg can be given.
Major For example: Intracranial, retroperitoneal, iliopsoas and neck bleeds, muscle bleeds with compartment syndrome, and bleeds associated with a significant decrease in the hemoglobin level	80	Additional doses of 40 IU/kg can be given.

Perioperative Management

Rebinyn® dosing for perioperative management is provided in the following table.

Dosing for perioperative management

Type of surgical procedure	Recommended dose IU/kg body weight	Additional information
Minor For example: Implanting pumps in subcutaneous tissue, skin biopsies, or simple dental procedures	40	A single pre-operative dose should be sufficient. Additional doses can be given if needed.
Major For example: Body cavity is entered, mesenchymal barrier is crossed, fascial plane is opened, organ is removed, normal anatomy is operatively altered	80	Pre-operative dose
	40	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. Due to the long half-life of Rebinyn®, the frequency of dosing in the post-surgical setting may be extended to once weekly after the first week until bleeding stops and healing is achieved.

Routine Prophylaxis

For prophylaxis use, the recommended dose is 40 IU/kg body weight once weekly. Adjust dosing regimen based on individual patient's bleeding pattern, and physical activity.

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rebinyn®
Coagulation Factor IX (Recombinant), GlycoPEGylated

8 DOSAGE RANGE (cont'd)

b. Use in specific populations

Pregnancy

Risk Summary

There are no data with Rebinyn® use in pregnant women to determine whether there is a drug-associated risk. Animal reproduction studies have not been conducted with Rebinyn®. It is unknown whether Rebinyn® can cause fetal harm when administered to a pregnant woman or can affect fertility. Rebinyn® should be given to a pregnant woman only if clearly needed. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation

Risk Summary

There is no information regarding the presence of Rebinyn® in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rebinyn® and any potential adverse effects on the breastfed infant from Rebinyn® or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of Rebinyn® were evaluated in four clinical trials that included 43 previously treated pediatric patients and in one clinical trial that included 50 previously untreated pediatric patients. Twelve of these subjects were ≤6 years of age; 13 subjects were 7 to 12 years of age; and 18 subjects were 13 to 17 years of age. Pharmacokinetic parameters were evaluated for 28 of the previously treated pediatric patients who were treated with Rebinyn® 40 IU/kg.

Body weight-adjusted clearance was observed to be higher for pediatric subjects than for adult subjects. However, in clinical trials, no dose adjustment was needed in pediatric subjects who received a fixed dose of 40 IU/kg every week for routine prophylaxis.

Juvenile Animal Toxicity Data

A juvenile animal neurotoxicity study was conducted to evaluate the potential neurotoxicity of Rebinyn® when administered intravenously at dosages of 120 to 1200 IU/kg twice weekly in immature male rats from 3 to 13 weeks of age, followed by a 13-week treatment-free period. Accumulation of PEG was observed in the choroid plexus, pituitary, circumventricular organs, and cranial motor neurons. PEG levels in these tissues increased with dose and dose duration (10 weeks) and remained detectable after the 13-week treatment-free period. Treatment-related PEG-positive vacuolated macrophages were observed in the pituitary. The accumulation of PEG was not associated with neurobehavioral changes, fertility, or functional effects.

8 DOSAGE RANGE (cont'd)

b. Use in specific populations (cont'd)

Geriatric Use

Clinical studies of Rebinyn® did not include sufficient numbers of subjects age 65 and over to determine whether or not they respond differently than younger subjects.

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. No adverse neurologic effects of PEG have been reported in adults exposed to Rebinyn® during clinical trials; however, use in older adults with baseline cognitive dysfunction has not been fully evaluated.

9 SAFETY

a. Adverse reactions, toxicities, and special precautions

Adverse Reactions

Common adverse reactions (incidence ≥1%) in previously treated patients reported in clinical trials for Rebinyn® were itching and injection site reactions. Common adverse reactions (incidence ≥1%) in previously untreated patients reported in clinical trials for Rebinyn® were rash, FIX inhibitors, hypersensitivity, itching, injection site reaction, and anaphylactic reaction.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients

In five multicenter, prospective, non-controlled, open-label clinical trials, 115 previously treated patients [0 to 6 years old: 12 subjects (10%); 7 to 12 years old: 13 subjects (11%); 13 to 17 years old: 18 subjects (16%); ≥-18 years old: 72 subjects (63%)] received at least one dose of Rebinyn® as part of routine prophylaxis, on-demand treatment of bleeding episodes, perioperative management of major and minor surgery, or PK evaluation. A previously treated patient was defined as a subject with a history of at least 150 exposure days (adolescent/adult subjects) to other Factor IX products or 50 exposure days to other Factor IX products (pediatric subjects), and no history of inhibitors. A total of 15,167 injections were administered over a median of 733 days (range, 29-2951 days), equivalent to 15,137 exposure days and 292 patient-years.

9 SAFETY (cont'd)

Adverse reactions in previously treated patients are listed in the following table.

Summary of adverse reactions in previously treated patients

System Organ Class	Adverse Reaction	Number of subjects (%) N = 115
General disorders and administration site conditions	Injection site reactions	4 (4)
Immune system disorders	Hypersensitivity	1 (1)
Skin and subcutaneous tissue disorders	Itching	3 (3)

Previously Untreated Patients

In one multicenter, prospective, non-controlled, open-label clinical trial conducted in previously untreated patients, 50 subjects (≤6 years of age) received at least one dose of Rebinyn®. A previously untreated patient was defined as a subject previously untreated or exposed to FIX-containing products for ≤3 exposure days (5 previous exposures to blood components was acceptable). A total of 6737 injections were administered over a median of 996 days (range, 61-2233 days), equivalent to 6709 exposure days and 142 patient-years.

Adverse reactions in previously treated patients are listed in the following table.

Summary of adverse reactions in previously untreated patients

System Organ Class	Adverse Reaction	Number of subjects (%) N = 50
Blood and lymphatic system disorders	Factor IX inhibition	4 (8)
General disorders and administration site conditions	Injection site reaction	1 (2)
Immune system disorders	Anaphylactic reaction Hypersensitivity	1 (2) 3 (6)
Skin and subcutaneous tissue disorders	Rash Itching	9 (18) 2 (4)

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9 SAFETY (cont'd)

a. Adverse reactions, toxicities, and special precautions (cont'd)

Immunogenicity

Subjects were monitored for inhibitory antibodies to Factor IX prior to dosing, on a monthly basis for the first 3 months, every 2 months up to 1 year, every 3 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.

In an ongoing trial in previously untreated patients, one anaphylactic reaction has occurred with development of a Factor IX inhibitor following treatment with Rebinyn®. Inhibitor development and anaphylactic reactions are more likely to occur during the early phases of Factor IX replacement therapy.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Neurologic Considerations

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.

In the pediatric studies, 47 PUPs and 25 PTPs receiving routine prophylaxis with Rebinyn® at a weekly dose of 40 IU/kg were followed for central nervous system (CNS)-related adverse reactions (ADRs) for 6 and 8 years, respectively. The median duration of follow-up of ADRs in the PUP and PTP studies were 2 and 7 years, respectively. Furthermore, neurological examinations were prospectively conducted in 44 PUPs and 17 PTPs with a median follow-up of 2 years, and neurocognitive assessments were prospectively performed in 38 PUPs and 16 PTPs with a median follow-up of 1 year.

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 comorbidities that may increase risk of adverse neurologic and/or neurocognitive events should be considered when prescribing Rebinyn®. Report adverse neurocognitive and neurologic reactions.

9 SAFETY (cont'd)

a. Adverse reactions, toxicities, and special precautions (cont'd)

Postmarketing Experience

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.

b. Contraindications, Warnings, and Precautions

Rebinyn® is contraindicated in patients who have known hypersensitivity to Rebinyn® or its components (including hamster proteins).

Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with Rebinyn®. The product may contain traces of hamster proteins, which in some patients may cause allergic reactions. Early signs of allergic reactions, which can progress to anaphylaxis, may include angioedema, chest tightness, difficulty breathing, wheezing, urticaria, and itching. Observe patients for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of exposure to the product. Discontinue use of Rebinyn® if allergic- or anaphylactic type reactions occur, and initiate appropriate treatment.

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.

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.

9 SAFETY (cont'd)

Thrombotic Events

The use of Factor IX-containing products has been associated with thromboembolic complications. Due to the potential risk of thromboembolic complications, monitor patients for early signs of thrombotic and consumptive coagulopathy when administering this product to patients with liver disease, post-operatively, to newborn infants, or to patients at risk of thrombosis or disseminated intravascular coagulation (DIC). In each of these situations, the benefit of treatment with Rebinyn® should be weighed against the risk of these complications.

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.

Monitoring Laboratory Tests

If monitoring of Factor IX activity is performed, use a chromogenic assay or selected one-stage clotting assay validated for use with Rebinyn®.

The one-stage clotting assay results can be significantly affected by the type of activated partial thromboplastin time (aPTT) reagent used, which can result in overestimation or underestimation of Factor IX activity. Avoid the use of silica-based reagents, as some may overestimate the activity of Rebinyn®. If a validated one-stage clotting or chromogenic assay is not available locally, then use of a reference laboratory is recommended.

If bleeding is not controlled with the recommended dose of Rebinyn®, or if the expected Factor IX activity levels in plasma are not attained, then perform a Bethesda assay to determine if Factor IX inhibitors are present.

c. List potential drug-drug interactions if deemed clinically significant

N/A

10 COMPARISONS

N/A

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.

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.
- **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.
- **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.

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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