

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REBINYN safely and effectively. See full prescribing information for REBINYN.

REBINYN® (Coagulation Factor IX (Recombinant), GlycoPEGylated) lyophilized powder for solution for intravenous injection
Initial U.S. Approval: 2017

-----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 for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Limitations of Use: REBINYN is not indicated for routine prophylaxis in the treatment of patients with hemophilia B. REBINYN is not indicated for immune tolerance induction in patients with hemophilia B (1).

-----DOSAGE AND ADMINISTRATION-----

For intravenous infusion after reconstitution only (2).

- Each carton and vial label for REBINYN states the actual Factor IX potency in international units (IU) (2.1).
- 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 (2.1).
- Recommended dose for perioperative management: 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 (2.1).

-----DOSAGE FORMS AND STRENGTHS-----

REBINYN is available as a lyophilized powder in single-use vials of 500, 1000, and 2000 IU (3).

-----CONTRAINDICATIONS-----

Do not use in patients who have known hypersensitivity to REBINYN or its components, including hamster proteins (4).

-----WARNINGS AND PRECAUTIONS-----

- Hypersensitivity reactions, including anaphylaxis, may occur. Should hypersensitivity reactions occur, discontinue REBINYN and administer appropriate treatment (5.1).
- Development of neutralizing antibodies (inhibitors) may occur. Perform an assay that measures Factor IX inhibitor concentration if bleeding is not controlled with the recommended dose of REBINYN or if the expected plasma Factor IX activity levels are not attained (5.2, 5.5).
- The use of Factor IX-containing products has been associated with the development of thrombotic complications (5.3).
- Factor IX activity assay results may vary with the type of activated partial thromboplastin time reagent used (5.5).

-----ADVERSE REACTIONS-----

The most frequently reported adverse reactions (≥ 1%) were itching and injection site reactions (6).

Animals administered repeat doses of REBINYN showed accumulation of PEG in the choroid plexus. The potential clinical implications of these animal findings are unknown (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-668-6777 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

Pediatric Use: No dose adjustment is needed (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 06/2017

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FULL PRESCRIBING INFORMATION

1 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 for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Limitations of Use:

REBINYN is not indicated for routine prophylaxis in the treatment of patients with hemophilia B. REBINYN is not indicated for immune tolerance induction in patients with hemophilia B.

2 DOSAGE AND ADMINISTRATION

For intravenous infusion after reconstitution only.

2.1 Dosing Guidelines

- 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 [*see Warnings and Precautions (5.5)*].
- Each carton and vial label for REBINYN states the actual Factor IX potency in IU.

On-demand Treatment and Control of Bleeding Episodes

REBINYN dosing for on-demand treatment and control of bleeding episodes is provided in Table 1.

Table 1: 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 Table 2.

Table 2: 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,	80	Pre-operative dose

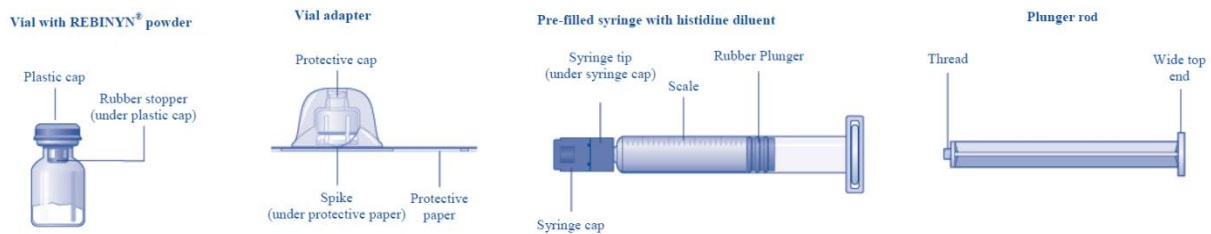
fascial plane is opened, organ is removed, normal anatomy is operatively altered	40	<p>As clinically needed for the perioperative management of bleeding, repeated doses of 40 IU/kg (in 1-3 day intervals) within the first week after major surgery may be administered.*</p> <p>Due to the long half-life 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.</p>
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*See 12.3 Pharmacokinetics, Table 8

2.2 Reconstitution

- Always wash hands and ensure that the area is clean before performing the reconstitution procedures.
- Use aseptic technique during the reconstitution procedures.
- If the patient uses more than one vial of REBINYN per infusion, reconstitute each vial according to the following instructions.

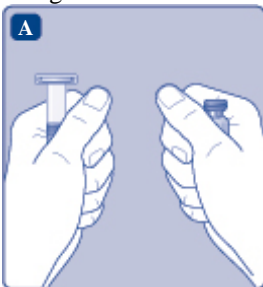
Overview of REBINYN Package



The instructions below serve as a general guideline for reconstitution of REBINYN. For full instructions, refer to the FDA-approved patient information and Instructions for Use.

Reconstitution

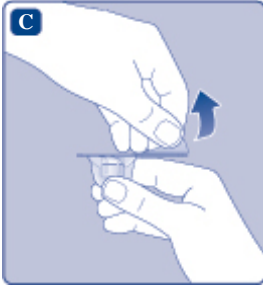
1. Bring the REBINYN vial and the pre-filled diluent syringe to room temperature.



2. Remove the plastic cap from the REBINYN vial.



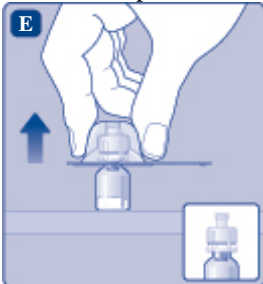
3. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to dry prior to use.
4. Remove the protective paper from the vial adapter. **Do not remove the vial adapter from the protective cap.**



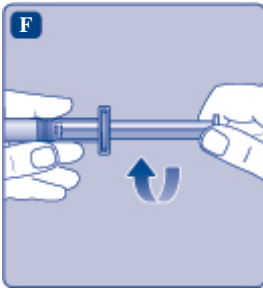
5. Place the vial on a flat and solid surface. While holding the protective cap, place the vial adapter over the REBINYN vial and press down firmly on the protective cap until the vial adapter spike penetrates the rubber stopper.



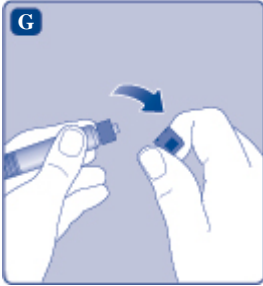
6. Remove the protective cap from the vial adapter.



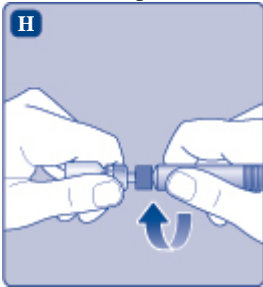
7. Grasp the plunger rod as shown in the diagram. Attach the plunger rod to the syringe by holding the plunger rod by the wide top end. Turn the plunger rod clockwise into the rubber plunger inside the pre-filled diluent syringe until resistance is felt.



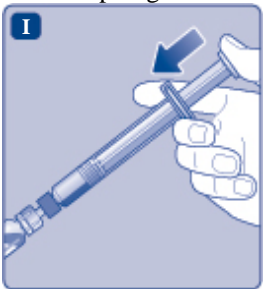
8. Break off the syringe cap from the pre-filled diluent syringe by snapping the perforation of the cap.



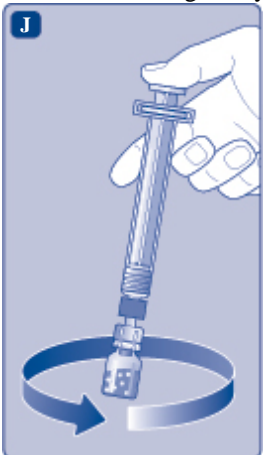
9. Connect the pre-filled diluent syringe to the vial adapter by turning it clockwise until it is secured.



10. Push the plunger rod to slowly inject all the diluent into the vial.



11. Without removing the syringe, gently swirl the REBINYN vial until all of the powder is dissolved.

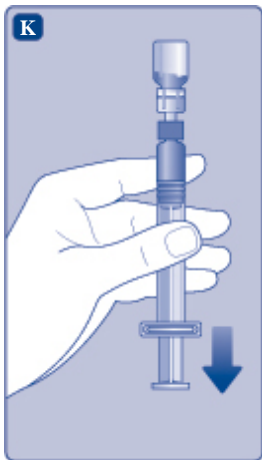


- Administer the REBINYN solution immediately [see *Administration (2.3)*]. If not used immediately after reconstitution, store the solution in the vial with the vial adapter and the syringe attached, at room temperature $\leq 86^{\circ}\text{F}$ (30°C). Do not store for longer than 4 hours.

2.3 Administration

For intravenous infusion only.

- Accidental needle stick with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. If a needle stick occurs, obtain immediate medical attention. Place needles in a sharps container after single use.
 - Inspect the reconstituted REBINYN solution visually prior to administration [see *Description (11)*]. The solution should be clear and have no particles. Do not use if particulate matter or discoloration is observed.
 - Do not administer REBINYN in the same tubing or container with other medicinal products.
- Invert the REBINYN vial and slowly draw the solution into the syringe.



- Detach the syringe from the vial adapter by turning the syringe counterclockwise.
- Attach the syringe to the luer end of an infusion needle set.
- Infuse the reconstituted REBINYN intravenously slowly over 1 to 4 minutes.
- After infusion, safely dispose of the syringe with the infusion set, the vial with the vial adapter, any unused REBINYN, and other waste materials.

Caution: The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector.

Some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave[®] /MicroClave[®], InVision-Plus[®], InVision-Plus CS[®], Invision-Plus Junior[®], Bionector[®]), and their use can damage the connector and affect administration. To administer REBINYN through incompatible needleless connectors, withdraw the reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe.

If you encounter any problems with attaching the pre-filled histidine-diluent syringe to any Luer-lock compatible device, please contact Novo Nordisk at (844) 303-4448.

3 DOSAGE FORMS AND STRENGTHS

REBINYN is available as a white to off-white lyophilized powder in single-use vials containing nominally 500, 1000, or 2000 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 or 500 IU per mL of REBINYN respectively.

4 CONTRAINDICATIONS

REBINYN is contraindicated in patients who have known hypersensitivity to REBINYN or its components (including hamster proteins) [see *Warnings and Precautions (5.1) and Description (11)*]

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 Inhibitors

The formation of inhibitors (neutralizing antibodies) to Factor IX may occur during Factor replacement therapy in the treatment of hemophilia B. Monitor all patients using clinical observations and laboratory tests for the development of inhibitors [see *Warnings and Precautions (5.5)*].

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.

5.3 Thrombotic Events

The use of Factor IX-containing products has been associated with thrombotic complications. Due to the potential risk of thrombotic 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.

5.4 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.

5.5 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 [see *Dosage and Administration (2)*].

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 over- or under-estimation 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.

6 ADVERSE REACTIONS

Common adverse reactions (incidence \geq 1%) reported in clinical trials for REBINYN were itching and injection site reactions.

6.1 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.

During the clinical development program, 115 previously treated male patients received at least one dose of REBINYN [see *Clinical Studies (14)*]. A previously treated patient was defined as a subject with a history of at least 150 exposure days to other Factor IX products (adolescent/adult subjects) or 50 exposure days to other Factor IX products (pediatric subjects), and no history of inhibitors. There were a total of 8801 exposure days, equivalent to 170 patient-years. A total of 40 patients (35%) were treated for more than 2 years.

Adverse reactions are shown in Table 3.

Table 3: Summary of Adverse Reactions in Previously Treated Patients

System Organ Class	Adverse Reaction	Number of subjects (%)
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)

6.2 Immunogenicity

Subjects 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.

In an ongoing trial in previously untreated patients, anaphylaxis 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 [see *Warnings and Precautions (5.1, 5.2)*].

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.

6.3 Neurologic Considerations

Animals administered repeat doses of REBINYN showed accumulation of PEG in the choroid plexus [see *Animal Toxicology and/or Pharmacology (13.2)*]. The potential clinical implications of these animal findings are unknown. The physician should consider whether the patient may be vulnerable, such as infants and children who have developing brains and patients who are cognitively impaired. Physician's discretion is advised with regard to neurocognitive assessments, taking into consideration factors such as duration of use, cumulative dose, age of the patient and related comorbidities that are likely to increase the risks to patients. Adverse neurologic reactions should be reported.

8 USE IN SPECIFIC POPULATIONS

8.1 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 U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 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.

8.4 Pediatric Use

Safety and efficacy of REBINYN were evaluated in 43 previously treated pediatric patients [*see Clinical Studies (14)*]. Twelve of these subjects (28%) were 1 to 6 years of age; 13 subjects (30%) were 7 to 12 years of age; and 18 subjects (42%) were 13 to 17 years of age. Pharmacokinetic parameters were evaluated for 28 of these subjects who were treated with REBINYN 40 IU/kg [*see Clinical Pharmacology (12.3)*].

No difference in the safety profile of REBINYN was observed between previously treated pediatric subjects and adult subjects. Body weight-adjusted clearance was higher for pediatric subjects than for adult subjects. Fixed doses were studied in the clinical trials and no dose adjustment was required for pediatric subjects.

Twenty-eight of the forty-three previously treated pediatric subjects (1 to 17 years old) were treated with REBINYN for 137 bleeding episodes. Results are provided in Table 4.

Table 4: Efficacy in treatment of bleeding episodes in pediatric subjects by age

	≤ 6 years	7-12 years	13-17 years
New bleeding episodes	n=11	n=31	n=95*
Efficacy assessment**			
Excellent or good	10 (91%)	29 (94%)	91 (97%)
Moderate or poor	1 (9%)	2 (6%)	3 (3%)
Number of injections to treat a bleeding episode			
1 injection	9 (82%)	27 (87%)	78 (82%)
2 injections	1 (9%)	4 (13%)	12 (13%)
> 2 injections	1 (9%)	-	5 (5%)

*Efficacy assessment was missing for one bleeding episode.

**Efficacy assessment [Response] was assessed according to a four-point scale using:

Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single injection;

Good: Noticeable pain relief and/or improvement in signs of bleeding within 8 hours after a single injection;

Moderate: Probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one injection within 8 hours;

Poor: No improvement, or worsening of symptoms within 8 hours after the second of two injections.

Animals administered repeat doses of REBINYN showed accumulation of PEG in the choroid plexus [*see Animal Toxicology and/or Pharmacology (13.2)*]. The potential clinical implications of these animal findings are unknown. No adverse neurologic effects of PEG have been reported in infants, children, and adolescents exposed to REBINYN during clinical trials. The potential consequences of long term exposure have not been fully evaluated [*see Section 6.3*].

8.5 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 [*see Animal Toxicology and/or Pharmacology (13.2)*]. 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 [*see Section 6.3*].

11 DESCRIPTION

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 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 or 2000 IU. REBINYN potency is assigned using an *in vitro*, activated partial thromboplastin time (aPTT)-based, one-stage clotting assay calibrated against the World Health Organization (WHO) international standard for Factor IX concentrates. REBINYN contains no preservatives.

REBINYN is a purified recombinant human Factor IX (rFIX) with a 40 kilodalton (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 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.

REBINYN is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. No additives of human or animal origin are used in the cell culture, purification, conjugation, or formulation of REBINYN. The rFIX protein is purified by a series of chromatographic steps, including an affinity chromatography step using a monoclonal antibody (produced in CHO cells), to selectively isolate rFIX from the cell culture medium. The production process includes two dedicated viral clearance steps, namely a detergent treatment step for inactivation and a 20 nm filtration step for removal of viruses. The conjugation of the PEG-group is done by an enzymatic reaction during the purification process, followed by final purification of REBINYN.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

The administration of REBINYN increases plasma levels of Factor IX and can temporarily correct the coagulation defect in hemophilia B patients, as reflected by a decrease in aPTT.

12.3 Pharmacokinetics

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 [see *Clinical Studies (14)*]. 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 pharmacokinetic parameters for adolescents and adults following once-weekly prophylactic treatment of REBINYN 40 IU/kg are shown in Table 5.

Table 5: 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)
V _{ss} (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; V_{ss}= volume of distribution at steady state; CV=coefficient of variation.

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 Table 6.

Table 6: 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	≥18years 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)	15.4 (13.2; 17.9)	18.7 (16.2; 21.6)	23.7 (19.9; 28.2)	29.3 (26.0; 33.0)
Min, Max**	9.2; 24.5	8.3; 28.3	18.6; 34.6	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 pharmacokinetic parameters of REBINYN in children, adolescents and adults are listed in Table 7.

Table 7: 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)
V _{ss} (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; V_{ss} = volume of distribution at steady state; CV = coefficient of variation.

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/m²) and 4 were overweight (BMI 25 to <29.9 kg/m²). The pharmacokinetic parameters were not affected by BMI.

The Factor IX activity following 80 IU/kg infusion in major surgery is shown in Table 8.

Table 8: Factor IX activity following 80 IU/kg bolus for major surgery

	30 minutes	8 hours ¹	24 hours ¹	48 hours ²
	N=13	N=12	N=12	N=7

Factor IX activity (%) Median (Range)	143 (123-224)	138 (101-175)	112 (62-146)	73 (40-110)
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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 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 2nd day after surgery (range 47-57 hours).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to evaluate the carcinogenic or genotoxic potential of REBINYN, or studies to determine the effects of REBINYN on fertility, have not been performed.

13.2 Animal Toxicology and/or Pharmacology

REBINYN was intravenously administered in repeat-dose toxicity studies in immune-deficient rats (40-1200 IU/kg/week for 26 weeks) and immune-competent monkeys (350-3750 IU/kg/week for four weeks). Accumulation of the 40-kDa polyethylene-glycol (PEG) was detected by immunohistochemical staining in epithelial cells of the choroid plexus in the brain of the majority of animals. This finding was not associated with morphological changes or abnormal clinical signs.

14 CLINICAL STUDIES

Four multicenter, non-controlled trials were conducted to evaluate the safety and efficacy of REBINYN in routine treatment, on-demand treatment and control of bleeding episodes, and perioperative management in previously treated male patients with hemophilia B (Factor IX activity \leq 2%). Previously treated patients were defined as patients receiving treatment with other Factor IX products for \geq 150 exposure days for adolescents and adults, and \geq 50 exposure days for pediatric patients. The key exclusion criteria across trials included known or suspected hypersensitivity to trial or related products, known history of Factor IX inhibitors or current inhibitor \geq 0.6 BU, HIV-positive with a viral load \geq 400,000 copies/mL or CD4+ lymphocyte count \leq 200/ μ L, additional congenital or acquired coagulation disorders, previous arterial thrombotic events, and recipients of immune modulating or chemotherapeutic medication.

The efficacy evaluation included 105 subjects: 62 adults (18 to 65 years old), 18 adolescents (13 to 17 years old), and 25 children (1 to 12 years old).

- Adult/adolescent trial: The trial included 74 adolescent and adult previously treated patients. There were two routine treatment arms, with single-blind randomization to either 10 IU/kg or 40 IU/kg once-weekly for approximately 52 weeks, and an open-label on-demand treatment arm for approximately 28 weeks.
- Surgery trial: The surgery trial included 13 previously treated adolescent and adult patients who received one infusion of REBINYN 80 IU/kg on the day of surgery, and post-operatively received infusions of 40 IU/kg, at the investigator's discretion, for up to 3 weeks after surgery.
- Adult/adolescent extension trial: There were 71 subjects from the adult/adolescent trial and surgery trial who continued routine treatment or on-demand treatment with REBINYN in an open-label extension trial, with the possibility to switch regimens during the trial.
- Pediatric trial: The main phase of the pediatric trial included 25 pediatric previously treated patients (1-12 years old) in which subjects received routine treatment with REBINYN 40 IU/kg once-weekly for approximately 52 weeks.

Treatment of Bleeding Episodes

A total of 597 bleeding episodes were reported in 79 out of 105 subjects in the clinical program in previously treated patients. Bleeding episodes were treated with REBINYN at 40 IU/kg for minor or moderate bleeds or 80 IU/kg for major bleeds, with additional doses of 40 IU/kg as needed. The median dose to treat a bleeding episode was 42.3 IU/kg.

An overall assessment of efficacy was performed by the subject (for home treatment) or the study site investigator (for treatment under medical supervision) using a 4-point scale of excellent, good, moderate, or poor. The overall success rate (defined as excellent or good) for treatment of bleeding episodes was 93.2% as shown in Table 9.

The success rate and dose needed for treatment of bleeding episodes were independent of the location of the bleeding. The success rate for treatment of bleeding episodes was also independent of whether the bleed was traumatic or spontaneous.

Table 9: Efficacy in treatment of bleeding episodes in previously treated patients

New Bleeding Episodes	n = 597
Efficacy assessment*	
Excellent or Good	551 (93%)
Moderate or Poor	40 (7%)
Number of injections to treat a bleeding episode	
1 injection	521 (87%)
2 injections	60 (10%)
>2 injections	16 (3%)

*Efficacy assessment was based on 591 evaluated bleeding episodes (data missing for six bleeding episodes). Efficacy was assessed according to a four-point scale using:

Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single injection;

Good: Noticeable pain relief and/or improvement in signs of bleeding within 8 hours after a single injection;

Moderate: Probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one injection within 8 hours;

Poor: No improvement, or worsening of symptoms within 8 hours after the second of two injections.

In the on-demand arm there were 143 bleeding episodes in 14 of 15 subjects. The overall success rate was 95.1% (135 of 142 evaluated bleeds). A total of 120 bleeds (83.9%) of the 143 bleeding episodes were treated with one injection, and 20 (14.0%) were treated with two injections.

Perioperative Management

In the surgery trial, the efficacy analysis of REBINYN in perioperative management included 13 surgical procedures of which 9 were major and performed in 13 previously treated adolescent and adult patients. The procedures included 9 orthopedic, 1 gastrointestinal and 3 in the oral cavity.

The hemostatic effect during surgery was evaluated on a four-point scale of excellent, good, moderate, or poor. The intraoperative hemostatic effect was rated as excellent or good for the 13 surgeries, for a success rate of 100%. A pre-operative dose of 80 IU/kg REBINYN was effective, and no subjects required additional doses on the day of surgery. The median number of additional 40 IU/kg doses in the post-operative period was 2.0 for Days 1 to 6, 1.5 for Days 7-13, and 3.0 for Days 1 to 13. The mean total consumption of REBINYN in the pre- and post-operative period was 241 IU/kg (range: 81 to 460 IU/kg). There was no unexpected postoperative bleeding.

Three additional major surgeries and 18 minor surgery procedures were evaluated in the extension trial for REBINYN in previously treated patients. The hemostatic effect during major and minor surgery was confirmed with a success rate of 100%.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- REBINYN is supplied in packages comprised of a single-use vial containing nominally 500, 1000, or 2000 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 IU is stated on each REBINYN carton and vial.

Table 10: REBINYN Presentations

Presentation (Nominal Product Strength; IU)	Cap Color Indicator	Carton NDC Number	Components

500	Red	NDC 0169 7905 01	<ul style="list-style-type: none"> • REBINYN in single-use vial [NDC 0169 7955 11] • Pre-filled histidine diluent in syringe, 4 mL [NDC 0169 7009 98] • Vial adapter
1000	Green	NDC 0169 7901 01	<ul style="list-style-type: none"> • REBINYN in single-use vial [NDC 0169 7911 11] • Pre-filled histidine diluent in syringe, 4 mL [NDC 0169 7009 98] • Vial adapter
2000	Yellow	NDC 0169 7902 01	<ul style="list-style-type: none"> • REBINYN in single-use vial [NDC 0169 7922 11] • Pre-filled histidine diluent in syringe, 4 mL [NDC 0169 7009 98] • Vial adapter

- The REBINYN vials are made of glass, closed with a chlorobutyl rubber stopper (not made with natural rubber latex), and sealed with an aluminum cap.
- The pre-filled diluent syringes are made of glass, with a siliconised bromobutyl rubber plunger (not made with rubber latex).
- The closed vials and pre-filled diluent syringes are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Storage and Handling

- 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 stored at room temperature for more than 4 hours.

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Inform patients of the early signs of hypersensitivity reactions including rash, hives, itching, facial swelling, tightness of the chest and wheezing. Advise patients to discontinue use of the product and contact their healthcare provider if these symptoms occur.
- Advise patients to contact their healthcare provider for further treatment and/or assessment if they experience a lack of a clinical response to Factor IX therapy, as in some cases this may be a manifestation of an inhibitor.
- Advise patients to contact their healthcare provider if they experience any thrombotic complications.
- Advise patients to follow the recommendations regarding proper sharps disposal provided in the FDA-approved Instructions for Use.

Version: 1

License Number: 1261

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For Patent Information, refer to:

<http://novonordisk-us.com/patients/products/product-patents.html>

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