

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**REBINYN<sup>®</sup>**

Coagulation Factor IX (Recombinant), Pegylated

nonacog beta pegol

Lyophilized Powder  
500, 1000 and 2000 IU/vial

Blood Coagulation Factor IX

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# REBINYN®

Coagulation Factor IX (Recombinant), Pegylated

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength  | Clinically Relevant Nonmedicinal Ingredients  |
|-------------------------|---|---|
| Intravenous injection   | Lyophilized powder for solution nominally containing 500, 1000 and 2000 IU/vial | Sodium chloride, sucrose, histidine<br><i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

### DESCRIPTION

REBINYN® is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution with the provided histidine solvent for intravenous injection. After reconstitution the solution appears as a clear and colourless liquid, free from visible particles. REBINYN® is available in single use vials containing the labeled amount of factor IX activity, expressed in international units. REBINYN® potency is assigned using an *in vitro*, 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. The histidine solvent for reconstitution is provided in a prefilled syringe.

REBINYN® is a purified recombinant human factor IX (rFIX) with a 40 kDa polyethylene-glycol (PEG) conjugated to the protein. The average molecular weight of REBINYN® is approximately 98 kDa and the molecular weight of the protein moiety alone is 56 kDa. The rFIX protein in REBINYN® consists of a gamma-carboxylated domain (Gla domain), two epidermal growth factor-like (EGF-like) domains, an activation peptide (which is cleaved off upon activation) and a protease domain. A 40 kDa PEG-group is selectively attached to specific N-linked glycans in the rFIX activation peptide, with monoPEGylated rFIX as the predominant form of REBINYN®. Once activated, the resulting rFIX has structural and functional properties similar to those of plasma derived factor IX. 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 conjugation of the PEG-group is done by an enzymatic reaction during the purification of REBINYN®. The production process includes two dedicated and validated viral clearance steps, namely a detergent treatment step for inactivation and a 20 nm filtration step for removal of viruses.

## INDICATIONS AND CLINICAL USE

REBINYN<sup>®</sup> (Coagulation Factor IX (Recombinant), pegylated) is an anti-hemophilic factor indicated in adults and children with hemophilia B (congenital factor IX deficiency or Christmas disease) for:

- control and prevention of bleeding episodes
- control and prevention of bleeding in the perioperative setting

REBINYN<sup>®</sup> is also indicated in patients 18 years and above with hemophilia B for:

- routine prophylaxis to prevent or reduce the frequency of bleeding episodes

**Limitations of Use:** REBINYN<sup>®</sup> is not indicated for immune tolerance induction in patients with hemophilia B.

### **Geriatrics (> 65 years of age):**

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

### **Pediatrics (< 18 years of age):**

Safety and efficacy of REBINYN<sup>®</sup> have been evaluated in 43 previously treated pediatric patients from 1 to <18 years old.

## CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation (including hamster protein), or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

## WARNINGS AND PRECAUTIONS

### **Carcinogenesis**

Studies in animals to evaluate the carcinogenic potential of REBINYN<sup>®</sup>, or studies to determine the effects of REBINYN<sup>®</sup> on genotoxicity, fertility, developmental or reproductive studies have not been performed.

### **Hematologic**

**Thromboembolic events:** The use of factor IX containing products has been associated with thrombotic complications. Due to the potential risk of thrombotic complications, it is recommended to monitor patients for early signs of thrombotic and consumptive coagulopathy when administering this product to patients with liver disease, post-operatively, new-born infants or patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with REBINYN<sup>®</sup> should be weighed against the risk of these complications.

## **Immune**

**Hypersensitivity:** As with any intravenous protein product, allergic type hypersensitivity reactions including anaphylactic reactions are possible with REBINYN<sup>®</sup>. 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, dyspnea, wheezing, urticaria, and pruritus. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician who should ensure appropriate treatment.

In case of anaphylactic shock, standard medical treatment should be implemented.

Patients should be informed of the early signs of hypersensitivity reactions.

Because of the risk of severe allergic reactions seen in relation to inhibitor development with any factor IX product, the initial administration of factor IX should be performed under medical observation where proper medical care for allergic reactions can be provided.

**Inhibitors:** The formation of inhibitors (neutralizing antibodies) to factor IX may occur in connection with factor replacement therapy in the treatment of hemophilia B. All patients should be monitored regularly for the development of inhibitors that should be quantified in Bethesda Units (BU) using appropriate biological testing (see Monitoring and Laboratory Tests Section).

An association between the occurrence of a factor IX inhibitor and allergic reactions has been reported. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of severe allergic reactions with subsequent challenge with factor IX.

## **Renal**

**Nephrotic syndrome:** Nephrotic syndrome has been reported following attempted immune tolerance induction therapy in hemophilia B patients with factor IX inhibitors often with a history of allergic reaction. The safety and efficacy of using REBINYN<sup>®</sup> for immune tolerance induction has not been established.

## **Special Populations**

**Pregnant Women:** Animal reproduction studies have not been conducted with REBINYN<sup>®</sup>. Based on the rare occurrence of hemophilia B (an X-linked recessive disorder) in women, experience regarding the use of factor IX during pregnancy is not available. Therefore, REBINYN<sup>®</sup> should only be used during pregnancy if clearly indicated.

**Nursing Women:** It is not known if REBINYN<sup>®</sup> is excreted in human milk. Based on the rare occurrence of hemophilia B in women, experience regarding the use of factor IX during breastfeeding is not available. Therefore, REBINYN<sup>®</sup> should only be used during breastfeeding if clearly indicated.

**Pediatrics (< 18 years of age):** The safety profile of REBINYN<sup>®</sup> for the previously treated pediatric patients was consistent with the previously treated adult patients in the clinical trials.

Repeat dose animal studies of REBINYN<sup>®</sup> showed accumulation of PEG in the choroid plexus [see TOXICOLOGY]. The potential clinical implications of these animal findings are unknown. No adverse neurologic effects of PEG have been reported in pediatric patients exposed to REBINYN<sup>®</sup> during clinical trials. The potential consequences of long term exposure have not been fully evaluated.

**Geriatrics (> 65 years of age):** Clinical studies of REBINYN<sup>®</sup> did not include sufficient numbers of subjects age 65 and over to determine whether or not they respond differently than younger subjects.

Repeat dose animal studies of REBINYN<sup>®</sup> showed accumulation of PEG in the choroid plexus [see TOXICOLOGY]. The potential clinical implications of these animal findings are unknown. No adverse neurologic effects of PEG have been reported in adult patients exposed to REBINYN<sup>®</sup> during clinical trials; however use in older adults with baseline cognitive dysfunction has not been fully evaluated.

### **Monitoring and Laboratory Tests**

Due to the interference of polyethylene glycol (PEG) in the one-stage clotting assay with various aPTT reagents, it is recommended to use a chromogenic assay (e.g. Rox Factor IX or Biophen) when monitoring is needed. If a chromogenic assay is not available, it is recommended to use a one-stage clotting assay with an aPTT reagent (e.g. Cephascreen) qualified for use with REBINYN<sup>®</sup>. For REBINYN<sup>®</sup> some reagents will cause underestimation (30–50%), while most silica containing reagents will cause severe overestimation of the factor IX activity (more than 400%). Therefore, silica based reagents should be avoided.

Use of a reference laboratory is recommended when a chromogenic assay or a qualified one-stage clotting assay is not available locally.

### **Inhibitors**

If bleeding is not controlled with an appropriate dose and there is a suspicion of inhibitor development, a Bethesda assay should be performed to determine if a factor IX inhibitor is present. In patients with an inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with hemophilia and factor IX inhibitors.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

Common adverse reactions (incidence  $\geq 1\%$ ) reported in clinical trials in previously treated patients were pruritus and injection site reactions.

Rarely, hypersensitivity and/or allergic reactions have been observed and may in some cases progress to severe anaphylaxis (including anaphylactic shock). Occasionally, these reactions have occurred in close temporal association with development of factor IX inhibitors (see WARNINGS AND PRECAUTIONS). On rare occasions, patients with hemophilia B may develop inhibitors (neutralizing antibodies) to factor IX. In such cases, the presence of inhibitors will manifest itself as an insufficient or lack of clinical response and it is recommended that a hemophilia centre is contacted.

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

During the clinical development program, 115 previously treated male patients received at least one dose of REBINYN<sup>®</sup> for routine prophylaxis, treatment of bleeding episodes, perioperative management and in a single dose pharmacokinetic study. 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.

**Table 1-1: Summary of adverse drug reactions in previously treated patients**

| System Organ Class                                   | Preferred Term              | Number of Subjects* (%) | Frequency Category |
|--|-----------------------------|-------------------------|--------------------|
| General disorders and administration site conditions | Injection site reactions*** | 4 (3.5)                 | Common             |
| Immune system disorders                              | Hypersensitivity            | 1 (0.9)                 | Uncommon           |
| Skin and subcutaneous tissue disorders               | Pruritus**                  | 3 (2.6)                 | Common             |

\*Number of patients with reaction by total number of unique patients exposed in all clinical studies (115)

\*\* Pruritus includes the terms pruritus and ear pruritus

\*\*\*Injection site reactions includes the terms injection site pain, infusion site pain, injection site swelling, injection site erythema and injection site rash.

No inhibitors were reported in the clinical trials in previously treated patients.

In an ongoing trial in previously untreated patients, anaphylaxis has occurred in close temporal association with development of factor IX inhibitor following treatment with REBINYN<sup>®</sup>. Inhibitor development and anaphylactic reactions are more likely to occur during the early phases of replacement therapy.

## DRUG INTERACTIONS

No interaction studies have been performed and no interactions of REBINYN<sup>®</sup> with other medicinal products have been reported.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- Treatment should be initiated under the supervision of a health care professional experienced in the treatment of hemophilia B.
- The dose recommendations in children are the same as for adults.
- There is limited experience with REBINYN<sup>®</sup> in patients of 65 years and above.
- Dose and duration of treatment depends on the location, 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<sup>®</sup> [see WARNINGS AND PRECAUTIONS/ Monitoring and Laboratory Tests].

### Recommended Dose and Dosage Adjustment

#### Control and Prevention of Bleeding Episodes

REBINYN<sup>®</sup> dosing for the control and prevention of bleeding episodes is provided in Table 1-2.

**Table 1-2: Dosing for control and prevention of bleeding episodes**

| Type of bleeding  | Recommended dose IU/kg body weight | Additional Information  |
|---|------------------------------------|---|
| <b><u>Mild and moderate</u></b><br>Uncomplicated hemarthrosis, muscle bleed, oral bleed or hematoma                                 | 40 IU/kg                           | A single dose should be sufficient for minor and moderate bleeds.<br><br>Additional doses of 40 IU/kg can be given. |
| <b><u>Severe and life threatening</u></b><br>Iliopsoas, significant muscle bleed, pharyngeal, retroperitoneal, retropharyngeal, CNS | 80 IU/kg                           | Additional doses of 40 IU/kg can be given.  |



### Routine Prophylaxis

The recommended dose is 40 IU/kg body weight once weekly.

Routine monitoring of factor IX activity levels for the purpose of dose adjustment is not required. In the clinical trial program, dose adjustment was not performed.

### Perioperative Management

REBINYN<sup>®</sup> dosing for perioperative management is provided in Table 1-3.

**Table 1-3: Dosing for perioperative management**

| Type of surgical procedure  | Recommended dose IU/kg body weight | Additional Information   |
|---|------------------------------------|--|
| <b><u>Minor Surgery</u></b><br>Including tooth extraction                             | 40 IU/kg                           | A single pre-operative dose should be sufficient.<br>Additional doses can be given if needed.  |
| <b><u>Major Surgery</u></b><br>Including intraabdominal and joint replacement surgery | 80 IU/kg                           | Pre-operative dose.  |
|   | 40 IU/kg                           | Consider two repeated doses of 40 IU/kg (in 1-3 day intervals) within the first week after surgery.<br><br>The frequency of dosing in the post-surgical period may be extended to once weekly after the first week until bleeding stops and healing is achieved. |

### **Missed Dose**

Patients in routine prophylaxis, who forget a dose, are advised to take their dose upon discovery and thereafter continue with the usual once weekly dosing schedule. A double dose should be avoided.

### **Reconstitution**

| Vial Size    | Volume of Histidine Solvent to be Added to Vial | Approximate Concentration After Reconstitution |
|--------------|---|--|
| 500 IU/vial  | 4 mL  | 125 IU/mL                                      |
| 1000 IU/vial | 4 mL  | 250 IU/mL                                      |
| 2000 IU/vial | 4 mL  | 500 IU/mL                                      |

**For detailed instructions on how to prepare and administer REBINYN<sup>®</sup> refer to PART III: PATIENT MEDICATION INFORMATION of the Product Monograph.**

## **Administration**

- The reconstituted product should be used immediately.
- If you cannot use the reconstituted solution immediately, it should be used within 4 hours when stored at room temperature (up to 30°C) and within 24 hours when stored in a refrigerator (at 2°C – 8°C). Store the reconstituted product in the vial.
- Do not freeze reconstituted REBINYN<sup>®</sup> solution or store it in syringes. Keep reconstituted REBINYN<sup>®</sup> solution out of direct light.
- Reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.
- REBINYN<sup>®</sup> is administered by intravenous bolus injection over several minutes after reconstitution of the lyophilized powder with the histidine solvent. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 mL/min.
- REBINYN<sup>®</sup> should not be mixed or reconstituted with infusion solutions other than the contained histidine solvent. Do not administer reconstituted REBINYN<sup>®</sup> in the same tubing or container with other medications.

### **Injecting REBINYN<sup>®</sup> via needleless connectors for intravenous (IV) catheters**

The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro<sup>®</sup>.

**Caution:** The MixPro<sup>®</sup> prefilled solvent syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Follow the instructions for use that come with the needleless connector. Administration through a needleless connector may require withdrawal of the reconstituted solution into a standard 10 mL sterile luer-lock plastic syringe.

If you have encountered any problems with attaching the prefilled solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

For detailed instructions on how to administer REBINYN<sup>®</sup> refer to PART III: PATIENT MEDICATION INFORMATION section of the Product Monograph.

## **OVERDOSAGE**

In the clinical trials, 6 out of 115 previously treated patients reported 7 overdose events. Dose ranged from 53 IU/kg to 169 IU/kg. No symptoms associated with overdoses have been reported.

For management of a suspected drug overdose, contact your hemophilia treatment centre or your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Patients with hemophilia B are deficient in coagulation factor IX, which is required for effective hemostasis. Treatment with REBINYN<sup>®</sup> temporarily replaces the missing clotting factor IX.

Factor IX is activated by factor XIa and by factor VII/tissue factor complex. Upon activation of REBINYN<sup>®</sup>, the activation peptide including the 40 kDa polyethylene-glycol moiety is cleaved off, leaving the native factor IX molecule. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X convert's prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed.

### Pharmacodynamics

The administration of REBINYN<sup>®</sup> increases plasma levels of factor IX and can temporarily correct the coagulation defect in hemophilia B patients, as reflected by a decrease in aPTT.

### Pharmacokinetics

REBINYN<sup>®</sup> has a prolonged half-life compared to unmodified factor IX. All pharmacokinetic studies with REBINYN<sup>®</sup> were conducted in previously treated patients with hemophilia B (factor IX  $\leq$  2%). The plasma samples were analyzed using the one-stage clotting assay. Steady-state pharmacokinetic parameters for adolescents and adults are shown in Table 1-4.

**Table 1-4: Steady-state pharmacokinetic parameters of REBINYN<sup>®</sup> (40 IU/kg) in adolescents and adults (geometric mean (CV))**

| PK Parameter   | 13-17 years<br>N=3 | $\geq$ 18 years<br>N=6 |
|--|--------------------|------------------------|
| Half-life ( $t_{1/2}$ ) (hours)                            | 103 (14)           | 115 (10)               |
| Incremental Recovery (IR) (IU/mL per IU/kg)                | 0.018 (28)         | 0.019 (20)             |
| Area under the curve (AUC) <sub>0-168h</sub> (IU*hours/mL) | 91 (22)            | 93 (15)                |
| Clearance (CL) (mL/hour/kg)                                | 0.4 (17)           | 0.4 (11)               |
| Mean residence time (MRT) (hours)                          | 144 (15)           | 158 (10)               |
| Volume of distribution ( $V_{ss}$ ) (mL/kg)                | 61 (31)            | 66 (12)                |
| Factor IX activity 168 h post dosing (IU/mL)               | 0.29 (19)          | 0.32 (17)              |

Clearance = body weight adjusted clearance; Incremental recovery = incremental recovery 30 min post dosing; Volume of distribution = body weight adjusted volume of distribution at steady state; CV = coefficient of variation.

Single-dose pharmacokinetic parameters of REBINYN<sup>®</sup> in children, adolescents and adults are listed by age in Table 1-5.

**Table 1-5: Single-dose pharmacokinetic parameters of REBINYN® (40 IU/kg) in pediatrics, adolescents and adults by age (geometric mean (CV))**

| PK Parameter  | ≤ 6 years<br>N=12 | 7-12 years<br>N=13 | 13-17 years<br>N=3 | ≥ 18 years<br>N=6 |
|---|-------------------|--------------------|--------------------|-------------------|
| Half-life (t <sub>1/2</sub> ) (hours)                   | 70 (16)           | 76 (26)            | 89 (24)            | 83 (23)           |
| Incremental Recovery (IR) (IU/mL per IU/kg)             | 0.015 (7)         | 0.016 (16)         | 0.020 (15)         | 0.023 (11)        |
| Area under the curve (AUC) <sub>inf</sub> (IU*hours/mL) | 46 (14)           | 56 (19)            | 80 (35)            | 91 (16)           |
| Clearance (CL) (mL/hour/kg)                             | 0.8 (13)          | 0.6 (22)           | 0.5 (30)           | 0.4 (15)          |
| Mean residence time (MRT) (hours)                       | 95 (15)           | 105 (24)           | 124 (24)           | 116 (22)          |
| Volume of distribution (V <sub>ss</sub> ) (mL/kg)       | 72 (15)           | 68 (22)            | 59 (8)             | 47 (16)           |
| Factor IX activity 168 h post dosing (IU/mL)            | 0.08 (16)         | 0.11 (19)          | 0.15 (60)          | 0.17 (31)         |

Clearance = body weight adjusted clearance; Incremental recovery = incremental recovery 30 min post dosing; Volume of distribution = body weight adjusted volume of distribution at steady state; CV=coefficient of variation.

As expected, body weight adjusted clearance in pediatric and adolescent patients was higher compared to adults. However, no dose adjustment was required in pediatric and adolescent patients in the clinical trials.

The estimated mean steady-state trough levels during trials with weekly dosing of 40 IU/kg can be found in Table 1-6.

**Table 1-6: Factor IX trough levels\* of REBINYN® (40 IU/kg) by age at steady-state**

|   | ≤ 6 years<br>N=12   | 7-12 years<br>N=13  | 13-17 years<br>N=9  | ≥ 18 years<br>N=20  |
|---|---------------------|---------------------|---------------------|---------------------|
| Estimated mean factor IX trough levels IU/mL (95% CI) | 0.15<br>(0.13;0.18) | 0.19<br>(0.16;0.22) | 0.24<br>(0.20;0.28) | 0.29<br>(0.26;0.33) |

\* Factor IX trough levels = factor IX activity measured prior to next weekly dose (5 to 10 days post dosing) at all visits.

The factor IX activity following 80 IU/kg injection in major surgery is shown in Table 1-7.

**Table 1-7: Factor IX activity following 80 IU/kg bolus for major surgery**

|                        | <b>30 minutes</b> | <b>8 hours</b> | <b>24 hours<sup>1</sup></b> | <b>48 hours<sup>2</sup></b> |
|------------------------|-------------------|----------------|-----------------------------|-----------------------------|
|                        | N=11              | N=11           | N=10                        | N=5                         |
| Factor IX activity (%) | 150               | 142            | 115                         | 72                          |
| Median (Range)         | (127-224)         | (101-175)      | (62-146)                    | (40-110)                    |

<sup>1</sup> Excludes one patient with no factor IX activity measurement obtained.

<sup>2</sup> Excludes two patients with no factor IX activity measurement obtained and additionally 4 patients 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)

## **STORAGE AND STABILITY**

Store refrigerated (2°C - 8°C). Do not freeze.

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

REBINYN<sup>®</sup> vials can be stored in the refrigerator (2°C - 8°C) up to the expiration date stated on the label. During the shelf-life, REBINYN<sup>®</sup> may also be stored at room temperature (up to 30°C) for a single period not exceeding 6 months. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Record the beginning of storage at room temperature on the product carton.

Do not use REBINYN<sup>®</sup> after the end of the 6 month period at room temperature storage, or after the expiration date stated on the carton, whichever occurs earlier.

### **After Reconstitution:**

The reconstituted product should be used immediately.

Chemical and physical in-use stability have been demonstrated for 24 hours when stored refrigerated (2°C -8°C) and 4 hours when stored at room temperature ( $\leq 30^{\circ}\text{C}$ ). If not used immediately, in-use storage times and conditions prior to use are the responsibility of the users and would normally not be recommended for longer than 4 hours when stored at room temperature ( $\leq 30^{\circ}\text{C}$ ) or 24 hours when stored refrigerated (2°C- 8°C), unless reconstitution has taken place under controlled and validated aseptic conditions.

Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

REBINYN<sup>®</sup> is supplied as a white to off-white, lyophilized powder in a single-use vial.

REBINYN<sup>®</sup> is available in strengths of 500, 1000 or 2000 IU/vial.

The solvent for reconstitution of REBINYN<sup>®</sup> is a 10 mM solution (1.6 mg/mL) of histidine in water for injection supplied in a prefilled syringe.

The REBINYN<sup>®</sup> package contains 1 vial of REBINYN<sup>®</sup> and 1 MixPro<sup>®</sup> prefilled solvent syringe with sterile vial adapter, which serves as a needleless reconstitution system.

Each REBINYN<sup>®</sup> package contains:

- 1 glass vial (type I) with REBINYN<sup>®</sup> powder and chlorobutyl rubber stopper
- 1 sterile vial adapter (with 25 micrometer filter) for reconstitution
- 1 prefilled syringe containing 4 mL of histidine solvent with a backstop (polypropylene), a rubber plunger (bromobutyl), and a tip cap with a stopper (bromobutyl)
- 1 plunger rod (polypropylene)

The rubber stopper and plunger are not made with natural rubber latex.

After reconstitution, REBINYN<sup>®</sup> contains the following excipients per mL:

| Component       | Quantity Per mL | Function        |
|-----------------|-----------------|-----------------|
| Sodium Chloride | 2.34 mg         | Tonicity agent  |
| Histidine       | 3.10 mg         | Buffering agent |
| Sucrose         | 10 mg           | Stabilizer      |
| Mannitol        | 25 mg           | Bulking agent   |
| Polysorbate 80  | 0.05 mg         | Surfactant      |

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: nonacog beta pegol

Chemical name: Coagulation Factor IX (Recombinant), Pegylated

Molecular formula: C<sub>2041</sub> H<sub>3114</sub> N<sub>558</sub> O<sub>641</sub> S<sub>25</sub>

Molecular mass: 98 kDa

Physicochemical properties:

|                                    |   |
|------------------------------------|---|
| Appearance, colour, physical state | The purified nonacog beta pegol drug substance is contained in a solution. The solution is clear and colourless to slightly yellow        |
| Solubility                         | The physical appearance of nonacog beta pegol drug substance (tested in concentration range 2-10 mg/ml) is a solution                     |
| Aqueous pH-solubility profile      | No visual precipitation is observed between pH 2.7 to pH 10.2. However, aggregation can be detected at pH lower than 5.5 and above pH 8.9 |
| pI value                           | The isoelectric point (pI) of nonacog beta pegol is approximately 5.5   |

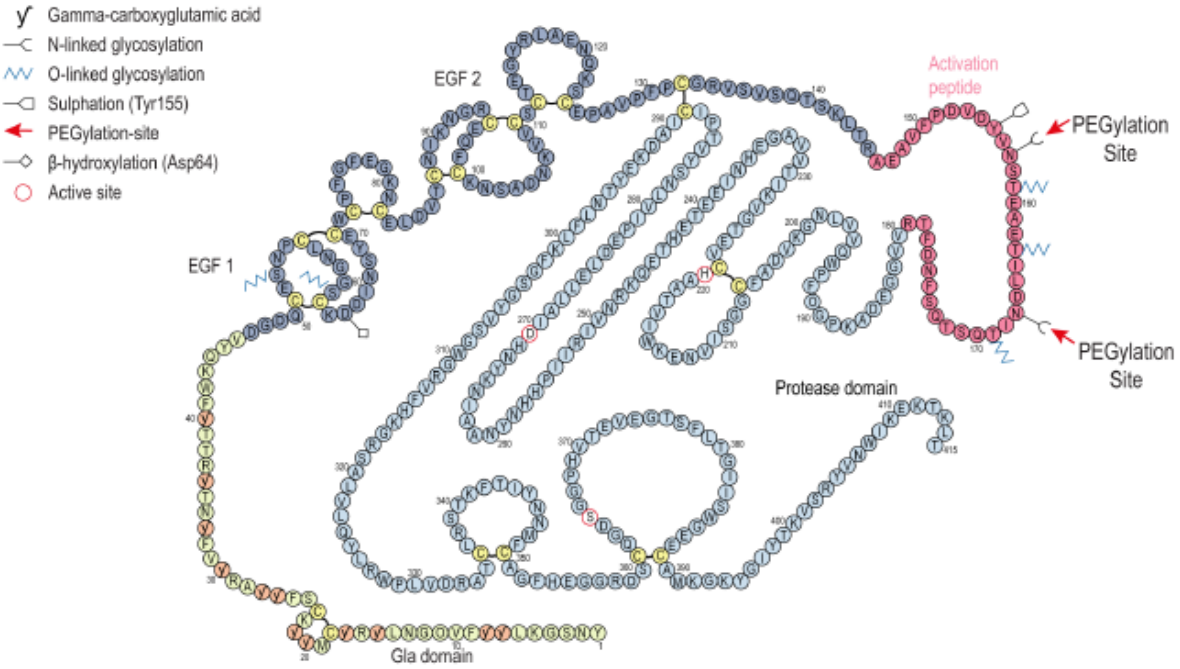
#### Product Characteristics

Nonacog beta pegol is a PEGylated recombinant human factor IX. The molecule consists of a Gla domain, two EGF-like (epidermal growth factor) domains, an activation peptide (which is cleaved from nonacog beta pegol upon activation), and a protease domain (see Figure 2-1).

Recombinant factor IX (rFIX) is an intermediate in the production of nonacog beta pegol. rFIX is produced in Chinese Hamster Ovary cells. The post translational modifications include disulphide bridges,  $\gamma$ -carboxylations, glycosylations, sulphation and hydroxylation.

For production of nonacog beta pegol, a 40 kDa PEG is covalently attached to N-linked carbohydrates (attachment sites: Asn157, Asn167) via a linker. The two possible PEGylation sites in the rFIX molecule (Asn157 and Asn167) are both situated on the activation peptide.

Nonacog beta pegol has a PEGylation profile for which the major form is mono-PEGylated rFIX (approximately 80%) and minor forms are the di- and tri-PEGylated rFIX, as well as non-PEGylated rFIX. For the mono-PEGylated nonacog beta pegol, the distribution between the two possible PEGylation sites (Asn157 and Asn167) is approximately equal.



**Figure 2-1: Nonacog beta pegol structure showing the amino acid sequence, disulphide bridges and post-translational modifications of nonacog beta pegol**



## CLINICAL TRIALS

### Study demographics and trial design in previously treated hemophilia B patients

| Study #  | Trial design  | Dosage, route of administration and duration <sup>a)</sup>  | Study subjects (n = number)  | Mean age (Range)                           | Gender |
|--|---|---|--|--|--------|
| Trial 3747<br><br>Pivotal trial                    | A multicentre, single-blind <sup>b)</sup> , non-controlled, randomized trial evaluating safety, efficacy and PK in routine prophylaxis and treatment of bleeds.<br><br>Three treatment arms: 10 or 40 IU/kg once weekly prophylaxis for 52 weeks (randomized), or on-demand treatment for 28 weeks.   | <u>Prophylaxis:</u><br>10 or 40 IU/kg once-weekly.<br><br><u>Treatment of bleeds:</u><br>Mild and moderate bleeds treated with injection(s) of 40 IU/kg; severe bleeds treated with 80 IU/kg.                                     | 74 previously treated adolescent or adult patients<br>- Prophylaxis: 59<br>- On-demand: 15<br><br>PK: 16 previously treated patients | Mean = 31 years<br><br>Range = 13-65 years | Male   |
| Trial 3773<br><br>Surgery trial                    | A multicentre, open-label, non-controlled trial evaluating efficacy and safety during major surgical procedures.  | <u>Pre-operative:</u><br>80 IU/kg on the day of surgery.<br><br><u>Post-operative:</u><br>Recommended to give 2 doses of 40 IU/kg within the first 6 days after surgery.  | 13 previously treated adolescent or adult patients   | Mean = 38 years<br><br>Range = 15-56 years | Male   |
| Trial 3775<br><br>Extension trial to 3747 and 3773 | A multicentre, open label, non-controlled trial evaluating long-term safety and efficacy in routine prophylaxis and treatment of bleeds.<br><br>Four treatment arms: 10 or 40 IU/kg once weekly prophylaxis, 80 IU/kg once every second week prophylaxis, or on-demand treatment.<br><br>Free choice between available treatment arms, and switching of treatment arm during the trial was allowed. | <u>Prophylaxis:</u><br>10 or 40 IU/kg once-weekly, or 80 IU/kg once every second week.<br><br><u>Treatment of bleeds:</u><br>Mild and moderate bleeds treated with injection(s) of 40 IU/kg; severe bleeds treated with 80 IU/kg. | 71 previously treated adolescent or adult patients<br>- Prophylaxis at baseline: 66<br>- On-demand at baseline: 5                    | Mean = 32 years<br><br>Range = 14-66 years | Male   |

| Study #                           | Trial design  | Dosage, route of administration and duration <sup>a)</sup>  | Study subjects (n = number)  | Mean age (Range)                           | Gender |
|-----------------------------------|---|---|--|--|--------|
| Trial 3774<br><br>Pediatric trial | A multicentre, open-label, non-controlled trial evaluating safety, efficacy and PK in routine prophylaxis and treatment of breakthrough bleeds.<br><br>The trial contained a main phase of 52 weeks, followed by an extension phase. One treatment arm with 40 IU/kg once-weekly prophylaxis. | <u>Prophylaxis:</u><br>40 IU/kg once-weekly.<br><br><u>Treatment of bleeds:</u><br>Mild and moderate bleeds treated with injection(s) of 40 IU/kg; severe bleeds treated with 80 IU/kg. | 25 previously treated pediatric patients<br><br>PK: 25 previously treated patients.<br><br>22 previously treated patients continued into the extension phase of the trial. | Mean = 6.5 years<br><br>Range = 1-12 years | Male   |

a) Additional doses for treatment of bleeds could be given at the investigator's discretion.

b) Single-blind in this trial meant that patients on prophylaxis did not know whether they were randomised to the 10 IU/kg or the 40 IU/kg once-weekly prophylaxis arm. This information was also concealed from the investigator, however, as the investigator had the possibility to measure FIX activity levels during the trial, the investigator could potentially become unblinded.

## Study results

The completed clinical trial program included one phase 1 trial and four phase 3 multicentre, non-controlled trials. The objectives of the phase 3 trials were to evaluate the safety and efficacy of REBINYN<sup>®</sup> in routine prophylaxis, control and prevention 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  $\leq 200/\mu\text{L}$ , additional congenital or acquired coagulation disorders, previous arterial thrombotic events as well as 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).

*Pivotal Trial:* The pivotal trial included 74 adolescent (13 to 17 years) and adult (18 to 65 years) previously treated patients. The trial included one open-label on-demand arm with treatment for approximately 28 weeks and two prophylaxis treatment arms, with single-blind randomization to either 10 IU/kg or 40 IU/kg once-weekly for approximately 52 weeks.

*Extension trial:* There were 71 subjects from the pivotal trial and surgery trial that continued prophylaxis or on-demand treatment with REBINYN<sup>®</sup> 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 prophylaxis treatment with REBINYN<sup>®</sup> 40 IU/kg once-weekly for approximately 52 weeks.

*Surgery trial:* The surgery trial included 13 previously treated adolescent and adult patients in which subjects received one injection of REBINYN<sup>®</sup> 80 IU/kg on the day of a major surgery, and post-operatively, injections of 40 IU/kg at the investigator's discretion for up to 3 weeks after surgery.

#### Control and Prevention 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<sup>®</sup> 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 patient (for home treatment) or 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 when pooling all trials was 93.2% (551 out of 591).

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 2-1: Efficacy in control of bleeding episodes**

| <b>New Bleeding Episodes</b>   |                                 | <b>n = 597</b>    |             |                 |             |                |
|--|---------------------------------|-------------------|-------------|-----------------|-------------|----------------|
| <b>Number of injections to treat bleeding episodes</b>                       |                                 |                   |             |                 |             |                |
| 1 injection  | 521 (87.3%)                     |                   |             |                 |             |                |
| 2 injections   | 60 (10.1%)                      |                   |             |                 |             |                |
| 3 injections   | 8 (1.3%)                        |                   |             |                 |             |                |
| >3 injections  | 8 (1.3%)                        |                   |             |                 |             |                |
| <b>Median dose per injection (IU/kg) to treat a bleeding episode (range)</b> |                                 | 42.0 (20.3;94.0)  |             |                 |             |                |
| <b>Median total dose (IU/kg) to treat a bleeding episode (range)</b>         |                                 | 42.3 (20.3;444.7) |             |                 |             |                |
|  | <b>Number of treated bleeds</b> | <b>Excellent</b>  | <b>Good</b> | <b>Moderate</b> | <b>Poor</b> | <b>Missing</b> |
| <b>Severity of Bleeds</b>  |                                 |                   |             |                 |             |                |
| Mild / moderate  | 594                             | 199 (33.5%)       | 349 (58.8%) | 33 (5.6%)       | 7 (1.2%)    | 6 (1.0%)       |
| Severe   | 1                               | 1 (100.0%)        | -           | -               | -           | -              |
| Missing  | 2                               | 1 (50%)           | 1 (50%)     | -               | -           | -              |
| <b>Type of Bleeds</b>  |                                 |                   |             |                 |             |                |
| Spontaneous Bleeding episodes  | 369                             | 111 (30.1%)       | 225 (61.0%) | 26 (7.0%)       | 4 (1.1%)    | 3 (0.8%)       |
| Traumatic bleeding episodes  | 215                             | 84 (39.1%)        | 118 (54.9%) | 7 (3.3%)        | 3 (1.4%)    | 3 (1.4%)       |
| After major surgery  | 4                               | -                 | 4 (100.0%)  | -               | -           | -              |
| After minor surgery  | 3                               | 1 (33.3%)         | 2 (66.7%)   | -               | -           | -              |
| Other  | 6                               | 5 (83.3%)         | 1 (16.7%)   | -               | -           | -              |
| <b>Location of Bleeds</b>  |                                 |                   |             |                 |             |                |
| Gastrointestinal   | 1                               | 1 (100.0%)        | -           | -               | -           | -              |
| Genitourinary  | 8                               | 2 (25.0%)         | 6 (75.0%)   | -               | -           | -              |
| Joint  | 434                             | 128 (29.5%)       | 270 (62.2%) | 27 (6.2%)       | 5 (1.2%)    | 4 (0.9%)       |
| Mouth/gums/nose  | 18                              | 9 (50%)           | 7 (38.9%)   | 2 (11.1%)       | -           | -              |
| Mucosal  | 7                               | 6 (85.7%)         | 1 (14.3%)   | -               | -           | -              |
| Muscle/muscular  | 67                              | 29 (43.3%)        | 36 (53.7%)  | 2 (3.0%)        | -           | -              |
| Skin or soft tissue  | 14                              | 6 (42.9%)         | 7 (50.0%)   | 1 (7.1%)        | -           | -              |
| Subcutaneous   | 9                               | 5 (55.6%)         | 3 (33.3%)   | -               | 1 (11.1%)   | -              |
| Other  | 13                              | 7 (53.8%)         | 5 (38.5%)   | -               | -           | 1 (7.7%)       |
| Unknown location   | 26                              | 8 (30.8%)         | 15 (57.7%)  | 1 (3.8%)        | 1 (3.8%)    | 1 (3.8%)       |

In the pivotal trial in adolescent and adult subjects, there were 70 breakthrough bleeding episodes for 16 out of 29 subjects in the 40 IU/kg prophylaxis arm. The overall success rate for treatment of breakthrough bleeds was 97.1% (67 out of 69 evaluated bleeds). A total of 69 (98.6%) of the 70 bleeding episodes were treated with one injection.

In the on-demand arm there were 143 bleeding episodes in 14 out of 15 subjects. The overall success rate was 95.1% (135 out 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.

Twenty-eight of the thirty-four previously treated pediatric patients (1 to 17 years old) were treated with REBINYN<sup>®</sup> for 137 bleeding episodes. Results are provided in Table 2-2.

**Table 2-2: Efficacy in control of bleeding episodes in pediatric patients**

| <b>New Bleeding Episodes</b>   |                                 | <b>n = 137</b>    |             |                 |             |                |
|--|---------------------------------|-------------------|-------------|-----------------|-------------|----------------|
| <b>Number of injections to treat bleeding episodes</b>                       |                                 |                   |             |                 |             |                |
| 1 injection  |                                 | 114 (83.2%)       |             |                 |             |                |
| 2 injections   |                                 | 17 (12.4%)        |             |                 |             |                |
| 3 injections   |                                 | 4 (2.9%)          |             |                 |             |                |
| >3 injections  |                                 | 2 (1.5%)          |             |                 |             |                |
| <b>Median dose per injection (IU/kg) to treat a bleeding episode (range)</b> |                                 | 42.4 (20.3;86.8)  |             |                 |             |                |
| <b>Median total dose (IU/kg) to treat a bleeding episode (range)</b>         |                                 | 42.7 (20.3;217.0) |             |                 |             |                |
|  | <b>Number of treated bleeds</b> | <b>Excellent</b>  | <b>Good</b> | <b>Moderate</b> | <b>Poor</b> | <b>Missing</b> |
| <b>Severity of Bleeds</b>  |                                 |                   |             |                 |             |                |
| Mild / moderate*   | 137                             | 51 (37.2%)        | 79 (57.7%)  | 5 (3.6%)        | 1 (0.7%)    | 1 (0.7%)       |
| <b>Type of Bleeds</b>  |                                 |                   |             |                 |             |                |
| Spontaneous Bleeding episodes  | 58                              | 12 (20.7%)        | 41 (70.7%)  | 4 (6.9%)        | -           | 1 (1.7%)       |
| Traumatic bleeding episodes  | 74                              | 34 (45.9%)        | 38 (51.4%)  | 1 (1.4%)        | 1 (1.4%)    | -              |
| Other  | 5                               | 5 (100.0%)        | -           | -               | -           | -              |
| <b>Location of Bleeds</b>  |                                 |                   |             |                 |             |                |
| Gastrointestinal   | 1                               | 1 (100%)          | -           | -               | -           | -              |
| Genitourinary  | 4                               | 1 (25.0%)         | 3 (75.0%)   | -               | -           | -              |
| Joint  | 68                              | 20 (29.4%)        | 43 (63.2%)  | 5 (7.4%)        | -           | -              |
| Mucosal  | 7                               | 6 (85.7%)         | 1 (14.3%)   | -               | -           | -              |
| Muscle/muscular  | 22                              | 9 (40.9%)         | 13 (59.1%)  | -               | -           | -              |
| Skin or soft tissue  | 6                               | 2 (33.3%)         | 4 (66.7%)   | -               | -           | -              |
| Subcutaneous   | 9                               | 5 (55.6%)         | 3 (33.3%)   | -               | 1 (11.1%)   | -              |
| Other  | 7                               | 6 (85.7%)         | 1 (14.3%)   | -               | -           | -              |
| Unknown location   | 13                              | 1 (7.7%)          | 11 (84.6%)  | -               | -           | 1 (7.7%)       |

\*All bleeds were mild or moderate

### Routine Prophylaxis

The annualized bleeding rate for subjects who received prophylaxis treatment with REBINYN<sup>®</sup> in the main phase of the pediatric trial and the pivotal trial in adolescents and adults is summarized in Table 2-3.

**Table 2-3: Annualised bleeding rates in patients treated with a prophylactic dose of 40 IU/kg once weekly (Median (min; max))**

|                                      | Previously treated patients (Factor IX<2%) |                      |                      |                       |                               |
|--------------------------------------|--|----------------------|----------------------|-----------------------|-------------------------------|
|                                      | ≤ 6 years<br>N=12                          | 7-12 years<br>N=13   | 13-17 years<br>N=9   | 18-65 years<br>N=20   | Overall<br>1-65 years<br>N=54 |
| Annualised spontaneous bleeding rate | 0.00<br>(0.00; 1.00)                       | 0.00<br>(0.00; 4.11) | 0.00<br>(0.00; 0.97) | 0.00<br>(0.00; 37.78) | 0.00<br>(0.00; 37.78)         |
| Annualised traumatic bleeding rate   | 0.00<br>(0.00; 2.45)                       | 0.68<br>(0.00; 4.88) | 1.93<br>(0.00; 6.76) | 0.00<br>(0.00; 5.33)  | 0.00<br>(0.00; 6.76)          |
| Annualised joint bleeding rate       | 0.00<br>(0.00; 0.98)                       | 0.68<br>(0.00; 2.74) | 0.97<br>(0.00; 3.87) | 0.51<br>(0.00; 37.78) | 0.00<br>(0.00; 37.78)         |
| Annualised overall bleeding rate     | 0.00<br>(0.00; 3.00)                       | 2.00<br>(0.00; 6.51) | 1.93<br>(0.00; 6.76) | 1.03<br>(0.00; 37.78) | 1.03<br>(0.00; 37.78)         |

The pivotal trial included an evaluation of bleeds in target joints (defined as a joint with 3 or more bleeds within a period of 6 months). At baseline, there were 24 target joints in 15 subjects in the 40 IU/kg arm. During the trial, there were no bleeds in target joints for 10 of these subjects (66.7%). The number of target joints with no bleeds was 17 (70.8%).

### Perioperative Management

In a dedicated surgery trial, the efficacy analysis of REBINYN<sup>®</sup> in perioperative management included 11 major surgical procedures performed in 11 previously treated adult and adolescent patients. The procedures included 9 orthopedic and 2 surgeries in the oral cavity. The patients received 1 pre-operative injection of REBINYN<sup>®</sup> 80 IU/kg on the day of surgery, and post-operatively, injections of 40 IU/kg.

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 11 surgeries, for a success rate of 100%. A pre-operative dose of 80 IU/kg REBINYN<sup>®</sup> was effective and no patients required additional doses on the day of surgery. In the post-surgery period (Day 1 to 6 and Day 7 to 13), the median number of additional 40 IU/kg doses administered was 2.0 and 1.5, respectively. The mean total consumption of REBINYN<sup>®</sup> during and after surgery was 236 IU/kg (range: 81 to 460 IU/kg).

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

## **DETAILED PHARMACOLOGY**

See ACTION AND CLINICAL PHARMACOLOGY

## **TOXICOLOGY**

### **Preclinical safety data**

In repeat dose toxicity studies in rats and monkeys, 40 kDa polyethylene-glycol (PEG) was detected by immunohistochemical staining in connective tissue and epithelial cells of choroid plexus in the brain (see Table 2-4). This finding was not associated with tissue damage or abnormal clinical signs in the animal studies.

In distribution and excretion studies in mice and rats, the 40 kDa polyethylene-glycol (PEG) moiety of REBINYN<sup>®</sup> was shown to be widely distributed to and eliminated from organs, and excreted via plasma in urine (42–56%) and feces (28–50%).

### **Carcinogenicity, Genotoxicity, Reproductive Toxicity**

Studies concerning carcinogenicity, genotoxicity and reproductive toxicity in animals have not been performed.

An overview of the non-clinical toxicity studies is listed in Table 2-4.

**Table 2-4: Overview of toxicity studies**

| <b>Study Title</b>  | <b>Species</b>    | <b>Dose and Frequency</b>  | <b>Key Findings</b>  |
|---|-------------------|--|--|
| <b>Single Dose</b>  |                   |  |  |
| Single dose - comparison phase 1 and phase 3 batch [Study 210259] | Wistar rats       | Single i.v. dose of 200, 1000 and 2000 IU/kg                               | Doses up to 2000 IU/kg were well tolerated. No clinical signs and no macroscopic or microscopic findings. No difference in hematology, clinical chemistry or histopathology at any dose level or between batches.  |
| <b>Repeat Dose – Non Pivotal</b>                                  |                   |  |  |
| 6-week repeat dose [Study 212143]                                 | Rowett nude rat   | Twice weekly i.v. doses of 0, 40, 1200 IU/kg                               | No treatment related macroscopic or histopathological findings. PEG was detected in the cytoplasm of choroid plexus epithelial cells and in the choroid plexus connective tissue at the 1200 IU/kg twice weekly dose. This finding was not associated with tissue damage or abnormal clinical signs.   |
| 13-week repeat dose [Study 208405]                                | Cynomolgus Monkey | Once weekly i.v. doses of 200 IU/kg  | Six of 8 animals developed neutralizing antibodies with effect on exposure. Signs of acquired hemophilia were seen in 4 of 6 antibody positive animals. No other treatment related macroscopic or microscopic findings.  |
| <b>Repeat Dose – Pivotal</b>                                      |                   |  |  |
| 26- week repeat dose [Study 212513]                               | Rowett nude rat   | Intravenous doses of 0, 40, 150, 600, 1200 IU/kg every 5 <sup>th</sup> day | Doses from 40-1200 IU/kg every fifth day were well tolerated. A treatment related increase in PT was seen, normalizing during recovery. No anti-drug antibodies developed. PEG was detected in small vesicles in the cytoplasm in the choroid plexus epithelial cells and in macrophages in the mesenteric lymph nodes at the 1200 IU/kg dose. This finding was not associated with tissue damage or abnormal clinical signs.  |
| 4-week repeat dose [Study 208260]                                 | Cynomolgus Monkey | Weekly i.v. doses of 0, 350, 1300, 3750 IU/kg (5 doses in total)           | Mild and transient tremors were seen in animals given the highest dose. A treatment related increase in PT was seen, normalizing during recovery. Anti-drug antibodies were detected in the treatment free period. Decrease in aPTT was seen post dose and is an expected pharmacological effect of FIX. From Day 15 and on-wards a time and dose dependent increase in number of animals with an increase in aPTT > 38.1 s prior to dosing was seen; indicating development of neutralizing cross reacting antibodies. Five high dose animals were terminated early due to signs of bleeding simultaneous with an increase in aPTT, indicating development of |



| <b>Study Title</b>                             | <b>Species</b>    | <b>Dose and Frequency</b>                        | <b>Key Findings</b>  |
|--|-------------------|--|--|
|  |                   |  | acquired hemophilia. PEG was detected in the connective tissue of the choroid plexus and in the cytoplasm of a few choroid plexus epithelial cells at the 1300 or 3750 IU/kg dose. |
| <b>Genotoxicity</b>                            | Not performed     | NA   | NA   |
| <b>Carcinogenicity</b>                         | Not performed     | NA   | NA   |
| <b>Reproductive and Developmental Toxicity</b> | Not performed     | NA   | NA   |
| <b>Juvenile Toxicity</b>                       | Not performed     | NA   | NA   |
| <b>Local Tolerance</b>                         |                   |  |  |
| Local tolerance-<br>[Study 210439]             | Rabbit            | Single i.v.; i.a; perivenous dose of 0, 40 IU/kg | Some local clinical (hemorrhage/bruising and swelling) and microscopic reactions. Reactions were more pronounced after intraarterial administration.                               |
| 26- week repeat dose<br>[Study 212513]         | Rowett nude rat   | i.v. doses of 0, 40, 150, 600, 1200 IU/kg        | No treatment related local reactions.  |
| 4- week repeat dose<br>[Study 208260]          | Cynomolgus Monkey | i.v. doses of 0, 350, 1300, 3750 IU/kg           | No treatment related local reactions.  |

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## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PATIENT MEDICATION INFORMATION

#### REBINYN<sup>®</sup> Coagulation Factor IX (Recombinant), Pegylated

Read this carefully before you start taking REBINYN<sup>®</sup> and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REBINYN<sup>®</sup>.

#### What is REBINYN<sup>®</sup> used for?

REBINYN<sup>®</sup> is a pegylated recombinant coagulation factor IX product. Factor IX is a protein naturally found in the blood that helps stop bleeding.

REBINYN<sup>®</sup> is used to treat and prevent bleeding in patients with hemophilia B (also called congenital factor IX deficiency).

#### How does REBINYN<sup>®</sup> work?

In patients with hemophilia B, factor IX is missing or does not work properly. REBINYN<sup>®</sup> replaces this faulty or missing factor IX and helps blood to form clots at the site of bleeding. When you experience a bleed, REBINYN<sup>®</sup> is activated in the blood to form the naturally found factor IX.

#### What are the ingredients in REBINYN<sup>®</sup>?

Medicinal ingredients: Coagulation Factor IX (Recombinant), Pegylated

Non-medicinal ingredients: Histidine, mannitol, polysorbate 80, sodium chloride, sucrose.

#### REBINYN<sup>®</sup> comes in the following dosage forms:

REBINYN<sup>®</sup> is available in single-dose vials that contain nominally 500, 1000 or 2000 International Units (IU) per vial. After reconstitution with the supplied solvent (histidine solution), the prepared solution for injection will have the following concentration:

| Vial size | Approximate concentration after reconstitution |
|-----------|--|
| 500 IU    | 125 IU/mL                                      |
| 1000 IU   | 250 IU/mL                                      |
| 2000 IU   | 500 IU/mL                                      |

Each pack of REBINYN<sup>®</sup> contains a vial with white to off-white powder, a 4 mL prefilled syringe with a clear and colourless solution, a plunger rod and a vial adapter.

#### Do not use REBINYN<sup>®</sup> if:

You are allergic to the medicinal ingredient, or to any ingredient in the formulation (including hamster protein), or component of the container.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REBINYN<sup>®</sup>. Talk about any health conditions or problems you may have, including if you:**

- Are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or herbal medicines.
- Are pregnant or breast-feeding, or if you think that you may be pregnant or are planning to have a baby.

**Other warnings you should know about:**

#### Allergic reactions and development of inhibitors

There is a rare risk that you may experience a sudden and severe allergic reaction (e.g. anaphylactic reaction) to REBINYN<sup>®</sup>. Stop the injection and contact your doctor or an emergency unit immediately if you experience early signs of an allergic reaction (see Serious Side Effects table).

Your doctor may need to treat you promptly for these reactions. Your doctor may also do a blood test to check if you have developed factor IX inhibitors (activity-neutralizing antibodies) against your medicine, as inhibitors may develop together with allergic reactions. If you have such antibodies, you may be at an increased risk of sudden and severe allergic reactions (e.g. anaphylactic reaction) during future treatment with factor IX.

Because of the risk of allergic reactions with factor IX, your first injections with REBINYN<sup>®</sup> should be given in a medical clinic or in the presence of health care professionals where proper medical care for allergic reactions can be provided.

Talk to your doctor immediately if bleeding does not stop as expected, or if you experience a significant increase in your usage of REBINYN<sup>®</sup> in order to stop a bleed. Your doctor will do a blood test to check if you have developed inhibitors (activity-neutralizing antibodies) against REBINYN<sup>®</sup>. The risk for developing inhibitors is highest if you have not been treated with factor IX medicines before i.e. for small children.

#### Blood clots

Inform your doctor, if any of the following apply to you as there is an increased risk of blood clots during treatment with REBINYN<sup>®</sup>:

- You have recently had surgery.
- You suffer from other serious illness e.g. liver, heart disease, or cancer.

#### Kidney disorder (nephrotic syndrome)

There is a rare risk of developing a specific kidney disorder called “nephrotic syndrome” following high doses of factor IX in hemophilia B patients with factor IX inhibitors and a history of allergic reactions.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with REBINYN<sup>®</sup>:**

There are no known interactions of REBINYN<sup>®</sup> with other medicinal products.

**How to take REBINYN<sup>®</sup>:**

Treatment with REBINYN<sup>®</sup> should be started by a doctor who is experienced in the care of patients with hemophilia B. Always use REBINYN<sup>®</sup> exactly as your doctor has told you. Check with your doctor if you are not sure how to use REBINYN<sup>®</sup>.

REBINYN<sup>®</sup> is given as an injection into a vein. Please refer to the end of this insert for instructions on how to prepare and administer REBINYN<sup>®</sup>.

Your doctor will calculate your dose for you. The dose will depend on your weight and what the medicine is being used for.

**Usual dose:**Prevention of bleeding

The dose of REBINYN<sup>®</sup> is 40 international units (IU) per kg of body weight. This is given as one injection every week.

Treatment of bleeding

The dose of REBINYN<sup>®</sup> is 40 international units (IU) per kg of body weight. Depending on the location and the severity of the bleed you may need a higher dose (80 IU per kg) or extra injection(s). Discuss with your doctor the dose and number of injections you need.

Use in children and adolescents

For the prevention of bleeding episodes, REBINYN<sup>®</sup> is only indicated for use in adults (18 years of age and older).

For the treatment of a bleeding episode, REBINYN<sup>®</sup> can be used in children and adolescents. The dose in children and adolescents is the same dose as in adults.

**Overdose:**

If you think you have taken too much REBINYN<sup>®</sup>, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you forget a dose, inject the missed dose when you discover the mistake. Do not inject a double dose to make up for a forgotten dose. Proceed with the next injections as scheduled and continue as advised by your healthcare provider.

**Stopping Treatment:**

If you stop using REBINYN<sup>®</sup> you may no longer be protected against bleeding or a current bleed may not stop. Do not stop using REBINYN<sup>®</sup> without talking to your doctor

### What are possible side effects from using REBINYN®?

These are not all the possible side effects you may feel when taking REBINYN®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The following side effects have been observed with REBINYN®:

#### Common side effects (may affect up to 1 in 10 people)

- Itching (pruritus)
- Skin reactions at the site of injection

#### Uncommon side effects (may affect up to 1 in 100 people)

- Allergic reactions (hypersensitivity)

#### Side effects with unknown frequency (it is not known how often these happen)

- Anaphylactic reactions
- Activity-neutralizing antibodies (inhibitors)

Inhibitors (activity-neutralizing antibodies) have occurred in connection with severe and sudden allergic reaction (e.g. anaphylactic reaction).

| Serious side effects and what to do about them  |                                      |              |   |
|---|--------------------------------------|--------------|---|
| Symptom / effect  | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|   | Only if severe                       | In all cases |   |
| <b>RARE</b>   |                                      |              |   |
| <b>Allergic reaction (anaphylactic reaction):</b> Difficulty in swallowing or breathing; shortness of breath or wheezing; chest tightness; redness and/or swelling of the lips, tongue, face or hands; rash, hives, wheals or generalized itching; having pale and cold skin, fast heartbeat, and/or dizziness (low blood pressure) |                                      | ✓            | ✓   |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### **Reporting Side Effects**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

#### **3 ways to report:**

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
  - By calling 1-866-234-2345 (toll-free);
  - By completing a Consumer Side Effect Reporting Form and sending it by:
    - Fax to 1-866-678-6789 (toll-free), or
    - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 1908C  
Ottawa, ON  
K1A 0K9
- Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### **Storage:**

Keep REBINYN<sup>®</sup> out of the sight and reach of children.

Do not use REBINYN<sup>®</sup> after the expiry date which is stated on the carton, on the vial, on the vial adapter, and on the prefilled syringe labels. The expiry date refers to the last day of that month.

The powder in the vial appears as a white to off-white powder. Do not use the powder if the colour has changed.

### **Prior to Reconstitution**

Store in original package in order to protect from light. Do not freeze.

REBINYN<sup>®</sup> vials can be stored in the refrigerator (2°C – 8°C) up to the expiration date, or at room temperature (up to 30°C) for a single period not exceeding 6 months.

If you choose to store REBINYN<sup>®</sup> at room temperature:

- Note the date that the product is removed from refrigeration on the carton.
- Do not use after 6 months from this date or the expiration date listed on the carton, whichever is earlier.
- Do not return the product to the refrigerator after it has been stored at room temperature.

### **After Reconstitution**

Once you have reconstituted REBINYN<sup>®</sup> it should be used immediately. If you cannot use the reconstituted REBINYN<sup>®</sup> solution immediately, it should be used within 4 hours when stored at room temperature (up to 30°C) and within 24 hours when stored in a refrigerator (2°C – 8°C). Store the reconstituted product in the vial. If not used immediately the medicine may no longer be sterile and could cause infection.

The reconstituted solution will be clear and colourless. Do not use the reconstituted solution if you notice any visible particles or discoloration.

**If you want more information about REBINYN®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website <http://www.novonordisk.ca> or by calling Novo Nordisk Canada Inc., at: 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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## INSTRUCTIONS ON HOW TO USE REBINYN®

### **READ THESE INSTRUCTIONS CAREFULLY BEFORE USING REBINYN®.**

REBINYN® is supplied as a powder. Before injection (administration) it must be reconstituted with the solvent supplied in the syringe. The solvent is a histidine solution. The reconstituted REBINYN® must be injected into your vein (intravenous [i.v.] injection). The equipment in this package is designed to reconstitute and inject REBINYN®.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the REBINYN® package.

**Do not use the equipment without proper training from your doctor or nurse.**

**Always wash your hands and ensure that the area around you is clean.**

When you prepare and inject medication directly into the veins, it is important to **use a clean and germ free (aseptic) technique**. Improper technique can introduce germs that can infect the blood.

**Do not open the equipment until you are ready to use it.**

**Do not use the equipment if it has been dropped, or if it is damaged.** Use a new package instead.

**Do not use the equipment if it is expired.** Use a new package instead. The expiry date is printed on the outer carton, on the vial, on the vial adapter, and on the prefilled syringe.

**Do not use the equipment if you suspect it is contaminated.** Use a new package instead.

**Do not dispose of any of the items until after you have injected the reconstituted solution.**

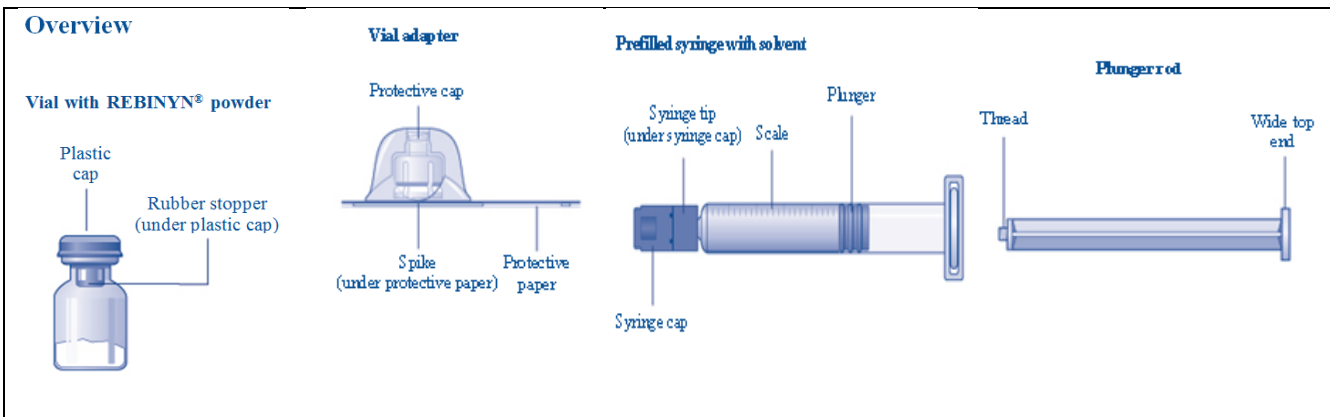
**The equipment is for single use only.**

### **Contents**

The package contains:

- 1 vial with REBINYN® powder
- 1 vial adapter
- 1 prefilled syringe with solvent
- 1 plunger rod (placed under the syringe)



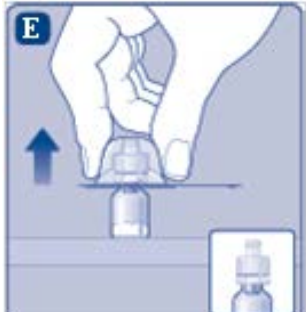
The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.



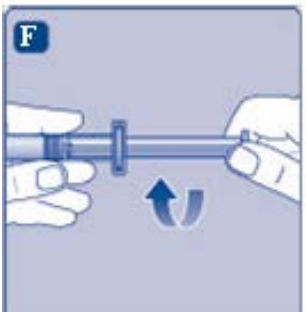
**1. Prepare the Vial and Syringe**



|                      |  |   |
|----------------------|--|---|
| <p><b>Step A</b></p> |  | <p><b>Take out the number of REBINYN® packages you need.</b></p> <p><b>Check the expiry date.</b></p> <p><b>Check the name, strength and colour</b> of the package, to make sure it contains the correct product.</p> <p><b>Wash your hands</b> and dry them properly using a clean towel or air dry.</p> <p>Take the vial, the vial adapter and the prefilled syringe out of the carton. <b>Leave the plunger rod untouched in the carton.</b></p> <p><b>Bring the vial and the prefilled syringe to room temperature.</b> You can do this by holding them in your hands until they feel as warm as your hands.</p> <p><b>Do not use any other way to warm</b> the vial and prefilled syringe.</p> |
| <p><b>Step B</b></p> |  | <p><b>Remove the plastic cap</b> from the vial. <b>If the plastic cap is loose or missing, do not use the vial.</b></p> <p><b>Wipe the rubber stopper with a sterile alcohol swab</b> and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible.</p> <p><b>Do not touch the rubber stopper with your fingers</b> as this can transfer germs.</p>   |

## 2. Attach the Vial Adapter



|               |   |  |
|---------------|---|--|
| <p>Step C</p> |    | <p>Remove the protective paper from the vial adapter.</p> <p>If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.</p> <p>Do not take the vial adapter out of the protective cap with your fingers. If you touch the spike on the vial adapter, germs from your fingers can be transferred.</p> |
| <p>Step D</p> |    | <p>Place the vial on a flat and solid surface.</p> <p>Turn over the protective cap, and snap the vial adapter onto the vial.</p> <p>Once attached, do not remove the vial adapter from the vial.</p>   |
| <p>Step E</p> |  | <p>Lightly squeeze the protective cap with your thumb and index finger as shown.</p> <p>Remove the protective cap from the vial adapter.</p> <p>Do not lift the vial adapter from the vial when removing the protective cap.</p>   |

## 3. Attach the Plunger Rod and the Syringe

|               |   |  |
|---------------|---|--|
| <p>Step F</p> |  | <p>Grasp the plunger rod by the wide top end and take it out of the carton. Do not touch the sides or the thread of the plunger rod. If you touch the sides or the thread, germs from your fingers can be transferred.</p> <p>Immediately connect the plunger rod to the syringe by turning it clockwise into the plunger inside the prefilled syringe until resistance is felt.</p> |
|---------------|---|--|

|                      |   |  |
|----------------------|---|--|
| <p><b>Step G</b></p> |  | <p><b>Remove the syringe cap</b> from the prefilled syringe by bending it down until the perforation breaks.</p> <p><b>Do not touch the syringe tip under the syringe cap.</b> If you touch the syringe tip, germs from your fingers can be transferred.</p> <p><b>If the syringe cap is loose or missing, do not use the prefilled syringe.</b></p> |
| <p><b>Step H</b></p> |  | <p><b>Screw the prefilled syringe securely</b> onto the vial adapter until resistance is felt.</p>   |

#### 4. Reconstitute the Powder with the Solvent

|                      |   |  |
|----------------------|---|--|
| <p><b>Step I</b></p> |  | <p><b>Hold the prefilled syringe slightly tilted</b> with the vial pointing downwards.</p> <p><b>Push the plunger rod</b> to inject all the solvent into the vial.</p>   |
| <p><b>Step J</b></p> |  | <p><b>Keep the plunger rod pressed down and swirl</b> the vial gently until all the powder is dissolved.</p> <p><b>Do not shake the vial as this will cause foaming.</b></p> <p><b>Check the reconstituted solution.</b></p> <p>It must be clear and colourless and free from particles that are clearly detectable. <b>If you notice visible particles or discoloration, do not use it.</b></p> <p>Use a new package instead.</p> |

**REBINYN<sup>®</sup> is recommended to be used immediately after it has been reconstituted.** This is because if left, the medicine may no longer be sterile and could cause infections.


**If you cannot use the reconstituted REBINYN<sup>®</sup> solution immediately,** it should be used within 4 hours when stored at room temperature (up to 30°C) and within 24 hours when stored in a refrigerator (at 2°C – 8°C). Store the reconstituted product in the vial.


**Do not freeze reconstituted REBINYN<sup>®</sup> solution or store it in syringes.**

**Keep reconstituted REBINYN<sup>®</sup> solution out of direct light.**



If your dose requires more than one vial, repeat step **A** to **J** with additional vials, vial adapters and prefilled syringes until you have reached your required dose.

|                      |  |   |
|----------------------|--|---|
| <p><b>Step K</b></p> |  | <p><b>Keep the plunger rod pushed completely in.</b></p> <p><b>Turn the syringe</b> with the vial upside down.</p> <p><b>Stop pushing the plunger rod and let it move back</b> on its own while the reconstituted solution fills the syringe.</p> <p><b>Pull the plunger rod slightly downwards</b> to draw the reconstituted solution into the syringe.</p> <p><b>In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted solution you withdraw, as instructed by your doctor or nurse.</b></p> <p>If, at any point, there is too much air in the syringe, inject the air back into the vial.</p> <p>While holding the vial upside down, <b>tap the syringe gently</b> to let any air bubbles rise to the top.</p> <p><b>Push the plunger rod</b> slowly until all air bubbles are gone.</p> |
|----------------------|--|---|

|                      |   |   |
|----------------------|---|---|
| <p><b>Step L</b></p> |  | <p><b>Unscrew the vial adapter</b> with the vial.</p> <p><b>Do not touch the syringe tip.</b> If you touch the syringe tip, germs from your fingers can be transferred.</p> |
|----------------------|---|---|

## 5. Inject the Reconstituted Solution

REBINYN<sup>®</sup> is now ready to inject into your vein.

- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 1 to 4 minutes.
- Do not mix REBINYN<sup>®</sup> with any other intravenous infusions or medications.

### Injecting REBINYN<sup>®</sup> via needleless connectors for intravenous (IV) catheters


**Caution:** The MixPro<sup>®</sup> prefilled solvent syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:

- Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 mL plastic syringe for withdrawal of the reconstituted solution. This should be done right after step J.
- If the CVAD line needs to be flushed before or after REBINYN<sup>®</sup> injection, use 0.9% Sodium Chloride solution for injection.

If you have encountered any problems with attaching the prefilled solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

## 6. Disposal

|                      |   |   |
|----------------------|---|---|
| <p><b>Step M</b></p> |  | <p><b>After injection, safely dispose</b> of all unused REBINYN<sup>®</sup> solution, the syringe with the infusion set, the vial with the vial adapter, and other waste materials as instructed by your healthcare provider.</p> <p>Do not throw it out with the ordinary household waste.</p> |
|----------------------|---|---|

**Do not disassemble the equipment before disposal.**

**Do not reuse the equipment.**