# Summary Basis for Regulatory Action

**Date:** May 31, 2017

**From:** Chava Kimchi-Sarfaty, Chair of the Review Committee <ESIG>

**STN#:** 125611/0

**Applicant Name:** Novo Nordisk, Inc.

**Date of Submission:** May 16, 2016

**Goal Date:** May 31, 2017

**Proprietary Name/ Established Name:** REBINYN, N9-GP, GlycoPEGylated rFIX

**Indication:**

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

**Recommended Action:**
The Review Committee recommends approval of this product.

**Review Office(s) Signatory Authority(ies):** Wilson Bryan, M.D., Office Director, Office of Tissues and Advanced Therapies

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

| **Document title** | **Reviewer name, Document date** |
|---|---|
| Clinical Review(s)<br>• *Clinical (product office)*<br>• *Postmarketing safety epidemiological review (OBE/DE)*<br>• *BIMO* | Megha Kaushal, M.D., M.S.H.S., OTAT/DCEPT<br><br>Ravi Goud, M.D., M.P.H., OBE/DE<br><br>Anthony Hawkins, M.S., OCBQ/DIS |
| Statistical Review(s)<br>• *Clinical data*<br>• *Non-clinical data* | Judy Li, Ph.D., OBE/DB |
| CMC Review(s)<br>• *CMC (product office)*<br>• *Facilities review (OCBQ/DMPQ)* | Chava Kimchi-Sarfaty, Ph.D., OTAT/DPPT<br>Nobuko Katagiri, Ph.D., OTAT/DPPT<br>Aikaterini Alexaki, Ph.D., OTAT/DPPT<br>Grainne Tobin, Ph.D., DBSCQ<br>Simleen Kaur, M.Sc., DBSCQ<br>Hsiaoling Wang, Ph.D., OCBQ/DBSQC<br>Jeremy Wally, Ph.D., OCBQ/DMPQ |
| Pharmacology/Toxicology Review(s)<br>• *Toxicology (product office)*<br>• *Developmental toxicology (product office)*<br>• *Animal pharmacology* | Becky Robinson-Zeigler, Ph.D., OTAT/DCEPT/PTB2<br>La'Nissa Brown-Baker, Ph.D., DABT, OTAT/DCEPT/PTB2 |
| Clinical Pharmacology Review(s) | Iftekhar Mahmood, Ph.D., OTAT/DCEPT |
| Labeling Review(s)<br>• *APLB (OCBQ/APLB)* | Kristine T. Khuc, Pharm.D., OCBQ/DCM/APLB |
| Other Review(s)<br>• *additional reviews not captured in above categories*<br>• *consult reviews* | Marie Anderson, M.S., Ph.D., OCBQ/DBSQC |
| Advisory Committee Transcript | |

1. Introduction

Novo Nordisk, Inc. has submitted an original Biologics License Application (BLA) to seek U.S. licensure for Coagulation Factor IX (Recombinant), GlycoPEGylated. The applicant uses the International Nonproprietary Name, nonacog beta pegol, mostly for the bulk drug substance (BDS), as well as the abbreviation, N9-GP, for the product. The proprietary name of the U.S. marketed product will be REBINYN. REBINYN is a lyophilized powder available in nominal dosage strengths of 500, 1000 or 2000 international units (IU) of recombinant Factor IX (hereafter, rFIX) potency. The product is reconstituted with the provided sterile Histidine Solution for intravenous administration.

The proposed indications are for adults and children with hemophilia B for: a) on-demand treatment and control of bleeding episodes; and b) perioperative management of bleeding.

2. Background

Hemophilia B is a blood clotting disorder caused by the deficiency or dysfunction in Factor IX. The activated form of Factor IX is a vitamin K-dependent serine protease, responsible for converting Factor X to its active form, Factor Xa. During blood clotting, Factor IX is activated by two distinct mechanisms: either by Factor XIa (intrinsic pathway) or FVIIa/tissue factor (extrinsic pathway). The activation of Factor IX results in the excision of the activation peptide that converts Factor IX into its active form, Factor IXαβ, where two polypeptide chains are linked together by a disulfide bond.

Factor IX is encoded by the *F9* gene, which is found on the X chromosome. As a result, hemophilia B is almost exclusively found in males, although heterozygous females may exhibit a mild form of the disease. The incidence of hemophilia B is estimated to be approximately 1 case per 25,000 - 30,000 male births and has a wide geographic and racial distribution.

The clinical hallmark of hemophilia is hemorrhage into the joints (typically the ankles in children, and the ankles, knees, and elbows in adolescents and adults) resulting in permanent deformities, misalignment, loss of mobility, and extremities of unequal lengths. With mild hemophilia, hemorrhage most likely occurs with trauma or surgery. The availability of virus-cleared, plasma-derived Factor IX concentrate, and its recombinant analogues, as effective treatment for bleeds and prophylaxis, has significantly improved outcomes in this disorder.

Treatment of hemophilia B requires regular infusions with Factor IX-containing preparations. FDA-approved products for the treatment of hemophilia B include recombinant Factor IX, plasma-derived Factor IX concentrates, and plasma-derived FIX complex. Also available are two long-acting rFIX fusion proteins, which allow the individual to infuse less frequently (on average, once every 7 days) in routine prophylaxis regimens.

The development of neutralizing anti-drug antibodies (often called “inhibitors” in coagulation literature) occurs in 3 - 5% of hemophilia B individuals. This is the most serious complication in the management of hemophilia B, and represents a major source of morbidity and mortality. The neutralizing anti-drug antibodies to a particular product often, though not always, cross-react with other Factor IX products, as well as the patient’s endogenous Factor IX.

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the REBINYN under the name REFIXIA, but the product has not yet been marketed in Europe.

This original BLA was reviewed under the PDUFA V program, which had a 12-month review schedule. The review milestones are listed in the table below:

**Review Milestones:**

| *Milestone* | *Date* |
|---|---|
| **Received** | June 3, 2016 |
| **Committee assignment** | June 13, 2016 |
| **Filing date** | July 15, 2016 |
| **Proprietary name review** | September 23, 2016 |
| **Inspections** | Waived |
| **Mid-cycle communication** | December 8, 2016 |
| **Late-cycle meeting** | February 14, 2017 |
| **Advisory Committee** | April 4, 2017 |
| **Action Due Date** | June 3, 2017 |

The evidence for safety and effectiveness for this product was collected under IND 14008. Key interactions were held with the FDA throughout the development process. In an End of Phase 2 meeting in October 2010, CMC agreements were made and clinical advice was given to the sponsor. The clinical advice included that routine prophylaxis would reduce the annualized bleeding rate (ABR) by at least 60%. For the safety co-primary endpoint, the trial design should be based on ruling out more than one subject forming an inhibitor in 50 subjects who have 50 exposure days to the product, at the 95% confidence level.FDA encouraged the applicant that each subject could serve as his own control. REBINYN was given orphan designation for the "routine prophylaxis" indication in 2012. In a pre-BLA meeting in April 2015, FDA stated that the "routine prophylaxis" indication may be blocked by exclusivity by Rixubis.

3. Clinical/Statistical/Pharmacovigilance

**a) Clinical Program**

To support licensure for the proposed indications, the clinical development program for REBINYN included data from three trials: a) Study 3747 - a phase 3 trial in adolescents and adults; b) Study 3773 - a surgery trial in adolescent and adults; c) Study 3774 - a pediatric trial for the following indication for adults and children: a) on-demand treatment and control of bleeding; b) routine prophylaxis for the treatment of bleeding episodes; and c) for perioperative management.

The routine prophylaxis indication is blocked by exclusivity by another Factor IX product until 2020; therefore, only on-demand treatment in Trial 3747 and 3774 is discussed below.

Study 3747 was a phase 3 multicenter, randomized study to evaluate the PK, efficacy, safety and immunogenicity of REBINYN in 74 adult and adolescent subjects to support routine prophylaxis and on-demand treatment. Subjects were randomized to once weekly prophylactic treatment with either 10 IU/kg or 40 IU/kg of REBINYN over a period of 12 months or at least 50 exposure days (EDs). Subjects were not randomized to the on-demand arm. There were 15 subjects exposed in the on-demand arm. There were a total of 345 bleeds (all were mild/moderate except one, classified as severe) in 55 subjects, which included subjects that were randomized in the routine prophylaxis arms. The majority of the bleeds were spontaneous (227/65.8%); 116 bleeds (33.6%) were traumatic bleeds and 0.6% were due to minor surgery. The most frequent location of bleeds was in a joint (78.5%). The majority of bleeds were treated by one injection (87%); 10.4% resolved with two injections and 2.6% resolved with ≥3 injections. The success rate for all bleeds (assessed based on a four-point scale for hemostatic response [excellent, good, moderate, and poor] until 8 hours after treatment) was 92.4% (95% CI: 87.0; 95.6). Successful outcomes for hemostatic efficacy assessment was defined as scoring excellent or good hemostatic response on the four point rating scale.
The hemostatic efficacy of REBINYN was considered acceptable if the lower bounds of the 95% CI exceeded 65%.
The clinical reviewer analysis confirmed this finding.

Study 3773 was a phase 3, multicenter, open-label, study to evaluate safety and efficacy during major surgical procedures in 13 adult and adolescents. Subjects received 80 IU/kg prior to the procedure and 40 IU/kg, if needed post-operatively. Per FDA analysis, nine of the 13 procedures were major procedures, and four were minor procedures. Hemostatic efficacy was defined as hemostatic response based on a rating scale of excellent, good, moderate and poor. The clinical reviewer rated perioperative hemostatic efficacy as excellent for ten surgeries and good for three surgeries. Postoperative blood loss was observed in seven subjects, which was expected, as in the accepted range for the type of surgery. The hemostatic effect of REBINYN during surgery was confirmed, as the success rate was 100%, with the expected quantity and duration of bleeding for the major surgeries.

The data from Studies 3747 and 3773 support the efficacy of on-demand bleeding treatment of acute bleeding and perioperative management. The dose of 80 IU/kg used for major surgeries can be extrapolated to treat major bleeds in on-demand use of this product.

Study 3774 was a phase 3, multicenter, open-label, study evaluating PK, safety, and efficacy of REBINYN when used for routine prophylaxis and treatment of breakthrough bleeding episodes in 25 children with Hemophilia B (FIX activity ≤2%). Fifteen subjects were treated for a total of 42 bleeds during the trial. In the older age group (7-12 years), 10 subjects experienced bleeds requiring treatment, whereas there were 5 subjects in the younger age group (0 to 6 years). Twenty-five of the bleeds were traumatic (60%), 13

were spontaneous (31%), and 4 were classified as of other origin (10%). All of the 42 bleeds were rated for hemostatic response with a success rate of 92.9%. The majority of bleeds (36 bleeds) resolved with 1 injection in both age groups.

*Bioresearch Monitoring*

The CBER Bioresearch Monitoring (BIMO) Branch issued inspection assignments for four clinical investigator study sites under Study 3747. Results from the BIMO inspections did not reveal problems that impact the data submitted in this application.

*Statistics*
The submission includes data from four completed studies on previously treated subjects.

In Study 3747, the hemostatic response rate for the treatment and control of bleeding episodes for subjects in both the prophylaxis treatment and on-demand treatment groups was 92.2% (95% CI: 86.9; 95.4). The lower limit of the two-sided CI meets the success criterion, i.e., above 65%.

In the pediatric study (Study 3774), the overall hemostatic efficacy success rate of REBINYN was 92.9%, and in the surgery study (Study 3773), the success rate was 100%.

None of the subjects in the four studies (Studies 3747, 3774, 3773 plus an extension study) developed inhibitory antibodies over 8785 exposure days. One death occurred but was unlikely to be related to REBINYN.

*Pharmacovigilance*
For the important identified risks (allergic reactions, and Factor IX inhibitor development) and important potential risks (thromboembolic events, nephrotic syndrome following immune tolerance induction, and inadequate treatment due to assay overestimation of Factor IX activity), routine pharmacovigilance activities are deemed adequate.
Regarding the important potential risk related to PEG accumulation, it was considered whether a postmarketing study of individuals who may have significant exposure to REBINYN through repeated administration of the product because of their acute intermittent use. However, it was determined that such a study would not be feasible to implement, and would be unlikely to gather useful information due to: the lack of a clearly defined threshold level at which one becomes concerned about REBINYN exposure; the difficulty of prospectively identifying patients who might receive frequent acute intermittent use; the difficulty in conducting the study in a manner that would permit baseline collection of data or the incorporation of an appropriate comparator group; and the low probability of collecting more extensive data than already collected in the preclinical trials.
Routine pharmacovigilance activities will be conducted.

**b) Pediatrics**

REBINYN triggered PREA for the on-demand and perioperative management indication.

The safety and efficacy of REBINYN was evaluated in Study 3773, as described above.

The Pediatric Review Committee concurred with the pediatric assessment made by the FDA reviewers. This assessment included the evaluation of all pediatric age groups (0-17 years for this BLA in Studies 3747, 3773 and 3774).

### c) Other Special Populations

N/A

4. Chemistry Manufacturing and Controls (CMC)

### a) Product quality

*Description*

REBINYN is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution, provided with 4 mL 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 labelled amount of Factor IX activity, expressed in international units. 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.

*Analytical Characterization*

REBINYN is a recombinant version of human Coagulation Factor IX (rFIX) on which a 40-kilodalton (kDa) polyethylene glycol (PEG) molecule is attached. The addition of the 40-kDa PEG moiety to rFIX is intended to increase its circulatory half-life. The rFIX protein is expressed in Chinese Hamster Ovary (CHO) cell line (b) (4) , and purified by several chromatographic steps. The 40-kDa PEG moiety is enzymatically attached to the N-linked glycans on rFIX with (b) (4) as a linker. The REBINYN product is then purified by (b) (4) to (b) (4)

With the use of (b) (4) , the primary structure of REBINYN was confirmed to correspond to the structure of native Factor IX and to be mostly mono-PEGylated (b) (4) forms are also present, as determined by (b) (4) and (b) (4)

*Impurities*

Adequate removal of product and process-related impurities by the commercial manufacturing process was demonstrated during process development and process validation.

Residual amounts of the following product and process-related impurities were characterized and monitored in (b) (4) drug product:

- Host cell and growth media-related impurities: CHO Host cell protein (tested by (b) (4)
- Process-related impurities: (b) (4)
- Product-related impurities: (b) (4)

*Drug Product Release Specification*

The applicant used characterization data and risk assessment to propose the final drug product release specification presented below, based on (b) (4) conformance lots. The release specifications in the table below are considered adequate to confirm product quality and manufacturing consistency.

**Final Drug Product (FDP) specifications: analytical procedures and acceptance criteria:**

| ***Test*** | ***Analytical procedure*** | ***Acceptance criteria*** |
|---|---|---|
| **Solid state** | | |
| **Appearance of powder** | Visual inspection<br>(b) (4) | Complies[1] |
| **Reconstitution time/solubility** | Visual inspection<br>(b) (4) | Complies[2] |
| **Water content** | (b) (4)<br>(b) (4) | (b) (4) |
| | (b) (4) | |

| | | |
|---|---|---|
| | (reference method)[3]<br>(b) (4) | |
| **Liquid state** | | |
| **Appearance of solution** | Visual inspection<br>(b) (4) | Complies[4] |
| (b) (4) | (b) (4) | (b) (4) |
| **Identity** | (b) (4) | Complies[5] |
| **Total impurities** | (b) (4) | Release limit: (b) (4)<br>Shelf life limit: (b) (4) |
| **rFIX** (b) (4) | | Release limit: (b) (4)<br>Shelf life limit: (b) (4) |
| **rFIX** (b) (4) | | Release limit: (b) (4)<br>Shelf life limit: (b) (4) |
| **PEG profile** | (b) (4) | Mono-PEG rFIX:<br>Release limit: (b) (4)<br>Shelf life limit: (b) (4)<br><br>(b) (4) rFIX:<br>Release limit: (b) (4)<br>Shelf life limit: (b) (4)<br><br>rFIX:<br>Release limit: (b) (4)<br>Shelf life limit: (b) (4) |
| **rFIX** (b) (4) | (b) (4) | Release limit: (b) (4)<br>Shelf life limit: (b) (4) |
| **Protein content** | (b) (4) | 500 IU: (b) (4) mg/mL |
| | | 1000 IU: (b) (4) |
| | | 2000 IU: (b) (4) |
| (b) (4) | (b) (4) | Release limit: (b) (4)<br>Shelf life limit: (b) (4) |
| **Potency** | One-stage clotting assay<br>*M056* | 500 IU:<br>Release limits: (b) (4)<br>Shelf life limits: (b) (4) |

| | | |
|---|---|---|
| | | IU/mL |
| | | 1000 IU:<br>Release limits: (b) (4) IU/mL<br>Shelf life limits: (b) (4) IU/mL |
| | | 2000 IU:<br>Release limits: (b) (4) IU/mL<br>Shelf life limits: (b) (4) IU/mL |
| | | 500 IU: (b) (4) |
| | | 1000 IU: (b) (4) IU/vial[6] |
| | | 2000 IU: (b) (4) IU/vial[6] |
| **Specific activity** | Calculated from One-stage clotting assay and (b) (4) *M056* (b) (4) | (b) (4) |
| (b) (4) **content** | (b) (4) | (b) (4) |
| **Polysorbate 80** | (b) (4) | (b) (4) |
| **Sucrose** | (b) (4) | (b) (4) |
| **Mannitol** | | (b) (4) |
| **Particulate matter** | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| **Bacterial endotoxins** | (b) (4) | (b) (4) |
| **Sterility** | (b) (4) *CFR 610.12* | Complies[7] |

[1] Complies means that the lyophilized powder appears as white to off-white.

[2] Complies means that the lyophilized powder dissolves within 10 minutes at 20 - 25°C

[3] The (b) (4) method is based on the (b) (4) method. The (b) (4) method will be used on samples out of the (b) (4) calibration range or with threshold values higher than the acceptance threshold for the (b) (4) method.
[4] Complies means that the reconstituted solution appears as a clear and colorless liquid and free from particles that are clearly detectable. The visual inspection is performed according to (b) (4) The analysis of Appearance of solution consists of three tests: Clarity, Color and Foreign insoluble matter.
[5] Complies corresponds to: (b) (4) of the sample is comparable to the (b) (4) of REBINYN reference material. The difference in retention time for (b) (4) of the REBINYN reference material and the samples must not be more than (b) (4)
[6] The unit IU/vial is (b) (4) (withdrawal volume)
[7] Complies means the product meets the requirement of test for sterility in (b) (4) 21 CFR 610.12

At each significant phase of pre-market development, product quality was linked to manufacturing control through a comparability program that integrated nonclinical animal studies and clinical trial experience with extensive analytical characterization.

*Process Description*

The manufacturing process of REBINYN starts with the (b) (4)

(b) (4)

The potency of REBINYN is measured using a Factor IX One-stage clotting assay. 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 underestimation of Factor IX activity level; therefore silica-based reagents should be avoided, as some may overestimate the activity of REBINYN. The primary standard is a highly purified REBINYN drug product which is calibrated against the WHO 4th International Standard for Factor IX Concentrate, 07/182.

*Critical process steps, parameters and their control*
The manufacturing process for REBINYN incorporates three manufacturing steps for the control of viruses: (1) testing for adventitious viruses performed on the cell culture (b) (4) (2) a solvent–detergent wash at the immunoaffinity capture step for virus inactivation, and (3) a 20 nm filtration step for virus exclusion.

The applicant assessed the process at manufacturing scale for removal of product- and process-related impurities.

*Process validation*
Three process performance qualification (PPQ) batches and the first (b) (4) commercial batches after the PPQ were validated for the manufacturing process. Three PPQ batches were also validated for the removal of process-related impurities. The drug product conformance lots are summarized in the tables below.

*Conformance lots manufacture*
**FDP Conformance Lots:**

| ***Lot Number*** | ***Potency*** | ***Date of Manufacture*** | ***Batch Size*** (b) (4) |
|---|---|---|---|
| (b) (4) | 500 IU | (b) (4) | |
| | 500 IU | | |
| | 500 IU | | |
| | 1000 IU | | |
| | 2000 IU | | |
| | 2000 IU | | |

*Viral Testing Controls and Clearance*
No animal- or human-derived raw materials are used in the manufacture of REBINYN. The viral safety evaluation on REBINYN (b) (4) is as follows:

1) Testing of all mammalian cell banks for the absence of infectious viruses:
MCB and WCB for the production of REBINYN are well controlled regarding the potential of viral contamination according to ICH Q5A. REBINYN is produced in a genetically modified CHO cell line (b) (4) . All the tests were found negative for the presence of viruses except for the expected presence of (b) (4) (b) (4) .
(b) (4)
.

2) Control of materials used in the manufacturing process:
The potential risk of adventitious virus or (b) (4) agent contamination is minimized in the manufacturing process of REBINYN. The cell line for the production of REBINYN has been adapted in a culture medium that does not contain additives of human or animal origin. No animal- or human-derived raw materials are added in the PEGylation process. Additionally, no raw materials or ingredients of human or animal origin are used in the formulation of REBINYN FDP.

3) Testing the capacity of the REBINYN purification process to clear viruses:
Two viral clearance steps are qualified in the manufacture of REBINYN (b) (4). The virus filtration (b) (4) 20 nm) in Step (b) (4) is a dedicated virus reduction step in the manufacture of REBINYN. The wash of the immunoaffinity chromatography column (b) (4) detergent in Step (b) (4) also contributes to viral inactivation. The viruses selected in the viral clearance studies for these steps at laboratory-scale include (b) (4)
(b) (4)

*Analytical Methods*
The lot-release test methods, including rFIXa (b) (4) Assay, (b) (4) , and tests for other critical impurities (b) (4) were adequately validated for suitability of their intended use.
The potency of REBINYN is measured using a Factor IX One-stage clotting assay. The primary standard is a highly purified REBINYN drug product which is calibrated against

the WHO 4th International Standard for Factor IX Concentrate, 07/182. The method was adequately validated for its intended use. The results of in-support testing for potency of the drug product were within specifications.

*Stability*

The proposed shelf-life for REBINYN FDP is 24 months when stored at 5 °C and 6 months at 30 °C. The proposed shelf-life of the BDS is for (b) (4). The available stability data indicate no critical trends during the observed long-term storage period.

REBINYN should be stored away from light.

### b) CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot release by CBER is not required for REBINYN because it is a well-characterized recombinant product. Thus, exemption of REBINYN from CBER Lot Release is justified. CBER has performed in-support testing of commercial scale REBINYN product lots of 500 IU, 1000 IU, and 2000 IU nominal potencies. Test results were deemed consistent with the proposed commercial release specifications.

### c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of REBINYN are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

**Manufacturing Facilities Table for** REBINYN**:**

| *Name/Address* | *FEI Number* | *DUNS Number* | *Inspection/ Waiver* | *Results/ Justification* |
|---|---|---|---|---|
| **Drug Substance Manufacturing** | | | | |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | Team Biologics (b) (4) VAI* |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | ORA (b) (4) NAI** |
| **Drug Product Manufacturing and Release Testing** | | | | |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | ORA (b) (4) NAI |
| **Diluent Manufacturing and Release Testing** | | | | |
| (b) (4) , | (b) (4) | (b) (4) | (b) (4) | Team Biologics (b) (4) VAI |

| | | | | |
|---|---|---|---|---|
| (b) (4) | | | | |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | ORA (b) (4) VAI |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | ORA (b) (4) NAI |

* NAI: No Action Indicated
** Voluntary Action Indicated

Team Biologics conducted surveillance inspections of the Novo Nordisk A/S manufacturing facility in (b) (4) from (b) (4), and the (b) (4) manufacturing facility in (b) (4) and ORA conducted a surveillance inspection of the (b) (4) manufacturing facility in (b) (4) from (b) (4). These inspections were all classified as VAI and all inspectional 483 observations were resolved.

The Office of Regulatory Affairs (ORA) also conducted surveillance inspections of the Novo Nordisk A/S manufacturing facility in (b) (4) from (b) (4), and the (b) (4) manufacturing facility in (b) (4) from (b) (4). These inspections were classified as NAI.

**Container Closure System**

The drug product container closure system consists of a 12 mL (b) (4) glass vial (supplied by (b) (4)), siliconized grey chlorobutyl rubber stopper (supplied by (b) (4) and snap-off aluminum and plastic cap (supplied by Novo Nordisk and (b) (4). Container closure integrity testing was performed by Novo Nordisk A/S on container closures sealed at the (b) (4) facility employing the (b) (4) method; all of the acceptance criteria were met.

The diluent container closure system consists of a siliconized (b) (4) glass syringe barrel (manufactured by (b) (4) syringe closure system (b) (4) bromobutyl rubber tip cap, (b) (4) luer lock and (b) (4) plastic sleeve; manufactured by (b) (4), and siliconized (b) (4) bromobutyl rubber plunger (manufactured by (b) (4) Container closure integrity testing was performed by (b) (4) on container closures sealed at the (b) (4) facility employing the (b) (4) method; all of the acceptance criteria were met.

**d) Environmental Assessment**

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as

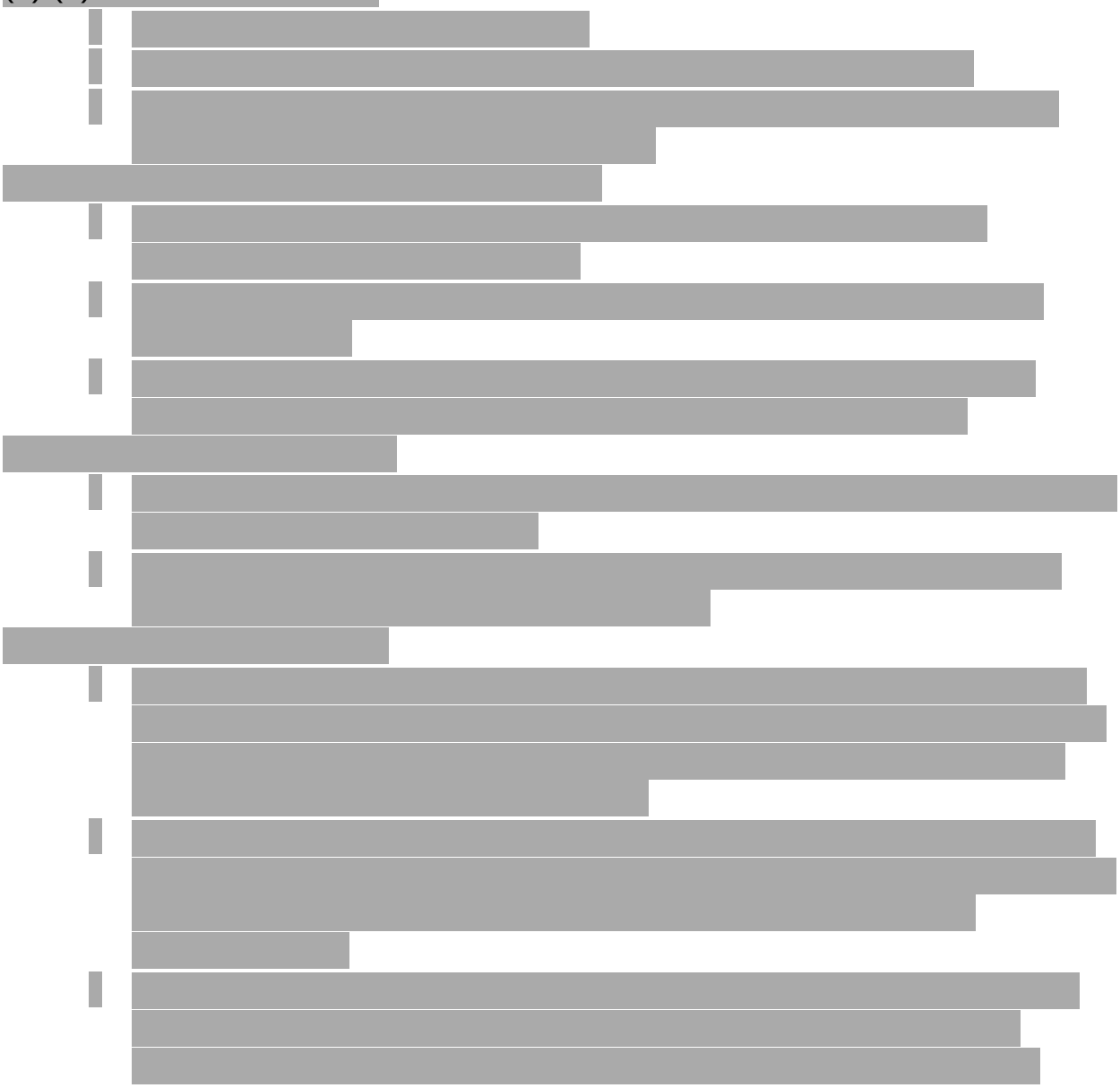
the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

**e) Product Comparability**

Manufacture of REBINYN BDS was modified during the development process to improve virus safety, overall yield and purity; Comparability studies show comparable quality of the product.

The changes that were introduced in each phase are outlined here:

(b) (4)



5. Nonclinical Pharmacology/Toxicology

The nonclinical program for REBINYN consisted of multiple proof-of-concept (POC) activity and safety studies. Safety pharmacology studies were conducted in murine and canine models of hemophilia, and in healthy cynomolgus monkeys. Pharmacokinetic (PK) studies included general PK and absorption, distribution, metabolism, and excretion (ADME) studies. Autoradiography studies were conducted to determine the distribution of REBINYN and the 40-kDa poly(ethylene glycol) (PEG) moiety. Local tolerance studies were also conducted in healthy rabbits.

For their definitive nonclinical safety studies, the applicant conducted single and repeat-dose toxicity studies in healthy Wistar rats and cynomolgus monkeys, and in immune-deficient, Rowett nude rats. These definitive nonclinical safety studies evaluated the proposed prophylactic clinical dose level of 40 IU/kg and dose levels ranging from five-fold to almost 100-fold higher than the clinical dose. The applicant conducted a second set of studies evaluating the toxicity of 40-kDa PEG alone in healthy cynomolgus monkeys and Wistar rats. All studies administered REBINYN using the intravenous (IV) route of administration, which is also the proposed clinical route of administration.

The majority of animals evaluated in the toxicity studies remained healthy until their scheduled sacrifice time point and had no overt signs of toxicity (e.g., irregularities in heart rate, body weight, food consumption, etc.). Any irregularities observed were transient, related to the species of the animal, or related to the development of cross-reacting neutralizing antibodies. These irregularities were not related to the REBINYN. However, the exception to this was monkeys administered 3750 IU/kg/week for four weeks.

In this four-week repeat-dose toxicity study, cynomolgus monkeys were administered REBINYN weekly for four weeks by bolus intravenous injection with dose levels equal to 350, 1300 and 3750 IU/kg. Six out of eight monkeys in the 3750 IU/kg/week dose level group exhibited mild but transient tremors. The cause of these tremors is unknown. Upon microscopic examination, five of these monkeys had substantial sub-meningeal congestion/hemorrhage in the brain, acute inflammatory cell infiltration in the spinal cord, and hemorrhage associated with cellulitis in the skin/subcutis. The hemorrhage observed in these animals was most likely related to the development of cross-reacting neutralizing antibodies, resulting in acquired hemophilia. This conclusion is based on the prolongation of activated partial thromboplastin time (aPTT) in most animals, confirmation of neutralizing antibodies during the recovery period, and the clinical and pathological signs associated with a bleeding tendency (i.e., signs of bruising and/or swelling and hemorrhage). It must also be noted that these animals were administered a dose level almost 100-fold higher than the proposed prophylactic clinical dose level of 40 IU/kg/week. Therefore, the likelihood of development of CNS tremors, cellulitis, and

meningeal hemorrhage following chronic administration of REBINYN in humans may be low.

The most notable observations in the histology of the animals in the toxicity studies were the accumulation of PEG in the choroid plexus and vacuolation in various organs. Vacuolation did not appear to be time- or dose-dependent, and was noted in control animals as well as animals dosed with REBINYN. Also, the majority of the observed vacuolation was minimal or slight, per the pathology reports. Furthermore, vacuolation was noted in a sparse number of animals, indicating no pattern. Vacuolation did not appear to cause any adverse structural effects to the cells, affect the metabolism of REBINYN, or result in adverse clinical effects, neurological or otherwise.

Accumulation of PEG in the connective tissue and cytoplasm of epithelial cells in the choroid plexus, and in blood within brain blood vessels was one of the most consistent observations in the histology. This observation was observed irrespective of the dose level of REBINYN, though to a lesser extent at the lowest dose administered. Although saturation occurs, PEG metabolism is a continuous process that eliminates PEG in a time- and dose-proportional manner. It is unclear how PEG accumulation in the choroid plexus could affect neurological function. The mechanism of clearance of PEG from the choroid plexus remains unknown. However, there were no neurological deficits observed in monkeys that were administered 350 or 1300 IU/kg/week for four weeks, even though PEG accumulation was observed in these animals. Although PEG accumulation was observed in the Rowett nude rat studies, no clinical abnormalities were detected. CSF samples were taken from Rowett nude rats administered REBINYN for 26 weeks, but these samples were not analyzed. Therefore, it is unclear whether accumulation of PEG in the choroid plexus is clinically important for patients using REBINYN for prophylaxis.

6. Clinical Pharmacology

The Clinical pharmacology program consisted of the following three Pharmacokinetic (PK) studies.

- A single-dose PK study in patients with hemophilia B in 15 adult male subjects (21-55 years of age) who received a single intravenous dose of 25 IU/kg, 50 IU/kg or 100 IU/kg REBINYN. Blood samples were collected till 168 hours. PK parameters were estimated by non-compartmental analysis.
- A multinational, multi-center, randomized, single-blind trial in which PK study was conducted in 17 patients (14-57 years of age) with hemophilia B. PK assessments of REBINYN were conducted at visit 2 (single-dose) and between visits 5-9 (multiple dose). Blood samples were collected till 168 hours and PK parameters were estimated by non-compartmental analysis.

- A multicenter, multinational, open-label, non-controlled, single-arm, trial evaluating safety, efficacy and pharmacokinetics of REBINYN in prophylaxis and on-demand treatment of bleeding episodes in previously treated children with hemophilia B. There were 25 patients in the PK study, 12 patients were in the age group of 0-6 years, and 13 patients were in the 7-12 years age group. Blood samples for PK study were taken till 168 hours following 40 IU/kg intravenous administration of REBINYN. The results of the study indicated that PK parameters such as half-life, AUC, and clearance of REBINYN were substantially different in children ≤12 years of age as compared with adults.

The following conclusions can be drawn from the aforementioned PK studies:

- The PK of REBINYN was linear over a dose range of 25-100U/kg. The mean half-life of REBINYN ranged from 83 to 110 hours. The half-life of REBINYN should be interpreted with caution because reported half-life of REBINYN is based on blood sampling till 168 hours.
- Following 10 IU/kg or 40 IU/kg single or multiple dosing of REBINYN, no difference in AUC, clearance and half-life was noted between single and multiple dosing, indicating that REBINYN did not accumulate in the systemic circulation following multiple dosing.
- Age has a substantial impact on the PK of REBINYN. On average, the half-life was approximately 13 hours and 7 hours shorter in children ≤6 years and 7-12 years of age, respectively, than adults. The body weight-adjusted clearance of REBINYN in children ≤6 years and 7-12 years of age was 100% and 50% higher than adults. Despite this high clearance in children, a dose of 40 IU/kg (also an adult dose) provided therapeutic benefit to children. The magnitude of difference in clearance between adult and children indicates that a REBINYN dose of <40 IU/kg (20-25 IU/kg) may provide therapeutic benefit to adult patients.

7. Safety

In Study 3747, the primary objective was to assess the incidence of Factor IX inhibitory antibodies (≥0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay). No subject developed inhibitory antibodies to Factor IX. There were 215 adverse events (AEs) in 60 subjects. Four serious AEs (SAEs) were reported, and judged not to be related to the study drug. No subjects were withdrawn due to AEs. There were no deaths. No thromboembolic events and no allergic reactions related to REBINYN occurred during the study.

In Study 3773, there were no deaths and no serious adverse events related to REBINYN. In Study 3774, the primary objective was to assess the incidence of Factor IX inhibitory antibodies No subject developed inhibitory antibodies to Factor IX. There were 250 AEs in 23 subjects. One serious AE was reported in one subject and not judged to be related to the study drug. No subjects were withdrawn due to AEs. There were no reported

deaths. No thromboembolic events and no allergic reactions related to REBINYN occurred during the study.

A total of 12 SAEs occurred in 11 subjects. One of the events was fatal (hepatocellular carcinoma, described above), and one event (skin ulcer) did not resolve completely. One SAE (hypersensitivity) was judged to be severe and related to REBINYN due to the temporal relationship with administration of the study drug. All other SAE's were unlikely related to the study drug.

A preclinical safety signal was noted during this review. Specifically, the nonclinical studies indicated PEG accumulation and vacuolation resulting from repeat REBINYN dosing. Moreover, accumulation of PEG and vacuolation were found in the choroid plexus and were present following repeat use in nonclinical studies. This finding in nonclinical studies raises the issue of the safety of REBINYN in humans. The clinical implications are unknown at this time. No clear safety signal from accumulation of PEG was observed in the clinical trials. The neurologic adverse events in the clinical studies were non-specific. Of particular concern may be the use of REBINYN in infants and children who have developing brains, and the use of REBINYN in patients who are cognitively impaired. Factors such as duration of use, cumulative dose, age of the patient, and related comorbidities may increase the neurologic risks to patients exposed to REBINYN. Upon review of the data from the clinical studies, it is unclear whether monitoring of neurologic function was adequate to detect all clinically important neurologic signs or symptoms or if this would be useful to mitigate any neurologic risks from REBINYN. Therefore, additional clinical studies may be necessary to assess the neurological risks to patients who require chronic use especially if future considerations for marketing approval for routine prophylaxis is planned.

Based on the risk/benefit profile including the duration of exposure and total dose necessary in this indication, it is reasonable to assume that the safety profile favors marketing approval of REBINYN for short-term use (on-demand treatment and perioperative management). However, the exposure to PEG accumulation in the animal studies is not available, and the clinical study was not designed to evaluate exposure to PEG toxicity. Therefore, prolonged exposure is not recommended and a specific duration of use cannot be included in the label.

8. Advisory Committee Meeting

The Blood Product Advisory Committee (AC) was convened on April 4th, 2017 to discuss the implications of preclinical findings noted during the review of this BLA. Specifically, this meeting was held to seek advice regarding the preclinical findings of PEG accumulation in the choroid plexus. Of interest was the Committee's assessment regarding safety in the intended population, particularly in the pediatric and elderly populations, and in the setting of chronic administration. The AC was asked to consider:

- Whether specific monitoring of neurologic/cognitive function should be done to evaluate for any clinical sequelae from PEG accumulation in the choroid plexus and

- Whether additional data are necessary to evaluate the significance of PEG accumulation in the choroid plexus.

Below are some of the opinions expressed by members of the Committee:

- The AC expressed concerns regarding the use of REBINYN for routine prophylaxis in the pediatric (less than 2 years of age) and elderly populations, but commented that no arbitrary age cutoff should limit the use of the product.
- If postmarketing neurocognitive assessments are conducted, they should use a standardized approach.
- If additional preclinical testing is necessary, such studies could be done post-approval.
- No concerns were raised regarding the short-term use of REBINYN (perioperative and on-demand treatment).

9. Other Relevant Regulatory Issues

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests, teleconferences, and advice from the Advisory Committee. There were no other relevant regulatory issues.

10. Labeling

The proposed proprietary name, REBINYN, was reviewed by the Advertising and Labeling Branch (APLB), and found to be acceptable on September 23, 2016. On October 04, 2016, the product office determined REBINYN to be acceptable as the proprietary name for the product.

The product labeling (i.e., prescribing information, patient package insert, instructions for use) and the product carton and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers and by the APLB from a comprehension and promotional perspective.

Key statements regarding the nonclinical safety data were also included in the Warning and Precautions section (monitoring of neurocognitive function) and the potential risks in the pediatric and geriatric population.

The final version of the Full Prescribing Information (FPI) was determined to be acceptable. Carton and container labels were considered acceptable. A copy of the FPI is attached.

11. Recommendations and Risk/ Benefit Assessment

**a) Recommended Regulatory Action**

The review committee recommends the approval of the BLA for Coagulation Factor IX (Recombinant), GlycoPEGylated, under the proprietary name of REBINYN, for the

following indication to treat children and adults with hemophilia B (congenital Factor IX deficiency) for:

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

### b) Risk/ Benefit Assessment

The benefits of REBINYN are:

- On-demand REBINYN is effective for treatment of, and prevention of, spontaneous or traumatic bleeding in patients with Hemophilia B.
- REBINYN is effective in the perioperative setting for reduction of bleeding during surgery.
- REBINYN is effective in all age groups.

The risks of REBINYN are:

- Based on the animal data, there may be risks due to PEG accumulation in the choroid plexus. The nature and frequency of these risks, if any, are unknown. However, there is concern that REBINYN could be associated with neurologic dysfunction, particularly in pediatric patients undergoing cognitive development and elderly patients who may have baseline cognitive difficulties.
- Although no reports of inhibitory antibodies to REBINYN were noted in Studies 3747, 3773 and 3774, these antibodies have been reported as part of the IND safety reporting in the ongoing study in previously untreated patients (PUPs). The quantification of the risks in PUPs will be completed after completion of this study. The risks from inhibitory antibodies are expected as with the class of recombinant FIX products for treatment of Hemophilia B.
- Overall, there were no serious adverse events related to REBINYN. The risk of development of inhibitory antibodies is considered an expected adverse event. The potential for neurologic risks from REBINYN were considered when making the recommendation in favor of a marketing approval for REBINYN for short-term use. Clinical judgment was exercised due to the paucity of safety data to assess this neurological risk, when making a recommendation to support a marketing approval of REBINYN for short-term use. These clinical considerations included a) the lower risk for PEG accumulation given the short-term use in both pediatric and adult patients, and b) the recommendations with regard to short-term use from the members of the Advisory Committee. In addition, given the uncertainties of neurological risks with long-term use, the prescribing information for REBINYN includes a limitation of use statement related to routine prophylaxis and neurological considerations for chronic use and use in pediatric and geriatric age groups.

Available therapies for Hemophilia B:
Two other long-acting drugs are available with once weekly dosing and similar Annualized Bleeding Rates (ABR).

Considering that the clinical studies were not designed to investigate the possible clinical effects of PEG accumulation/vacuolation, no clear safety signal from

accumulation of PEG was observed. It is unclear whether monitoring of neurologic function, including neurocognitive assessments, would be useful to mitigate any neurologic risks from REBINYN during long-term use. However, the benefits of short-term use of REBINYN are sufficient to justify the risks.

### c) Recommendation for Postmarketing Activities

The possibility of postmarketing studies or REMS was considered for Rebinyn. A postmarketing study for exposure from repeated administration of the product through acute intermittent use, as discussed in the pharmacovigilance section, was determined to not be necessary. The concerns and recommendations of the AC for potential PEG accumulation with prophylactic use, and the usefulness of postmarketing studies to monitor for potential adverse events, were also considered. Since the product is being approved for the following short-term uses: on-demand treatment and control of bleeding, and perioperative management of bleeding, but not for prophylactic use, a postmarketing study or REMS is not necessary.

The product will be under routine pharmacovigilance.