Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE)
From:	Ravi Goud, MD MPH Medical Officer, Analytic Epidemiology Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Novo Nordisk Inc
Product:	REBINYN (nonacog beta pegol (N9-GP))
STN:	125611/187
Indication:	For use in adults and children with hemophilia B for: • on-demand treatment and control of bleeding episodes • perioperative management of bleeding
Meeting Date:	Pediatric Advisory Committee Meeting, April 2020

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the initial approval of BLA 125611/0 for REBINYN on May 31, 2017.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

REBINYN (nonacog beta pegol (N9-GP)) is a glycopegylated recombinant human factor IX (rFIX) product that is administered intravenously. A 40 KDa polyethylene glycol (PEG) moiety is covalently attached to the activation peptide of rFIX. The PEGylation performed at the activation peptide results in an inactive molecule circulating in the body with a long plasma half-life. N9-GP is expressed by a genetically engineered Chinese hamster ovary (CHO) cell line, which produces rFIX into the cell culture medium.

1.3 Regulatory History

FDA approved REBINYN on May 31, 2017 for use in adults and children with hemophilia B for:

- on-demand treatment and control of bleeding episodes
- perioperative management of bleeding

EMA approved Rebinyn June 2, 2017. EMA granted marketing authorization for nonacog beta pegol under Trade Name Refixia, and their approval is broader than the US with approval for prophylaxis as well as treatment, but EMA limited use to 12 years and older due to neurodevelopment concerns from PEG accumulation observed in animal studies.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS) reports for REBINYN from May 31, 2017 to September 30, 2020 (PAC review period)
- Manufacturer's Submissions
    - REBINYN US package insert, dated June 30, 2020
    - Sponsor response to information request regarding dose distribution data, dated October 30, 2020

- Pharmacovigilance Plan, dated October 27, 2016

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for REBINYN since licensure.

4 PRODUCT UTILIZATION DATA

Novo Nordisk provided distribution data for the US and worldwide for the time interval from May 31, 2017 to September 30, 2020:

U.S. Distribution Data (IU)	Worldwide Distribution Data (IU)
9,566,000	67,776,500

IU = International Unit

These data were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review. The manufacturer stated that patient ages and their specific type of treatment is not available, so it is not possible to disaggregate exact patient exposures for adult and pediatric populations.

The manufacturer did provide estimates on exposure in the US and worldwide based on assumptions of the annual bleeding rate (ABR), the approved indication in the country, an average dose of 40 IU/kg, and average pediatric weight of 50kg, and adult weight of 70kg. The manufacturer estimated 92 patient-years of exposure (PYE) in the US pediatric population and 147 PYE in the US adult population compared to 104 pediatric PYE and 391 adult PYE worldwide.

The estimate of the number of patients is an approximation because all distributed doses may not have been administered to patients. Dose adjustment, baseline FIX levels, indication, and off-label use may impact this estimation.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) for REBINYN (version 1, dated 27 Oct 2016) describes the important identified risks, important potential risks, and missing information for REBINYN.

Table 1: REBINYN Safety Concerns and Planned Pharmacovigilance Actions

Areas requiring confirmation or further investigation	Proposed routine and additional pharmacovigilance activities	Objectives
Important identified risk: Allergic/hypersensitivity reactions		
Incidence and clinical significance of allergic reactions	• Routine pharmacovigilance activities, including hypersensitivity questionnaire (Annex 7A). • Ongoing trials: NN7999-3774, NN7999-3895	To assess and characterize the risk of allergic reactions associated with nonacog beta pegol.
Important identified risk: FIX inhibitors		
Incidence and clinical significance of FIX inhibitor development	• Routine pharmacovigilance activities, including FIX inhibitor questionnaire (Annex 7B). • Ongoing trials: NN7999-3774, NN7999-3895	To assess and characterize the risk of FIX inhibitor development with nonacog beta pegol.
Important potential risk: Thromboembolic events		
Incidence and clinical significance of thromboembolic events	• Routine pharmacovigilance activities, including targeted follow-up questions (Annex 7C). • Ongoing trials: NN7999-3774, NN7999-3895	To assess and characterize the risk of thromboembolic events with nonacog beta pegol.
Important potential risk: Nephrotic syndrome following ITI		
Incidence and clinical significance of nephrotic syndrome following ITI	Routine pharmacovigilance activities	To assess and characterize the risk of nephrotic syndrome with nonacog beta pegol when used for ITI.
Important potential risk: Inadequate treatment due to assay overestimation of FIX activity		
Incidence and clinical significance of inadequate treatment due to assay overestimation of FIX activity	Routine pharmacovigilance activities	To assess and characterize the risk of inadequate treatment with nonacog beta pegol due to assay overestimation of FIX activity, by capturing the consequences of assay overestimation such as lack of effect and medication error.
Important potential risk: Accumulation of PEG after long-term treatment		
Incidence and clinical significance of adverse reactions from PEG accumulation	• Routine pharmacovigilance activities including targeted follow-up questions regarding renal impairment (Annex 7C). • Collection of data relating to use of nonacog beta pegol in the EUHASS registry.	To assess and characterize the potential risk of PEG accumulation after long-term treatment.

EUHASS: European Haemophilia Safety Surveillance System

5.2 Postmarketing Studies

FDA did not ask the manufacturer to conduct any safety-related post marketing studies as part of its approval.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of REBINYN between May 31, 2017 (PAC trigger) to September 30, 2020. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of AE reports for REBINYN during the PAC review period are listed in Table 2 below. There were 47 US and 72 foreign reports for review during the period from March 16, 2016 to September 30, 2020.

Table 2: FAERS Reports for REBINYN during March 16, 2016 to September 30, 2020 (PAC review period)

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	1	0	0	0	0	0	1	0
≥18 years	0	2	0	0	0	0	0	2
Unknown	0	1	0	0	0	0	0	1
All ages	1	3	0	0	0	0	1	3

Note: Serious non-fatal adverse events include otherwise medically important conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.

6.2.1 Deaths

There were no reported deaths following REBINYN during the PAC review period submitted to FAERS.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 4 serious, non-fatal reports. The pediatric report is of a literature case describing a 2- month old that developed an inhibitor, but upon review of the article, the patient did not seem to have actually received Rebinyn. Among the other reports, 2 reported incidental events or pathology not related to Rebinyn administration (surgery and osteomyelitis/sepsis). The remaining report described the nonspecific symptoms of dizziness and shortness of breath without identifying any other specific pathology.

6.2.3 Non-serious Reports

During the reporting period, there were no non-serious reports.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of REBINYN were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis of November 15, 2020. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. The Empirica Signal Product Name (S) run did not identify any preferred terms (PTs) that were disproportionately reported.

6.4 Periodic safety reports

The manufacturer's post marketing periodic safety reports for REBINYN were reviewed. The adverse events reported were consistent with those seen in FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database was conducted with the search terms "REBINYN" and "SAFETY," limited by human species, and dates from licensure (May 31, 2017) to date of search (January 12, 2021). No new safety concerns for REBINYN were identified in the review of these publications, which are summarized in the table below:

Publication	Authors' Safety Conclusion
Ezban M, Hermit MB, Persson E. FIXing postinfusion monitoring: Assay experiences with N9-GP (nonacog beta pegol; Refixia(®) ; Rebinyn(®)). Haemophilia. 2019 Jan;25(1):154-161. doi:	Pegylation affects interpretation of aPTT test results, so article describes methods to accurately assess Rebinyn activity.

10.1111/hae.13671. Review. PubMed PMID: 30664825.	
Sternebring O, Gabel-Jensen C, Jacobsen H, Benie AJ, Bjørnsdottir I. Steady-State Plasma Concentrations of Polyethylene Glycol (PEG) are Reached in Children and Adults During Once-Weekly Prophylactic Treatment with Nonacog Beta Pegol (N9-GP). BioDrugs. 2019 Sep 23. doi: 10.1007/s40259-019-00380-3.	Study examining plasma PEG levels with long-term prophylactic treatment. It found steady state plasma levels that correlated with FIX activity. No new safety issues were identified. Study states that no further PEG accumulation was observed, but the study did seem to collect any new data beyond the data that were submitted in clinical trials as part of the original approval application.
Carcao M, Kearney S, Lu MY, Taki M, Rubens D, Shen C, Santagostino E Long-Term Safety and Efficacy of Nonacog Beta Pegol (N9-GP) Administered for at Least 5 Years in Previously Treated Children with Hemophilia B. *Thromb Haemost*. 2020;120(5):737-746. doi:10.1055/s-0040-1709521	This is a follow-up study with 17 subjects followed and treated for a median of 5.6 years. It demonstrated no inhibitor development, and that steady state plasma PEG levels were achieved after 6 months. Low Annual Bleeding Rates (ABR) were also observed. General neurological monitoring did not reveal significant new findings, but one subject did have Tourettes. Reported AEs did not suggest a new safety concern.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for REBINYN does not indicate any new safety concerns. The PAC review was initiated due to initial approval of REBINYN in adults and children on May 31, 2017. There were no pediatric deaths. Review of reports did not identify a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of REBINYN.