

## **MEMORANDUM**

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**FDA / CBER / OTAT / DCEPT**

**BLA 125611/0**

**Submission date** May 16, 2016

**Review date** May 26, 2017

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<b>Regulatory Project Manager</b>	Edward Thompson
<b>Applicant</b>	Novo Nordisk, Inc.
<b>Product/Trade Name</b>	Coagulation Factor IX (Recombinant), glycoPEGylated/REBINYN
<b>Proposed Indication</b>	<ul style="list-style-type: none"><li>• On- demand treatment and control of bleeding episodes</li><li>• Perioperative management of bleeding</li></ul>
<b>Recommendation</b>	Approval

**Executive Summary**

Novo Nordisk, Inc. submitted this Biologics License Application (BLA) to seek U.S. licensure for Coagulation Factor IX (Recombinant), GlycoPEGylated (REBINYN). The proposed indications are for 1) on-demand treatment and control of bleeding episodes; 2) perioperative management of bleeding and 3) routine prophylaxis in adults and children with hemophilia B, a blood clotting disorder caused by the deficiency or dysfunction in Factor IX.

Please see primary reviews from Dr. Megha Kaushal (clinical), Dr. Judy Li (statistical), Drs. Brown-Baker and Robinson-Zeigler (pharmacology/toxicology), and Dr. Ravi Goud (pharmacovigilance) for detailed reviews of this original BLA. The review team recommends approval of this BLA for 1) on-demand treatment and control of bleeding episodes and 2) perioperative management of bleeding. The routine prophylaxis is not recommended at this time as it is blocked by exclusivity. Additionally, findings of PEG accumulation in the choroid plexus in animals raised potential concerns for neurocognitive sequelae in humans, which could warrant additional preclinical/clinical data to support this indication.

I concur with the review team's recommendation on approval of the BLA for the indications of on-demand treatment of bleeding episodes and perioperative management of bleeding.

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**Notable Review Issues**

Although, the nonclinical and clinical programs for REBINYN support the proposed indications of on-demand treatment and perioperative management of bleeding, some concerns were raised regarding nonclinical findings from the animal toxicity studies.

The definitive nonclinical safety studies included single and repeat-dose toxicity studies in healthy, immune-competent Wistar rats and cynomolgus monkeys, and in immune-deficient, Rowett nude rats as well as studies evaluating the toxicity of 40-kDa PEG alone in healthy cynomolgus monkeys and Wistar rats.

The most notable histologic findings in the animal toxicity studies were vacuolation in various organs and the accumulation of PEG in the choroid plexus. As vacuolation did not appear to be time- or dose-dependent, and was noted in control animals as well as animals dosed with REBINYN, this finding may not be a clinically significant observation. However, accumulation of PEG in the connective tissue and cytoplasm of epithelial cells in the choroid plexus, was the most consistent finding, and was observed irrespective of dose level. The clinical implications of this finding are unclear; however, there is concern that chronic use in humans as in the scenario of routine prophylaxis, could potentially result in neurocognitive impairment in young children with developing brains as well as adult patients with cognitive dysfunction.

Although no significant neurocognitive issues were noted in the 3 clinical studies that provided the primary evidence of safety/effectiveness of REBINYN, the studies were not specifically designed to evaluate neurocognitive function.

An Advisory Committee meeting was convened on April 4, 2017 to seek the AC's feedback on 1) the clinical relevance of the findings of PEG accumulation in the choroid

plexus of animals and 2) whether additional preclinical/clinical data would be warranted for the further evaluation of these findings. The Advisory Committee noted some concerns regarding the findings, especially for the use of REBINYN in young pediatric patients with developing brains as well as the elderly population with cognitive impairment. The concerns were pronounced for the proposed routine prophylaxis indication due to the chronic nature of use. Approval for the on-demand treatment and perioperative management of bleeding was recommended. However, the potential for additional preclinical/clinical data to support the routine prophylaxis use was also recommended as a consideration.

In general, the AC feedback was consistent with the FDA review team's assessment of the animal toxicity findings and the potential clinical implications with chronic use.

### **Recommendations**

Approval is recommended for the on-demand treatment and perioperative management of bleeding as the clinical evidence provided in this BLA supports the safety/effectiveness of REBINYN for these indications. Notwithstanding that the routine prophylaxis indication is blocked by exclusivity, the animal findings warrant additional discussion with the Applicant regarding consideration for additional preclinical/clinical data to support the routine prophylaxis indication.