

Our Reference: BLA 125611/0

Novo Nordisk Inc.  
Attention: Ms. Patricia D. Wilson  
December 5, 2016  
Sent by email

Dear Ms. Wilson:

We are reviewing your May 16, 2016 biologics license application for Coagulation Factor IX (Recombinant), GlycoPEGylated. We are providing the following comments and request for additional information to continue our review:

1. Based on the available nonclinical data provided in the submission, we continue to be concerned about the effects of poly(ethylene glycol) (PEG) accumulation in the brain in humans following dosing with REBINYN. In addition, the risk of dysfunction of the choroid plexus, with potential adverse effects on neurological function is unknown, and such adverse effects could be difficult to adequately assess in humans. Furthermore, no new relevant data are available that could provide reassurance regarding the potential impact of PEG accumulation on brain development in infants and children. Lastly, the possible consequences of accumulation of PEG in other tissues after long-term treatment, with potential safety implications, cannot be excluded with reasonable certainty. Hence, a risk remains with regard to the impact of PEG accumulation in patients' tissues. To permit further evaluation of this risk, please provide the following information in an amendment to the BLA:
  - a. A benefit-risk analysis on chronic exposure to REBINYN, and possible accumulation of PEG in the brain and other tissues.
  - b. Data demonstrating PEG exposure in humans versus animals (e.g., area under the curve following repeat dosing of REBINYN, adjusted for dose).
  - c. A discussion on the nature and feasibility of any potential risk-mitigation strategies that could address the risk of vacuole formation of the choroid plexus in pediatric and adult patients.
  - d. Data to substantiate the statement in Table 2-24 (pages 49 and 50) of your Risk Management Plan (Amendment 15, submitted 10/31/2016) that accumulation of PEG in peripheral organs in humans will achieve steady state after approximately 1 year of dosing, and in the choroid plexus at 2.5 years after dosing with REBINYN.

The review of this application is on-going and issues may be added, expanded upon, or modified as we continue the review.

Please submit your response and your notification of the shipment for this request as an amendment to this file by December 19, 2016 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is June 3, 2017.

Please send an acknowledgement message for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,  
Edward Thompson  
Regulatory Project Manager  
FDA/CBER/OTAT/DRPM

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Thank you.