



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Division of Epidemiology (DE)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**To:** Chava Kimchi-Sarfaty PhD  
Chair of the Review Committee

**Through:** Deepa Arya MD, MPH, MBA  
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(stamped by Division Director in place of Dr. Arya)

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**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** Novo Nordisk

**Product:** Rebinyn®, Nonacog beta pegol (N9-GP), is a glycopegylated recombinant human factor IX

**Application Type/Number:** BLA/ STN 125611/0.0

**Proposed Indication:** Nonacog beta pegol is indicated in adults and children with haemophilia B for control and prevention of bleeding episodes, perioperative management and routine prophylaxis.

**Submission Date:** June 3, 2016

**Action Due Date:** June 3, 2017

## 1. Objective

The purpose of this review is to assess the adequacy of the pharmacovigilance plan (PVP) based on the safety profile of Rebinyn®.

## 2. Product Information

### 7.1. 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. No additives of human or animal origin are used in the cell culture, purification, conjugation and formulation of N9-GP.

### 7.2. Proposed dosing regimen(s) and formulation(s)

Control and prevention of bleeding episodes: 40 IU/kg body weight for minor and moderate bleeds, and 80 IU/kg body weight for major bleeds. Additional doses of 40 IU/kg can be given.

Perioperative management: Pre-operative dose of 40 IU/kg body weight for minor surgery, and 80 IU/kg body weight for major surgery. Consider two repeated doses of 40 IU/kg (in 1-3 day intervals) within the first week after major surgery. Frequency may be extended to once weekly after the first week until bleeding stops and healing is achieved.

Routine prophylaxis: 40 IU/kg once-weekly

Rebinyn is available as a lyophilized powder in single-use vials of 500, 1000, and 2000 IU reconstituted in histidine diluent.

## 3. Materials Reviewed

**Table 1: Materials reviewed in support of this assessment**

| Date      | Source       | Document Type        | Document(s) Reviewed   |
|-----------|--------------|----------------------|--|
| 6/2/2016  | Novo Nordisk | BLA<br>Sequence 0000 | Module 2.7.4, Summary of clinical safety (5.3.5.3, Integrated summary of safety directed, directed to 2.7.4) |
| 8/5/2016  | Novo Nordisk | BLA<br>Sequence 0005 | Module 1.11.3, Response to FDA request to update PVP to assess potential for PEG accumulation                |
| 9/30/2016 | Novo Nordisk | BLA<br>Sequence 0012 | 120 day safety update  |

| <b>Date</b> | <b>Source</b> | <b>Document Type</b> | <b>Document(s) Reviewed</b>  |
|-------------|---------------|----------------------|--|
| 10/31/2016  | Novo Nordisk  | BLA<br>Sequence 0015 | Module 16.1, Risk Management Plan (includes PVP)                             |
| 1/4/2017    | CDER OSE      | Consult              | PEG consult response   |
| 1/30/2017   | CDER DAVP     | Consult              | Pegasys® and PEG consult response  |
| 2/1/2017    | CDER DGIEP    | Consult              | Cimzia® and PEG consult response   |
| 2/1/2017    | CDER DNP      | Consult              | Monitoring for potential PEG and choroid plexus related AEs consult response |
| 3/7/2017    | CDER DOTP     | Consult              | Macugen® and PEG consult response  |
| 4/19/2017   | Novo Nordisk  | BLA<br>Sequence 0047 | Module 1.14.1.3 Draft PI   |

#### **4. Summary of Prior Marketed Experience**

Not applicable. Product does not have a history of regulatory approval and general use outside the US.

#### **5. Brief description of Safety Database**

The sponsor conducted 6 non-controlled studies to evaluate the safety of N9-GP, of which, 5 were completed. The ongoing study, trial 3895, is a trial of 16 previously untreated patients (PUPs) less than 6 years old.

A total of 115 unique patients participated in the 5 completed studies, and some of these individuals participated in more than one trial. The studies examined dosing for safety and pharmacokinetics, prophylaxis, treatment of bleeding, and perioperative treatment. The sponsor did not observe any differences in safety profile across studies, so they pooled the data in their analysis.

The clinical trials collected the following safety data: Adverse Events (AEs), clinical data including laboratory assessments, physical examinations, and vital signs.

## 6. Sponsor's Pharmacovigilance Plan

**Table 2: Pharmacovigilance Plan from Sponsor Risk Management Plan (page 51, BLA sequence 15)**

| Areas requiring confirmation or further investigation   | Proposed routine and additional pharmacovigilance activities   | Objectives  |
|---|--|---|
| <b>Important identified risk: Allergic/hypersensitivity reactions</b>                                   |  |   |
| Incidence and clinical significance of allergic reactions   | <ul style="list-style-type: none"> <li>Routine pharmacovigilance activities, including hypersensitivity questionnaire (Annex 7A).</li> <li>Ongoing trials: NN7999-3774, NN7999-3895</li> </ul>   | To assess and characterise the risk of allergic reactions associated with nonacog beta pegol.   |
| <b>Important identified risk: FIX inhibitors</b>  |  |   |
| Incidence and clinical significance of FIX inhibitor development  | <ul style="list-style-type: none"> <li>Routine pharmacovigilance activities, including FIX inhibitor questionnaire (Annex 7B).</li> <li>Ongoing trials: NN7999-3774, NN7999-3895</li> </ul>  | To assess and characterise the risk of FIX inhibitor development with nonacog beta pegol.   |
| <b>Important potential risk: Thromboembolic events</b>  |  |   |
| Incidence and clinical significance of thromboembolic events  | <ul style="list-style-type: none"> <li>Routine pharmacovigilance activities, including targeted follow-up questions (Annex 7C).</li> <li>Ongoing trials: NN7999-3774, NN7999-3895</li> </ul>   | To assess and characterise the risk of thromboembolic events with nonacog beta pegol.   |
| <b>Important potential risk: Nephrotic syndrome following ITI</b>                                       |  |   |
| Incidence and clinical significance of nephrotic syndrome following ITI                                 | Routine pharmacovigilance activities   | To assess and characterise the risk of nephrotic syndrome with nonacog beta pegol when used for ITI.  |
| <b>Important potential risk: Inadequate treatment due to assay overestimation of FIX activity</b>       |  |   |
| Incidence and clinical significance of inadequate treatment due to assay overestimation of FIX activity | Routine pharmacovigilance activities   | To assess and characterise 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. |
| <b>Important potential risk: Accumulation of PEG after long-term treatment</b>                          |  |   |
| Incidence and clinical significance of adverse reactions from PEG accumulation                          | <ul style="list-style-type: none"> <li>Routine pharmacovigilance activities including targeted follow-up questions regarding renal impairment (Annex 7C).</li> <li>Collection of data relating to use of nonacog beta pegol in the EUHASS registry.</li> </ul> | To assess and characterise the potential risk of PEG accumulation after long-term treatment.  |

## **7. Analysis of Sponsor's Pharmacovigilance Plan**

### **7.1. Allergic/hypersensitivity reactions**

The sponsor used narrow and broad term allergic-type hypersensitivity reaction queries to find cases in the safety database. Ten cases were identified in the narrow query vs. 31 in the broad query. The sponsor identified four subjects and five events that were evaluated as related to N9-GP exposure: hypersensitivity, pruritus, wheezing and eosinophilia, and injection site reaction. All reactions resolved spontaneously or with treatment, and all except for the hypersensitivity reaction were deemed non-serious.

One previously untreated patient (PUP) in an ongoing trial experienced anaphylaxis and developed a FIX inhibitor.

This is a well-recognized identified risk with factor replacement products. Many reactions are non-serious, and specific treatments are known and available, so the sponsor-recommended plans for routine pharmacovigilance and a hypersensitivity questionnaire are adequate.

### **7.2. FIX inhibitors**

The sponsor did not identify FIX inhibitor formation amongst previously treated patients in completed trials, but they did identify one case of inhibitor formation in an ongoing trial with PUPs. This subject experienced anaphylaxis and subsequent evaluation identified FIX inhibitor formation. The patient was treated, the symptoms resolved, and the patient was withdrawn from N9-GP treatment.

This is a well-recognized identified risk with factor replacement products, so the sponsor's proposal for routine pharmacovigilance and a FIX inhibitor questionnaire is adequate.

### **7.3. Thromboembolic events**

The sponsor did not identify any thromboembolic events in completed trials, but this remains an important identified risk with factor replacement products, so the sponsor's proposal for routine pharmacovigilance is adequate.

### **7.4. Nephrotic Syndrome following Immune Tolerance Induction (ITI)**

The sponsor did not investigate use of N9-GP during ITI, but this is a well-recognized pharmacological class effect, so the sponsor's plan to monitor through routine pharmacovigilance is adequate.

### **7.5. Inadequate treatment due to assay overestimation of FIX activity**

The sponsor recognizes that PEG interferes with some of the activated partial thromboplastin time (aPTT) reagents, and this can result in either over or underestimation of FIX activity. The sponsor notes that this does not occur with the chromogenic test, which is not currently approved in the US.

This risk is associated with aspects of laboratory processes and not reflective of biological characteristics of N9-GP. As such, the sponsor's plan to monitor this risk through routine

pharmacovigilance is appropriate, especially since the package insert conveys this concern for potentially inaccurate lab assays.

## **7.6. Accumulation of PEG after long-term treatment**

Nonclinical studies identified PEG accumulation in the choroid plexus after repeat dosing of N9-GP in terminally-sacrificed Cynomolgus monkeys and Rowett nude rats. The dosing in the monkeys was 30 to 200 times the proposed therapeutic dose in humans, and no neurological deficits were noted based on the endpoints evaluated, but the potential toxicity of PEG cannot be fully assessed in these animals due to the formation of neutralizing antibodies to N9-GP.

The rat studies dosed specimens at therapeutic and supratherapeutic levels. In the 26 week study without a recovery period, PEG accumulation occurred at all dose levels in the connective tissue and epithelial cells of the choroid plexus. Researchers also observed PEG accumulation in brain blood vessels, mesenteric lymph nodes, and spleen, but no clinical abnormalities were detected.

The clinical studies did not reveal a clustering of neurological or psychiatric AEs. There were 29 nervous system AEs reported in 16 subjects from all three Phase 3 studies. The vast majority of neurological complaints were nonspecific symptoms, headache and dizziness, which could be attributable to a variety of causes. In addition, there were individual reports of sciatic neuralgia, tongue biting, and speech disorder. There were also 3 psychiatric AEs: Attention deficit hyperactive disorder (ADHD), decreased libido, and sleep disorder.

The nonclinical studies did not note accumulation of PEG in the kidneys, but previous studies of PEG identified the possibility of accumulation in renal tubular epithelial cells.<sup>1</sup> The clinical studies identified only 3 renal AEs in 2 subjects (transitory pain, dysuria, and proteinuria).

In general, frequently reported AEs included frequent childhood conditions such as nasopharyngitis and URI, and the clinical studies did not identify any significant clustering of serious or concerning AEs attributable to PEG accumulation or other pathology.

Based on pharmacokinetic studies, the sponsor asserts that PEG reaches a steady state in humans within a year in most organs, and within 2.5 years in the choroid plexus. As of Oct 2016, 22 patients in the clinical trials were exposed to N9-GP for more than 2.5 years.

Due to the relatively small size of the safety database (115 subjects), relatively short duration of follow-up, and the nonclinical findings, concern for potential AEs due to accumulation of PEG persist, especially as routine prophylaxis with N9-GP may mean starting life-long treatment at a young age.

These safety concerns prompted CBER to consult CDER divisions that have greater experience with pegylated products. The goals of these consults were three-fold:

- Determine if CDER has identified any PEG related AEs or signals
- Identify whether pegylated CDER products could be good models to understand long-term safety of N9-GP
- Inquire if CDER expertise/experience could help identify potential AEs from the accumulation of PEG in the choroid plexus and suggest how this could be monitored

Review of literature on pegylation, and discussion with CDER identified four products that have similar pegylation: Omontys®, Cimzia®, Macugen®, and Pegasys®.

CBER contacted the Division of Gastroenterology and Inborn Errors Products (DGIEP) for Cimzia (certolizumab pegol), the Division of Antiviral Products (DAVP) for Pegasys (peginterferon alfa-2a), the Division of Hematology Products (DHP) for Omontys (peginesatide), and the Division of Transplant and Ophthalmology Products (DTOP) for Macugen (pegaptanib sodium injection). In addition, CBER contacted the Office of Surveillance and Epidemiology (OSE) in CDER to inquire about PEG related AEs observed through postmarketing surveillance, and the Division of Neurology Products (DNP) to glean their expertise on potential AEs that could arise from PEG vacuolization in the choroid plexus.

Communication with the CDER product offices determined that the four similarly pegylated products were not good models for understanding the long-term safety of N9-GP:

- Omontys was on the market for less than a year, as it was removed from the market due to hypersensitivity reactions including anaphylaxis.<sup>2</sup>
- Macugen is injected intravitreally, and its distribution in the body is not similar to a product that is administered intravenously.<sup>3</sup>
- Pegasys has a Box Warning stating that it may cause a variety of AEs, including neuropsychiatric and renal disorders due to the biologically active alpha interferon moiety, so it would be difficult to identify and evaluate any AEs in these systems due to PEG accumulation.<sup>4</sup>
- Cimzia, similar to Pegasys, is labeled for neuropsychiatric AEs, and DGIEP states this is due to characteristics of anti-TNF biologics as a class, and not due to pegylation. This product may have chronic use, but its administration is not likely to be continuous or life-long, as Crohn's disease tends to undulate; 40% of initial responders stop treatment within 6 months due to the development of antibodies; and long-term studies, which were conducted only in adults, had only 7 to 21% of patients remain on treatment after 5 to 7 years.<sup>5</sup>

In addition, OSE's review of FAERS and data mining did not identify any case where an AE was associated with vacuolization.<sup>6</sup>

The DNP consult stated that vacuolization in the choroid plexus is not clearly associated with any disease process, but that it could hypothetically affect CSF production, and that it is not apparent what signs or symptoms in humans could be associated with this nonclinical finding. DNP also could not identify specific clinical findings, laboratory, or radiologic tests that would be useful to monitor potential AEs due to accumulation of PEG in the choroid plexus.<sup>7</sup>

To summarize, nonclinical studies identified vacuolization of PEG in the choroid plexus in the brain, but this finding does not correlate with any clinical sequelae in the premarketing clinical trials. Few of the subjects in these trials, however, were enrolled long enough to reach steady-state PEG accumulation in the choroid plexus according to the sponsor. In addition, similarly-pegylated approved products are not associated with an AE correlating with vacuolization in the choroid plexus. These products, however, are not good models for understanding potential AEs with either long-term N9-GP exposure, or in children with developing nervous systems. Lastly, it is not clear what AEs in humans could specifically be associated with accumulation of PEG in the choroid plexus, or if any specific tests or clinical findings could be used to monitor for potential negative sequelae.

Due to these concerns, CBER presented the nonclinical findings with N9-GP to the Blood Product Advisory Committee (BPAC), and communicated with the European Medicines Agency (EMA), who was undergoing a parallel review process for N9-GP.

The BPAC was asked a variety of questions about the benefit-risk balance with N9-GP. This included: the significance of the nonclinical findings; the BPAC's concern for use in specific age groups, or for intermittent vs. chronic use; the utility of any specific tests to monitor for AEs; and whether further preclinical or clinical studies were warranted.

The BPAC did not vote on specific questions, and tended to discuss all the issues together, rather than address them individually. They seemed to convey a consensus sentiment that further clinical or nonclinical studies did not preclude further human use, and that the benefit outweighed the risk. They did think that further monitoring of patients was necessary to determine if the nonclinical findings could be associated with negative sequelae in humans. The BPAC members did not clarify if they thought all patients receiving N9-GP prophylactically should be monitored, or just some of them as part of a post-marketing study.

The BPAC did not identify a definite threshold age at which there was increased concern for administering N9-GP, but they stated concern that potential AEs from PEG accumulation may cause the most harm in the young and the elderly.

Lastly, the advisory committee did not identify any specific clinical findings, lab tests, or radiological tests that would be useful to monitor for vacuolization in the choroid plexus.

The EMA identified the same concerns as FDA regarding the findings in the nonclinical N9-GP studies. On March 23, 2017, an EMA committee recommended to grant market authorization to N9-GP, but to restrict use to patients aged 12 years and above with hemophilia B. They also required that the sponsor complete a non-interventional post-authorization safety study (PASS) to assess potential effects of PEG accumulation in the choroid plexus; the study will be derived from a registry of hemophilia patients.

Due to the concern for possible PEG accumulation, the BLA review team considered the sponsor's proposed indications, and they decided to approve the acute uses of N9-GP: on-demand treatment and control of bleeding episodes, and perioperative management of bleeding. Due to the concerns for possible PEG accumulation from prolonged exposure, and another product's (Rixubis®) exclusivity rights for routine prophylaxis, the review team decided against approval for routine prophylaxis. The review team also felt that an age restriction was not necessary for the acute treatment indications.

DE concurs with this assessment, and we determined that a postmarketing study or REMS is not necessary for this product with the planned approval of the acute-use indications only. The lack of an age restriction also seems reasonable, as 17 patients between the ages of 0 and 12 years have at least 12 months of exposure to N9-GP for prophylaxis and the control of breakthrough bleeds. These patients did not demonstrate any clustering of AEs that could be attributed to the accumulation of PEG.

DE also considered whether a postmarketing study would be useful for individuals who may have significant exposure to N9-GP through repeated administration of the product from intermittent acute use. We determined that such a study would not be necessary for the following reasons:

- Lack of a clearly defined threshold level at which one becomes concerned about N9-GP exposure
- Difficulty prospectively identifying patients who could receive frequent acute intermittent use
- Lack of a baseline assessment of subjects if the study identifies individuals after high levels of exposure (instead of enrolling individuals when they are first exposed to N9-GP, which would be inefficient as many of these individuals will not go on to have high levels of exposure)
- Lack of an appropriate comparator group, if using a specialized neurocognitive instrument
- Unlikelihood of getting data on exposures that would be longer than what was observed in the pre-clinical trials, where 17 subjects between 0-12 years old had at least a year of exposure.

In conclusion, DE has determined that a postmarketing study assessing the safety of N9-GP in patients who have frequent intermittent use would not be feasible to implement, and would be unlikely to gather useful information. In addition, the product will be under routine pharmacovigilance, and if concerns arise from surveillance activities, or from further clinical studies, the risk management strategy can be amended to address a newly identified concern.

DE does suggest that N9-GP be adequately labeled to discourage its frequent use in individuals, and that the nonclinical findings are conveyed in the product insert.

Based on the information submitted by the sponsor, communications with CDER, sentiments expressed by the BPAC, the EMA recommendation, and the CBER review team's decision to not approve prophylactic use, DE concludes that the current pharmacovigilance strategy for possible accumulation of PEG is adequate.

## 8. Recommended Amendments to the Sponsor's Pharmacovigilance Plan Based on Indications Being Approved

Indications Being Approved:

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

Due to the concerns for possible PEG accumulation from prolonged exposure, and another product's (Rixubis®) exclusivity rights for routine prophylaxis, the review team decided against approval for routine prophylaxis.

**Table 3: Summary of Important Safety Concerns and DE Recommendations**

|   | Important Safety Concern  | Pharmacovigilance Action  |
|---|---|---|
|   | Important identified safety concerns  |   |
| 1 | No additional concerns  |   |
|   | Important potential safety concerns   |   |
| 2 | Accumulation of PEG after frequent intermittent use. Specifically, the potential for adverse events due to accumulation of PEG in the choroid plexus, as observed in nonclinical studies. | <ul style="list-style-type: none"> <li>• Additional language added to PI: <ul style="list-style-type: none"> <li>○ section 1, Indications, discouraging frequent use</li> <li>○ section 13, Nonclinical Toxicology, describing the nonclinical findings in the</li> </ul> </li> </ul> |

|   | Important Safety Concern      | Pharmacovigilance Action |
|---|-------------------------------|--------------------------|
|   |                               | rat studies              |
|   | Important missing information |                          |
| 3 | No additional concerns        |                          |

### References

1. Rudmann DG, Alston JT, Hanson JC, Heidel S. High molecular weight polyethylene glycol cellular distribution and PEG-associated cytoplasmic vacuolation is molecular weight dependent and does not require conjugation to proteins. Toxicol Pathol. 2013;41(7):970-83. doi: 10.1177/0192623312474726. Epub 2013 Jun 20. PubMed PMID: 23788571.
2. Miller, Barry. "RE: Omontys information request from CBER/OBE/DE." Message to Ravi Goud. 4 January 2017. E-mail.
3. William Boyd. "Macugen information request from CBER/OBE/DE." Message to Michael Puglisi. 7 March 2017. E-mail.
4. Fleischer, Russell. Memorandum to Division of Epidemiology. Subject: Consult Request for Rebinyn (IND 125611). Dated 30 January 2017.
5. Lee, Kerry Jo. CDER Consult Memo to Ravi Goud. Subject: Medical Officer Consultation: The Division of Epidemiology in CBER requested the assistance of DGIEP in identifying adverse events potentially arising from lifelong use of nonacog beta pegol, a recombinant factor IX attached to PEG, which is found in Cimzia. Specifically, vacuolization is observed in nonclinical animal studies, and although this has not corresponded with AEs in clinical studies, there is concern, as emergent effects may occur with prolonged use beyond observed safety data. The Division of Epidemiology in CBER requested that DGIEP answer a series of safety questions regarding the postmarketing experience with Cimzia in CDER. Dated 1 February 2017.
6. Jason, Mihaela. Pharmacovigilance Memo. Subject: Vacuolization. Dated 4 January 2017.
7. Fitter, Heather. Consult Review and Evaluation: CBER/DE. Dated 1 February 2017.