



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

MEMORANDUM

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Subject: Novoeight Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC)

Sponsor: Novo Nordisk

Product: Novoeight (turoctocog alfa), Antihemophilic Factor (Recombinant)

Re: STN 125466/170

Indication: For use in adults and children with hemophilia A for:

- Control and prevention of bleeding
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

Meeting Date: Pediatric Advisory Committee Meeting: 06Mar2017 – 07Mar2017

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1 INTRODUCTION

1.1 Objective

The purpose of this memorandum is to provide the Pediatric Advisory Committee (PAC) with a comprehensive postmarketing safety review of Novoeight. The safety review will cover the period from 15Oct2013 to 13Oct2016, the 3 year period following initial approval of Novoeight by the Food and Drug Administration (FDA).

The accompanying abbreviated PAC presentation will cover the same 3 year period. An abbreviated presentation to the PAC is planned for this product because none of the criteria that would trigger a full oral presentation or justified abbreviated presentation to the PAC have been met. Specifically, there were no pediatric deaths reported in the review period, and while adult deaths were reported in the review period, they have not been attributed to Novoeight. Deaths were not attributed to Novoeight due to documentation of an alternate cause of death by the reporter where available, and due to careful examination of all reports of death by the FDA medical reviewer. In addition, no new safety signal was identified, no postmarketing requirement for a study or a Risk Evaluation and Mitigation Strategy (REMS) is planned or in place, and the pediatric label changes described below were not a result of serious adverse events. Although the PAC presentation is abbreviated, the analysis of the safety data is comprehensive, and this memorandum documents FDA's full and complete evaluation, including review of adverse event reports in passive surveillance data, data mining, postmarketing data provided by the sponsor and a review of the published literature.

1.2 Product Description

Novoeight is an antihemophilic recombinant Factor VIII (FVIII) product and is indicated for use in adults and children with hemophilia A for:

- Control and prevention of bleeding
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

The product has also been referred to in the published literature as NovoEight, N8 and turoctocog alfa. For purposes of clarity the product will be referred to in this memorandum as Novoeight.

1.3 Regulatory History

The original Biologics License Application (BLA, 125466/0) for Novoeight was approved by the FDA on 15Oct2013. At the time of initial FDA approval, Novoeight was indicated for use in both adults and children, triggering this presentation to the PAC. There have been no additional pediatric label changes since approval.

2 MATERIALS REVIEWED

Adverse event reports for Novoeight received in the FDA Adverse Events Reporting System (FAERS) from 15Oct2013 to 13Oct2016 have been reviewed and are discussed in detail in section 5 below. Materials obtained from the sponsor and reviewed as part of

this comprehensive evaluation are listed in Table 1 below. Additional citations are listed in the reference section of this memorandum.

Table 1. Safety Related Regulatory Documents Submitted by Novo Nordisk and Reviewed in Support of this Memorandum

Source	Document Date	Document
Novo Nordisk	September 2015	Novoeight US Package Insert
Novo Nordisk	15Nov2016	Distribution Data from 15Oct2013 to 13Oct2016
Novo Nordisk	05Oct2012	Novoeight Risk Management Plan. Version 1.0.
Novo Nordisk	February 2014 to August 2016	Novoeight Periodic Adverse Drug Experience Reports (PADERS)

3 PRODUCT DISTRIBUTION DATA

In response to FDA’s request, Novo Nordisk has provided both worldwide and US distribution data for this safety review (Table 2).¹ Novo Nordisk reports that this information is sourced from ex-factory sales data described by the sponsor as sales to direct customer locations. The sponsor further notes that the data reported are approximate based on the nominal value of each vial size sold.

Novo Nordisk reports that the first world-wide launch of Novoeight was in Germany in February 2014. Product launch in the US was delayed until 13Apr2015, after existing patents expired.² As a result, the worldwide distribution data provided by the sponsor therefore covers a time period approximating the 3 year period of this review, whereas the US distribution data covers a shorter period of about a year and a half. Also of note, the worldwide sales data in Table 2 below includes the US sales data.

Table 2. Distribution data for Novoeight

Worldwide Sales (IU) February 2014 – 31Oct2016	US Sales (IU) April 2015 – 15Oct2016
265,416,750	52, 323,750

While Novo Nordisk has provided distribution data for Novoeight, the sponsor reports that they do not have reliable external data sources that would permit calculation of estimates of the number of patients exposed to Novoeight nationwide. US patient exposure to Novoeight may, however, be estimated as follows. Data from the Hemophilia Surveillance System established by the US Center for Disease Control and Prevention (CDC), indicate that the prevalence of hemophilia A in the US can be estimated at 10.5 per 100,000 males and the incidence at 1 in 6,410 live male births.^{3,4} Using this data the proportion of incident cases or previously untreated patients (PUPs) can be calculated as approximately 2.6% of all US male hemophiliacs and that of previously treated patients (PTPs) as 97.4%.

The mean annual consumption of recombinant FVIII by PTPs and PUPs has been estimated from multiple international multi-center recombinant FVIII clinical trials published between 1993 and 2002. A meta-analysis of these studies used a fixed effect model with weighting by the inverse of the variance to calculate a pooled estimate of

148,700 IU consumed annually per PTP and 48,600 IU per PUP.⁴ Using these estimates, the number of patients exposed to Novoeight in the US from the time of US launch on 13Apr2015 through 15Oct2016 can be estimated as 6 PUPs and 231 PTPs for a total of 237 patients.

It is important to note that this estimate of the number of patients treated is at best an approximation since all the distributed doses may not have been administered to patients. In addition, other factors such as off-label use and dose adjustment at the discretion of the treating physician can affect this estimation. Also of note, data used in the calculation of this patient estimate use multiple sources including both US and international data.

4 PHARMACOVIGILANCE PLAN

The current pharmacovigilance plan for Novoeight dated 05Oct2012 has been reviewed in detail and is summarized below.

4.1 Safety Concerns Listed in the Pharmacovigilance Plan

Table 3. Pharmacovigilance Plan for Novoeight

SAFETY CONCERN	PLANNED ACTION(S)
Identified Risks None	N/A
Important Potential Risks Inhibitor Development	<ul style="list-style-type: none"> ○ Routine pharmacovigilance including structured follow-up questions ○ PUPs trial NN7008-3809 ○ Long-term Observational trial NN7008-3553
Allergic/Hypersensitivity Reactions	<ul style="list-style-type: none"> ○ Routine pharmacovigilance including structured follow-up questions ○ Long-term Observational trial NN7008-3553 ○ Hypersensitivity questionnaire
Important Missing Information Elderly patients (>65 years of age)	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Long-term Observational trial NN7008-3553
Previously Untreated Patients	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ PUPs trial NN7008-3809
Patients with HIV (CD4 <200 cells/μl) or HCV (viral load more than 200 particles/μl)	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Long-term Observational trial NN7008-3553
Patients with Renal or Hepatic Insufficiency	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Long-term Observational trial NN7008-3553
Patients with mild or moderate hemophilia	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Long-term Observational trial NN7008-3553

PUPs = Previously untreated patients

4.2 Planned Pharmacovigilance Activities

4.2.1 Routine Pharmacovigilance

Routine pharmacovigilance is described by the sponsor as daily surveillance, literature surveillance, regular safety reporting, risk communication via reference safety information as well as periodic review of safety information and reporting rates of adverse events. The sponsor plans to collect additional information on reports of inhibitor formation or allergic/hypersensitivity reactions via additional follow-up questionnaires.

4.2.2 Postmarketing Studies

In addition to routine pharmacovigilance, the sponsor plans two post-marketing studies which were listed on the approval letter at the time of FDA licensure and are also listed in the PVP – a trial in Previously Untreated Patients (PUPs) NN7008-3809 and an Observational trial NN7008-3553. The protocols for both trials were submitted by the sponsor with the original BLA and were reviewed in detail. Both studies are currently ongoing with estimated completion dates in 2018.^{5,6}

5 ADVERSE EVENT REVIEW

5.1 FDA Adverse Event Reporting System (FAERS)

5.1.1 Methods

A search of the FDA Adverse Event Reporting System (FAERS) was performed for adverse event reports following Novoeight received between 15Oct2013 to 13Oct2016. 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.

5.1.2 Results

The results of the FAERS search of reports of adverse events after Novoeight during the review period are listed in Table 4 below. Deaths, serious and non-serious reports are reviewed in detail in sections 5.1.2.1, 5.1.2.2 and 5.1.2.3 respectively.

Table 4. Adverse event reports for Novoeight received in FAERS from 15Oct2013 to 13Oct2016

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	3	0	0	4	0	5	3
≥18 years	1	2	1	2	5	0	7	4
Unknown	0	1	0	0	5	0	5	1
Total	2	6	1	2	14	0	17	8

5.1.2.1 Deaths

No pediatric deaths were reported in the review period. A total of 3 adult deaths were reported – these were reviewed in detail and are summarized below.

12579770 – 50-year-old man in Japan with hemophilia, atherosclerosis, hypertension and angina pectoris who underwent lumbar spine surgery which was complicated by post-operative aggravation of angina and diastolic heart failure. The patient died of diastolic heart failure.

11647971 – 42-year-old male in the US with severe hemophilia A died after he was hospitalized with a stroke and treated with both Novoseven and an unreported FVIII product (Novoeight was listed by the sponsor as an equivalent product). Cause of death and autopsy information were not reported.

10978006 – 52-year-old male in Japan with hepatitis C cirrhosis, reflux esophagitis and gastritis received Novoeight for hemophilia from 02Aug2014 to 06Mar -2015. On 18Mar2015 received FFP, PRBCs and Advate for management of GI bleed after he was hospitalized for melena. On (b) (6), the patient died with cause of death reported as hemorrhage of the digestive tract.

5.1.2.2 Pediatric Serious non-Fatal Reports

A total of 8 serious non-fatal reports were received, of which 4 were pediatric reports. All serious reports were reviewed in detail and the 4 pediatric reports are summarized below.

12481523 – 8-year-old male in the US was diagnosed with a Factor II disorder on an unspecified date while taking Novoeight. No action was taken with regard to Novoeight and the outcome for the event was not reported.

11700813 – 1-year-old male in Denmark with severe hemophilia A and FVIII inhibitors present was hospitalized for a spontaneous haemorrhage in spite of prophylactic treatment with Novoeight. The dose of Novoeight was increased and the outcome was not reported.

11563133 – 3-year-old male in Japan with hemophilia A and FVIII inhibitors present was treated with Novoeight for immune tolerance induction. The patient’s inhibitors remained elevated after 5 weeks but decreased 11 weeks later. The overall outcome was not reported.

11544702 – 5-year-old male in Japan with hemophilia and FVIII inhibitors present was treated with Novoseven and Novoeight for immune tolerance induction with increasing levels of inhibitors over 3 weeks. The dosage of both Novoseven and Novoeight was increased and the outcome was not reported.

5.1.2.3 Pediatric Non-Serious Reports

A total of 14 non-serious reports were received, of which 4 were pediatric reports. All non-serious reports were reviewed in detail. In two reports, the patients experienced nose bleeds following treatment with Novoeight. Novoeight was discontinued in both cases. The other two reports describe a patient who experienced a clotted port-a-cath and a patient who experienced a mild allergic reaction described as itching in the back of the throat.

5.2 Data Mining

Data mining was conducted using the Empirica Signal 7.2 [Trade (S)] run. The data lock point is 03Oct2016. There are a total of 2 Preferred Terms (PTs) with EB05 >2 listed in the table below.

Table 5. Data mining findings for Novoeight received in FAERS from 15Oct2013 to 13Oct2016

PT	N	EB05
Anti factor VIII antibody test	3	3.313
Factor VIII inhibition	3	2.095

The development of factor VIII inhibitors is a known safety concern for the class of antihemophilic factor products and is listed on the product label. These data mining findings do not therefore represent new safety information.

5.3 Periodic Adverse Drug Experience Reports (PADERs)

The manufacturer’s postmarket periodic safety reports for Novoeight covering the surveillance period were reviewed. The adverse events reported in the periodic safety reports were consistent with those seen in FAERS. No additional safety issues were identified.

6 LITERATURE REVIEW

A search of the US National Library of Medicine’s PubMed.gov database on 03Nov2016 for peer-reviewed literature with the search terms “Novoeight” and “safety” retrieved 4 articles published in the current review period. All articles were reviewed in detail and are summarized below. No new safety concerns were identified in these articles.

- a) Vakil NH, Fujinami N, Martin-Stone S.

Turoctocog Alfa for the Treatment of Hemophilia A.

Pharmacotherapy. 2014 Jul 23. doi: 10.1002/phar.1469. [Epub ahead of print]

In this review article, the authors comment on turoctocog alfa, the most recent FVIII product available for the treatment of Hemophilia A (HA). The authors note that pharmacokinetic trials in animals and humans have demonstrated characteristics similar to those of other recombinant FVIII concentrates and that while clinical trials have supported safety in the management of HA in treatment-experienced patients, study results of turoctocog alfa in treatment-naïve patients are pending. In addition, a smaller study in hemophilic patients undergoing surgery has demonstrated positive results. Thus the authors conclude that while turoctocog alfa appears to be a safe alternative to currently available rFVIII products at this time, its place in therapy among these products has yet to be fully elucidated.

- b) Santagostino E, Lentz SR, Misgav M *et al*.

Safety and efficacy of turoctocog alfa (NovoEight®) during surgery in patients with hemophilia A: results from the multinational guardian™ clinical trials.

Haemophilia. 2014 Oct 2. doi: 10.1111/hae.12518. [Epub ahead of print]

The multinational, open-label guardian™ clinical trials assessed the hemostatic response of turoctocog alfa (NovoEight®), a rFVIII product, in patients with severe hemophilia A (FVIII \leq 1%) undergoing surgery. A total of 41 procedures were performed in 33 patients aged 4-59 years. Of the 41 procedures, 15 were major surgeries in 13 patients and 26 were minor surgeries in 21 patients. The authors report that overall, no safety issues were identified, no thrombotic events were observed and none of the patients developed FVIII inhibitors. The authors conclude that the results show that turoctocog alfa was both safe and effective in controlling blood loss in patients with severe hemophilia A undergoing surgery.

- c) Ozelo M, Misgav M, Abdul Karim F *et al*

Long-term patterns of safety and efficacy of bleeding prophylaxis with turoctocog alfa (NovoEight®) in previously treated patients with severe haemophilia A: interim results of the guardian™ 2 extension trial.

Haemophilia. 2015 Jun 8. doi: 10.1111/hae.12737. [Epub ahead of print]

In this letter to the editor, the authors report on interim results of the guardian 2 extension trial (NCT00984126) – an open-label, non-controlled study investigating the long-term safety and efficacy of NovoEight when administered as prophylaxis and for treatment of bleeds. Patients who completed the precensure guardian 1 (adolescent and adult patients \geq 12 years) and guardian 3 (pediatric patients $<$ 12 years) trials could choose to continue in this extension trial. Thus far, a total of 188 patients with severe haemophilia A and no history of FVIII inhibitors have been enrolled. None of the study subjects developed FVIII inhibitors and the product was considered to be well tolerated, with no unexpected patterns seen in AEs or serious adverse events (SAEs).

d) Ozelo M, Chowdary P, Regnault A *et al*

Impact of severe haemophilia A on patients' health status: results from the guardian™ 1 clinical trial of turoctocog alfa (NovoEight®).

Haemophilia. 2015 Jul;21(4):451-7. doi: 10.1111/hae.12617. Epub 2015 Feb 12.

This study explored the impact of severe haemophilia A on patients' health status, in young adults aged 12 and older, using data from guardian 1, a prelicensure multinational, open-label, non-controlled phase 3 trial investigating safety and efficacy of NovoEight in previously treated patients with severe haemophilia A. The percentage of haemophilia patients reporting problems was consistently significantly greater than age-matched general population reference values. Likewise, for all age groups mean baseline scores of health status were significantly lower for haemophilia patients than for the general population. The authors conclude that the health status of patients with severe haemophilia A entering the guardian 1 study was poorer than that of the general population, particularly regarding mobility and pain.

7 CONCLUSION

This comprehensive postmarketing safety review of passive surveillance adverse event reports, PADERs, post-marketing data from the manufacturer, and the published literature does not indicate any new safety concerns for Novoeight. No pediatric deaths were reported. There were relatively few reports of adverse events received during the time period of this review, most of which were non-serious. The types of serious adverse events reported in pediatric patients, such as inhibitors or bleeding, are consistent with the known safety profile of the product or the patients' underlying conditions. No unusual frequency, clusters, or other trends for these or other adverse events were identified.

8 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Novoeight. No further regulatory action is indicated at this time.

¹ Novo Nordisk. Response to Information Request. 15Nov2016 eCTD 125366 seq 00995

² Novo Nordisk. Annual Report 2013 page 30. Available at <http://www.novonordisk.com/content/dam/Denmark/HQ/Commons/documents/Novo-Nordisk-Annual-Report-2013-UK.pdf>

³ Soucie JM, Evatt B, Jackson D *et al* Occurrence of Hemophilia in the United States *Am J Hem* (1998) 59:288-294

⁴ Ewenstein BM, Gomperts ED, Pearson S *et al* Inhibitor development in patients receiving recombinant factor VIII (Recombinate rAHF/Bioclata®): a prospective pharmacovigilance study. *Hemophilia* (2004) 10:491-498

⁵ Safety and Efficacy of Turoctocog Alfa in Prevention and Treatment of Bleeds in Previously Untreated Children With Haemophilia A (guardian™4) NN7008-3809 Available at www.clinicaltrials.gov

⁶ Safety and Efficacy of Turoctocog Alfa During Long-Term Treatment of Severe and Moderately Severe Haemophilia A (guardian™ 5) NN7008-3553 Available at www.clinicaltrials.gov