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Summary Basis for Regulatory Action

Date: November 30, 2018

From: Robert Le, MD, PhD, Chair of the Review Committee

BLA STN#: 125466/243

Applicant Name: Novo Nordisk Inc.

Date of Submission: January 31, 2018

Goal Date: November 30, 2018

Proprietary Name/ Established Name:

Novoeight® / Antihemophilic Factor (Recombinant)

Indication:

Novoeight is an Antihemophilic Factor (Recombinant) indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

Recommended Action:

The Review Committee recommends approval of this efficacy supplement.

Review Office Signatory Authority:

Tejashri Purohit- Sheth, M.D./ Director/Division of Clinical Evaluation and Pharmacology/Toxicology/OTAT/CBER/FDA

X I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Liang Yideng Ekaterina Allen
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Robert Le Ohenewaa Ahima Christine Drabick, August 17, 2018
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Lin Huo
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	N/A
Clinical Pharmacology Review(s)	Iftekhar Mahmood
Labeling Review(s) • *APLB (OCBQ/APLB)*	Kristine T. Khuc, October 19, 2018
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	N/A
Advisory Committee summary	N/A

1. Introduction

Novoeight was approved in October 15, 2013 for control and prevention of bleeding, routine prophylaxis and perioperative management of adults and children with hemophilia. Currently, the recommended dosing for routine prophylaxis against bleeding in adults and adolescents (> 12 years) is 20-50 international unit (IU)/kg three times weekly or 20-40 IU/kg every other day. In children <12 years, dosing for routine prophylaxis may be administered as 25-60 IU/kg three times weekly or 25-50 IU/kg every other day. Studies 3543 in adults and adolescents and 3545 in pediatrics were the primary studies evaluate to support this approval.

The purpose of this BLA 125466 supplement is to update the prescriber information for Novoeight to a) update the safety and efficacy sections of the PI based on data from Study 3568 that evaluated the extended treatment for on-demand treatment and control

of bleeding, perioperative management and routine prophylaxis in previously treated patients (PTP) that included both children and adults b) provide efficacy and safety data from Study 3809 in previously untreated patients (PUPS) c) revise the dosage recommendations in the PI to a less frequent (40–60IU/kg, twice weekly or every third day) based on data from Study 3568 and d) incorporate an editorial change based on CBER's prior request to revise the indication statement from control and prevention of bleeding to on-demand treatment and control of bleeding.

Recommendations:
This efficacy supplement was reviewed under the Prescription Drug User Fee Act (PDUFA) program (10 months). The Review Committee recommends approval of this supplement

2. Background

Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. It is the most common of the severe, inherited bleeding disorders, affecting 20,000 males in the United States and 1 of every 5,000 male births. Hemophilia A is classified as 'severe (<1%)', 'moderate (1–5%)' or 'mild (>5%)' according to the plasma activity of FVIII. Hemophilia is characterized by recurrent bleeding manifestations that often start at birth with bleeding after circumcision or immunization. Bleeding may occur after minor trauma or small surgical intervention, into skin, joints, mucosa, muscles, gastrointestinal tract or the brain. Primary prophylaxis, i.e., regular infusion of concentrates started after the first joint bleed and/or before the age of two years, is now recognized as first-line treatment in children with severe hemophilia.

The most serious complication of treatment in hemophilia is inhibitor formation, which occurs in up to 30% of patients with severe hemophilia A. Large deletions, inversions, and nonsense mutations are associated with the highest risk. The type of mutation is associated with the severity of hemophilia A.

The development of FVIII inhibitors is the most serious complication of FVIII replacement therapy and affect 29–45% of PUPs with severe hemophilia A based on prospective studies, and usually occurs within the first 2 to 3 weeks of treatment. The risk then declines with increasing exposure to FVIII products, but never completely disappears.

There was no pre-submission meeting for this BLA 125466 efficacy supplement. The BLA applicant does not claim new active ingredients, new indications, new dosage forms, or new routes of administration. The original BLA 125466.0 review process had Pediatric Review Committee (PeRC) on September 11, 2013. This BLA supplement is not subject to Pediatric Research Equity Act (PREA) as a new indication in pediatric patients is not being sought through the submission of this efficacy supplement.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

Novoeight is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (0.9% sodium chloride).

On July 11, 2018, the BLA applicant submitted amendment #4 to this BLA 125466 supplement 243, to update the USPI to include information from the CMC supplement, BLA 125466/238. This CMC labeling supplement was approved by FDA on May 17, 2018 to update the storage conditions for the drug product. The CMC reviewer reviewed and approved the CMC labeling update.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical pharmacology/toxicology information was submitted in this efficacy supplement.

5. CLINICAL PHARMACOLOGY

Mechanism of Action:
Novoeight temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

Human Pharmacokinetics (PK):
The pharmacokinetics (PK) of Novoeight were investigated in a small number of subjects with Hemophilia A with body mass index (BMI) ≥30 kg/m2 (30.5-37.2 kg/m^2)) who participated in the extension study, Study 3568. The PK parameters of Novoeight were calculated based on FVIII activity assessed by both the chromogenic (n =6) and the one-stage clotting assay (n= 6) in 6 adult subjects who received a single dose of 50IU/kg of Novoeight. The PK parameters of Novoeight were estimated by non-compartmental analysis. The results of the study indicated that the clearance of Novoeight was approximately 50% higher by both chromogenic and clotting assays in subjects with normal body weight than the subjects with BMI ≥30 kg/m^2. The volume of distribution of Novoeight at steady state was higher in subjects with normal body weight than the subjects with BMI ≥30 kg/m^2 approximately by 50% and 33% by chromogenic and the clotting assays, respectively.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

Clinical Summary:
In this supplement #243, the applicant is seeking approval to update the label with information regarding the extended duration of treatment for routine prophylaxis at the approved dose, as evaluated in Study 3568 and update the label to include efficacy and safety data from Study 3809 in PUPs. In addition, the applicant proposes to include "twice weekly dosing" for routine prophylaxis for all age groups based on 27 subjects who received the less frequent dosing regimen (twice weekly or every third day) from an unplanned subgroup analyses in Study 3568.

Four multicenter, open-label, non-controlled trials have been conducted to evaluate the safety and efficacy of Novoeight for routine prophylaxis, treatment of bleeds, and perioperative management in subjects with hemophilia A. Three of these trials (Studies 3543, 3545, 3568) were performed in PTPs and the fourth (Study 3809) in PUPs. Study 3543 (a Phase 3 pivotal trial in adolescent and adult subjects 12-65 years of age) and 3545 (a Phase 3 pivotal trial in pediatric subjects less than 12 years of age) were reviewed in the original BLA 125466 submission. In this efficacy supplement, the applicant submitted new data from Study 3568 (a Phase 3 extension trial including pediatric and adult subjects) and Study 3809 (a Phase 3 trial in previously untreated pediatric subjects less than 6 years of age). Studies 3568 and 3809 are reviewed individually.

Note that the mean ABR from the extension trial, Study 3568 is substantially different from that of the pivotal Studies 3543 and 3545. The ABR data from the extension trial, Study 3568, are not pooled together with the previous two trials (Studies 3543 and 3545) with respect to the evaluation of the integrated efficacy in routine prophylaxis.

Study 3568:
In this BLA supplement, the applicant submitted the updated safety and efficacy data for PTPs (including all age groups) from the completed safety extension trial conducted in PTPs, Study 3568 (Guardian 2) titled "Safety and Efficacy of Novoeight in Prevention and On Demand Treatment of Bleeding Episodes in Subjects with Hemophilia A".

Study 3568 was designed to provide long-term safety and efficacy in managing subjects on routine prophylaxis and on-demand regimens with Novoeight and using bolus administration of Novoeight during surgery. The population consisted of male subjects with severe hemophilia (FVIII activity ≤1%). A total of 214 patients were enrolled in Study 3568 and 213 patients were dosed with Novoeight in the trial. One patient withdrew before dosing and was therefore excluded from the full analysis set. Seven subjects received on-demand therapy only, thus a total of 207 patients were on routine prophylaxis in this trial. Twenty-seven patients changed to a less frequent (40–60IU/kg, twice weekly or every third day) dosing regimen and remained on this dosing regimen until the end of the trial.

Study 3568

Efficacy

Assessment of Routine Prophylaxis as extended treatment at currently approved doses

A total of 214 patients were enrolled in Study 3568 and 213 patients were dosed with Novoeight in the trial. One patient withdrew before dosing and was therefore excluded from the full analysis set. A total of 207 patients were on routine prophylaxis in the extension trial, Study 3568. The hemostatic outcomes for 206 subjects (1 subject withdrew prior to first dose) are provided in Table 1 below.

The primary endpoint was the frequency of development of FVIII inhibitors (≥0.6 Bethesda Units [BU]).

The annualized bleeding rates (ABRs) were estimated using a Poisson model allowing for over-dispersion and presented with a 95% confidence interval (95% CI).

One hundred and eighty-eight (188) subjects from the previous two trials (3543 and 3545) continued into the extension trial (up to 6 years duration). Additionally, 18 subjects (7 subjects from an on-demand sub-trial and 11 subjects from a pharmacokinetic trial) were included in the extension trial 3568. These previously treated patients received prophylaxis treatment every other day or three times weekly at the dose levels described in Table 1 below.

Table 1: Annualized Bleeding Rate (ABR[a]) for previously treated patients on Routine Prophylaxis from Study 3568

	Small children 0 - <6 years	**Older children 6 - <12 years**	**Adolescents 12 - <18 years**	**Adults ≥18 years**	**Total**
N[b]	27	28	23	128	206
Median (IQR)	1.08 (2.83)	1.57 (3.82)	1.57 (2.34)	1.38 (2.96)	1.39 (2.94)
Mean (95%CI)	1.87 (1.14; 3.09)	2.90 (2.01; 4.17)	1.93 (1.33; 2.82)	2.61 (2.08; 3.28)	2.45 (2.07; 2.90)

a: The ABRs were estimated using a Poisson model allowing for overdispersion.
b: Patients dosed every other day or three times weekly

Abbreviations: N: number of patients; IQR: interquartile range defined as the difference between the 75th percentile and the 25th percentile; CI: confidence interval.

Assessment of Routine Prophylaxis using the less frequent regimen (new dosing regimen)

Twenty-seven patients were changed to a less frequent (40–60IU/kg, twice weekly or every third day) dosing regimen and remained on it until the end of the trial. Of the 207 PTP subjects who were on routine prophylaxis, 106 PTPs were eligible to be dosed less frequently, but only 27 PTPs were dosed less frequently (twice weekly or every third day). Thus, subjects who received the dose of 40-60 IU/kg twice weekly or every third day were not randomized, but represented a group of subjects selected to receive this dosing regimen. The differences in bleeding frequency (ABR) of subjects who were eligible (n=79) to receive the less frequent regimen and subjects who received the less frequent regimen (n=27) prior to modification of the dosing regimen are provided below:

Table 2: Previous Treatment Details prior to Shifting/not-Shifting to Less Frequent (40–60IU/kg, twice weekly or every third day) Prophylaxis Dosing Regimen in Trial 3568

Pre-treatment ABR rates	**PTPs shifting to less frequent* prophylaxis dosing regimens regimen N=27**	**PTPs who did not receive less frequent prophylaxis dosing regimens N=79**
N		
Number of bleeds	26	79
Duration (in years)	25	160
Poisson estimate (95% CI)	25.72	78.6
Median (IQR)	**0.97** (0.61; 1.55)	**2.04** (1.33; 3.12)
Min; Max	1.00 (1.00) 0.00; 4.00	1.00 (2.00) 0.00; 19.88

Less frequent: *(40–60IU/kg, twice weekly or every third day)

Results

Results: The median ABR for the 27 subjects who received the less frequent regimen (40–60IU/kg, twice weekly or every third day) was 0.0 (IQR 3.6; Poisson estimates 2.0; 95% CI (1.2; 3.3)). Since subjects who completed the study were provided the opportunity to shift to the less frequent prophylaxis regimen, ABR data for the remaining 79 subjects were not available but it could be assumed that the ABR rates may be similar to the end of study ABR (2.04) as the dosing remain unchanged and ABR rates appeared to be consistent in the final 12 months of the study.

In addition, the less frequent (40–60IU/kg, twice weekly or every third day) prophylaxis dosing regimen is not supported based on data from 27 subjects who may have lower risk of bleeding. The selection of patients with lower bleeding risk profile without pre-specified parameters introduces a selection bias.

Control of Bleeding during routine prophylaxis

The success rate for the treatment of bleeds was 89.8% on the routine prophylaxis regimen, 94.1% on the routine prophylaxis less frequent (40–60IU/kg, twice weekly or every third day) dosing regimen and 96.7% on the on-demand regimen when bleeds with missing evaluation of hemostatic response were counted as failure. The mean number of injections required from start to stop of a bleed was 1.7 injections/bleed during the routine prophylaxis regimen, 1.3 injections/bleed during the routine prophylaxis less frequent (40–60IU/kg, twice weekly or every third day) dosing regimen and during the on-demand regimen. These data were consistent with the success rates (84%) observed in the approved label.

Perioperative Management

Eighteen major surgeries were performed in 14 subjects during the trial. The success rate during and after these surgeries was 100%. These data were consistent with the rates (100%) observed in the approved label.

Safety Results

Treatment with Novoeight was well tolerated and no safety concerns were identified in the subjects enrolled in Study 3568. No FVIII inhibitors were detected in Study 3568.

Conclusions: ABRs in Study 3568 were lower than that from previous Studies 3543 and 3545. The different sensitivity analyses confirmed the main findings in the trial and thereby provided confidence in the results. With respect to efficacy of the less frequent dosing regimen, there is concern for selection bias in the 27 subjects who switched to a less frequent dosing regimen in Study 3568 since these subjects had lower ABRs prior to shifting compared to the 79 subjects who had the option but did not shift to the less frequent prophylaxis dosing regimen. The absence of randomization and selection of subjects with lower ABRs makes the assessment of the benefit of the less frequent dosing challenging, and raises the question as to whether the efficacy of this dosing regimen may only be applicable to a population at lower risk of bleeding.

Study 3809:

The applicant also submitted the safety and efficacy results from the completed clinical trial conducted in **PUPs, Study 3809** (Guardian 4) titled "Safety and Efficacy of

Novoeight in Prevention and Treatment of Bleeds in Pediatric Previously Untreated Patients with Hemophilia A". Study 3809 was designed to evaluate the efficacy and safety of Novoeight in the treatment and prevention of bleeds in pediatric PUPs with hemophilia A. The study comprised a main phase and extension phase.

During Study 3809, a total of 59 patients were exposed to Novoeight. Fifty-seven (57) patients were treated prophylactically with Novoeight, as three subjects (2 in the inhibitor cohort and 1 in the non-inhibitor cohort withdrew from the main phase of the study. The disposition of subjects included in Table 3 is provided below. Table 3 represents the efficacy data for Novoeight as reported through ABR rates following routine prophylaxis and control of bleeding for breakthrough bleeding. Perioperative assessments were not planned in Study 3809.

Figure 1 Disposition of subjects in Study 3809

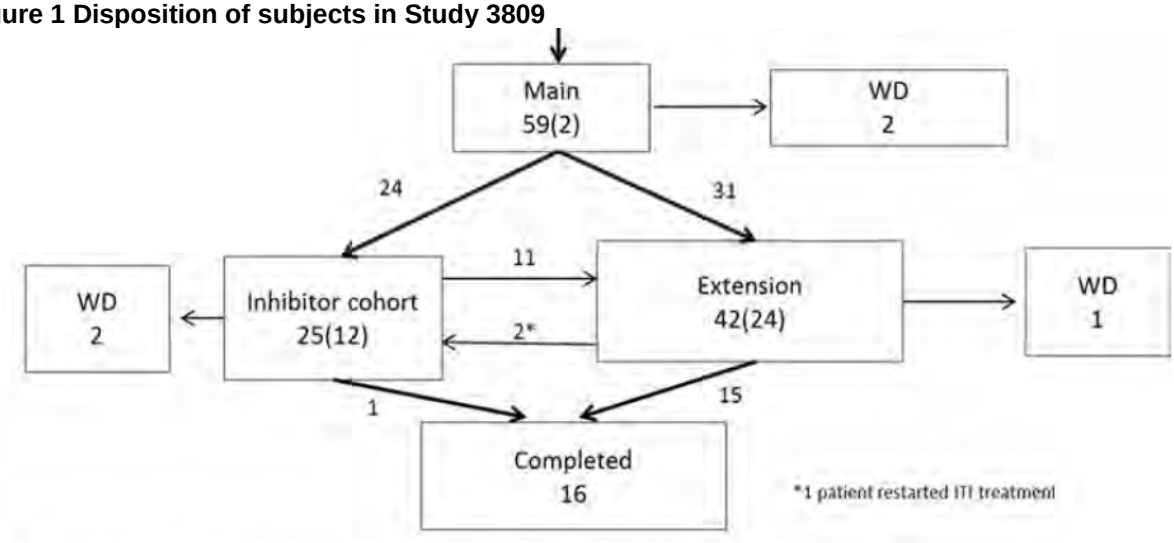

Table 3: Summary of Study 3809 Subjects and Outcomes

Outcomes	Main Phase PPX (completed)	Extension Phase PPX
Number of patients	57	42
Efficacy		
ABR bleeds/patient/year (95% CI)	5.45 (4.07, 7.30)	3.74 (2.60, 5.39)
Dose (IU/kg/month/patient) Mean (SD) Median (IQR) Min; Max	292.5 (285.0) 227.1 (153.6) 66; 1699	385.9 (200.9) 339.0 (229.2) 129; 1093
Number of patients with bleeds, N (%)	36 (64.3)	29 (69.0)
Number of bleeds	126	140
Hemostatic response Bleeds Success (%)	126 (100.0) 106 (84.1)	140 (100.0) 124 (88.6)
Safety		
Number of patients developed FVIII inhibitors, N (%)	24 (42.9)	1 (2.3)
Number of patients developed high titer FVIII inhibitors, N (%)	15 (26.8)	

Source: Based on FDA Analysis of data from BLA 125466 eCTD Module 5, and Tables 11-2 and 11-3 of NN7008-3809 report-body.
Note: N: number of patients; PPX: routine prophylaxis; ABR: Annualized bleeding rate; CI: Confidence interval; Patients could develop FVIII inhibitors at any time during the trial. Once patients developed inhibitors they were marked as inhibitor patients for the entire trial.

During Study 3809, the 57 patients administered a routine prophylaxis regimen had a mean 103.7 ED. The mean ABR in PUPs is acceptable, since these subjects develop inhibitors and are predisposed to a higher risk of bleeds. Therefore, the ABR rate of 5.45 observed in the inhibitor cohort is acceptable. The ABR rates in the non-inhibitor cohort is within the ABR rates observed in the pivotal study. Among the of 56 patients who completed the main phase, twenty-four (42.9%) patients developed FVIII inhibitors (Table 1). One patient in the extension phase developed FVIII inhibitors following exposure to Novoeight. The incidence rate of inhibitors (42.9%) in the completed main phase was within range of those reported from large studies with recombinant FVIII

products. Of the 25 patients with inhibitors (from both the main and extension phases of the trial), 15 developed high titer inhibitors defined as a peak titer ≥5 BU (Table 2). Treatment with Novoeight was well tolerated and no safety concerns other than inhibitors were identified.

Study 3568 included patient reported outcomes that were reviewed, but were not included in the label since the tools to assess quality of life metrics have not been validated. However, bleeding outcomes for routine prophylaxis and control of bleeding represent patient reported outcomes to a large extent with a small contribution by the investigator.

Conclusions: The inhibitor rate observed in PUPs is consistent with results observed in the SIPPET study and in patients at mutational risk of developing inhibitors. Therefore, these results do not warrant additional measures such as black box warnings or limitation of use. Overall, Novoeight was well tolerated and no safety concerns other than inhibitors were identified.

Conclusions for Clinical Efficacy Data Review

Review of the data from Studies 3568 and 3809 support the currently listed dosing regimens and indications in the package insert. The update of the label with respect to the on-demand and control of bleeding indication is acceptable as it maintains consistency of the indication across the product class.

The pooled representation of efficacy data from Studies 3568, 3543 and 3545 as proposed by the applicant is not acceptable. The ABRs varied between the pivotal trials in the original BLA (6.5 bleeds/patient/year in Study 3543 and 5.38 bleeds/patient/year in Study 3545) and the trials submitted in this supplement (2.44 bleeds/patient/year in Study 3568 and 4.40 bleeds/patient/year in Study 3809). During the original BLA submission, the interim data from Study 3568 was included in the original BLA and pooled ABR results for the trials was included in the labeling; however, the interim ABRs (5.3 for adults and 6 for adolescents) from Study 3568 were similar to the ABRs from Studies 3543 and 3545. Therefore, at the time of initial approval it was reasonable to pool data. However, additional subjects were enrolled subsequent to this analysis, and the resultant differences between the bleeding phenotype and mean dose in the final analysis population of the extension study (3568) are different from those of Studies 3543, 3545 and the interim analysis population in Study 3568. In this efficacy supplement, the ABR (2.44) from Study 3568 was significantly lower than the ABRs from Studies 3543 and 3545. These differences may have influenced the outcomes of the final analyses of 3568 and Studies 3543 and 3545. The ABR results of Study 3568 are compelling enough to warrant inclusion in the label as a separate analysis.

Submission of the study report for Study 3809 of 59 PUPs in this BLA 124466/243 fulfills PMC #1 as listed on the FDA approval letter dated October 15, 2013. The

incidence rate of inhibitors in Study 3809 of PUPs was within the expected range (27.8-44.5%) of those reported from large studies with recombinant FVIII products. No new safety concerns were identified.

Statistical Summary:
Based on the results of the 3543, 3545, 3568, and 3809 studies, the proposed updated labeling was verified for the previously approved indications of on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in adults and children with hemophilia A. However, there is no adequate statistical evidence to support the newly proposed less frequent dosing regimen, i.e., twice weekly dosing for routine prophylaxis. Therefore, from a statistical perspective, approval of the less frequent dosing regimen is not recommended. Also, due to the substantial difference in ABRs among the three individual PTP trials, pooling of the efficacy results is not recommended. Discussion of the individual trial results is recommended for inclusion in the label.

Pharmacovigilance:
On April 23, 2018, the BLA applicant submitted amendment #3 to this BLA125466 supplement 243, including updated Risk Management Plan (version 5.0) which included the Pharmacovigilance Plan. The Pharmacovigilance Plan proposed by the BLA applicant is adequate. The Division of Epidemiology (DE) recommendations are as follows: 1) It is appropriate for the applicant to move information about immunogenicity from sub-section 6.2 of the USPI to sub-section 6.1 because it pertains to clinical trial data. 2) It is appropriate for the sponsor to change the name of sub-section 6.2 of the USPI to Postmarketing Experience. The sponsor's statement in sub-section 6.2 that the AEs reported during the postmarketing period are similar to those observed during clinical trials is adequate because the clinical trials safety data are indeed similar to the postmarketing safety data available in FAERS and the data mining results.

Bioresearch Monitoring (BIMO):
Bioresearch Monitoring (BIMO) inspections of four clinical investigators did not reveal substantive problems that impact the integrity of the data submitted in the application.

b) Pediatrics

The BLA applicant does not claim new active ingredients, new indications, new dosage forms, or new routes of administration. The original BLA 125466.0 review process had Pediatric Review Committee (PeRC) on September 11, 2013. This BLA supplement is not subject to Pediatric Research Equity Act (PREA).

We note that the applicant has fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

c) Other Special Populations

Not applicable.

7. SAFETY

The safety data from Studies 3543, 3545 , 3658 were pooled to evaluate any new signals of safety and to assess the incidence of adverse reactions. No new safety signals were detected. Data from 3809 was not pooled for the safety analysis as this was a study conducted in PUPs, a group which represents a higher risk group for developing FVIII inhibitors.

The integrated safety analyses included 301 exposed subjects: 242 PTPs and 59 PUPs. Overall, Novoeight was well tolerated, and no unexpected patterns in the reported AEs and SAEs were observed. No differences in the safety profile of Novoeight were observed between children and adults. The overall rate of AEs decreased with time on Novoeight treatment, indicating that there is no increased risk based on increased duration of exposure to Novoeight. As of 13 February 2017, no PTPs developed FVIII inhibitors (≥0.6 BU). The PUPs developed inhibitors at an expected rate based on prospective trials with other marketed rFVIII products in PUPs. Serious adverse drug reactions reported were factor VIII inhibitors in PUPs. The most frequently reported adverse reactions observed in clinical trials (≥ 1%) were development of activity-neutralizing antibodies (inhibitors) in PUPs, injection site reactions, and pyrexia.

Novoeight was well-tolerated. No new safety concerns were identified. The rate of development of factor VIII inhibitors in study subjects with PUPs is on the upper limits of the expected rates, however, the study PUPs were at a higher risk of development of factor VIII inhibitors.

Overall, the submitted data support a favorable benefit-risk assessment for use of the product in all studied populations in all the currently approved indications.

8. ADVISORY COMMITTEE MEETING

No advisory meeting was held in conjunction with this this supplement, given that no issues regarding safety or efficacy arose that were judged to benefit from advisory committee input.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable.

10. LABELING

Several information requests were sent to the Applicant to make edits to the submitted draft package insert (PI). The APLB reviewed the efficacy supplement submitted by Novo Nordisk for NOVOEIGHT [antihemophilic factor (recombinant)]. The applicant proposed to revise the PI to: include data from their post-marketing trials, update safety information, update dosing information, and change the current indication to "on demand" treatment and control of bleeding episodes. APLB reviewed the draft PI received on July 11, 2018 and draft Patient Package Insert (PPI) received on October 5, 2018. The APLB review comments from a comprehension and promotional perspective were sent to the BLA applicant on October 29, 2018, and were resolved.

The following were key labeling recommendations were discussed and agreed upon with the applicant during the course of the review.

a) Efficacy updates from the extension trial (Trial 3568) are not pooled with the efficacy data from Study 3543 and Study 3545, the primary study intended to support the initial approval of the product in 2013. The ABR rates observed in Trial 3568 (ABR 2.45) in both pediatric and adults subjects are substantially lower than Study 3543 in adults and adolescents and 3545 in children < 12 years (ABR 6.24). It is unclear as to whether the a) differences in the proportion of patients on on-demand vs routine prophylaxis prior to enrollment to these studies and resultant improvement in joint conditions b) under-reporting of bleeding events or c) increase in the mean doses in Study 3568 were contributory to the differences in ABR. For these reasons, the efficacy data from the extension trial and the pivotal studies are not pooled but are included separately.

b) The dosage recommendations to include a less frequent dosing (40–60IU/kg, twice weekly or every third day) regimen is not included in the label. These dosage recommendations were based on hemostatic outcomes in 27 selected subjects who were at a lower risk of bleeding. The absence of randomization and selection of these subjects imply that the efficacy of this dosing regimen may only be applicable to a population at lower risk of bleeding.

c) The efficacy and safety data, particularly the inhibitor rate in PUPs, will be included in the label.

d) Editorial changes to the indication statement are acceptable.

e) The Special Populations Section is updated to include Clinical Pharmacological information regarding decreased clearance and increased AUC in patients with BMI ≥ 30kg/m^2.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee recommends approval of this efficacy supplement.

b) Risk/ Benefit Assessment

Novoeight appears reasonably safe and likely to provide therapeutic benefit to patients with hemophilia A. The clinical results support the previously approved indications of: on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in adults and children with hemophilia A.

The product appears well-tolerated. No new safety concerns were identified. Overall the benefit/risk profile of Novoeight remains favorable for the proposed indications.

c) Recommendation for Postmarketing Activities

There are no safety concerns that warrant a postmarketing requirement (PMR) or postmarketing commitment (PMC). Therefore, no new PMRs or PMCs are recommended.

The study report Study 3809 of 59 PUPs in this BLA 124466/243 fulfills PMC #1 listed on the FDA approval letter dated October 15, 2013.