Summary Basis for Regulatory Action

Date	15 October 2013
From	Natalya Ananyeva, PhD, Committee Chairperson
Subject	Summary Basis for Regulatory Action
BLA #	STN 125466/0
Applicant	Novo Nordisk Inc.
Date of Submission	October 16, 2012
PDUFA Goal Date	October 16, 2013
Proprietary Name / Established name	Novoeight / Antihemophilic Factor (Recombinant)
Dosage form	Novoeight is available as a lyophilized powder in single-use vials containing nominally 250, 500, 1000, 1500, 2000 and 3000 international units per vial. Each vial is reconstituted with 4 mL of 0.9% sodium chloride solution prior to intravenous injection.
Proposed Indications	Novoeight is indicated for use in adults and children with hemophilia A for: • Control and prevention of bleeding episodes • Perioperative management • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
Orphan Designation	No
Recommended Action	**Approval**
Signatory Authorities Action	**Jay S. Epstein, MD**_____ *Office Signatory Authority:* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* **Mary Malarkey**_____ *Office Signatory Authority:* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

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Advisory Committee	Product not presented to Advisory Committee

1. Introduction

Novo Nordisk Inc. submitted an original Biologics License Application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), under the proprietary name Novoeight, with the following indications in adults and children with hemophilia A: (1) Control and prevention of bleeding episodes, (2) Perioperative management and (3) Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. This product, with an International Nonproprietary Name of turoctocog alfa, is currently not licensed or authorized to be marketed in any country.

The active ingredient in Novoeight is a recombinant (r) analogue of human coagulation factor VIII (FVIII), with a truncated B-domain. Novoeight is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology, and purified using a process that includes two validated viral inactivation/reduction steps - detergent treatment and nanofiltration. No material of human or animal origin is used in the establishment of the CHO cell line, cell culture, purification or formulation of Novoeight.

The safety and efficacy of Novoeight were evaluated in three Phase 3 clinical trials, including a pivotal trial in adolescents and adults, a pediatric trial in children < 12 years old, and an ongoing extension trial. All studies were designed as multi-center, open-label, uncontrolled trials with the objectives of assessing the incidence of inhibitor formation and hemostatic efficacy.

2. Background

Currently, several rFVIII products (Recombinate, Kogenate FS, Advate, and Xyntha) and plasma-derived FVIII concentrates are licensed in the U.S. for the treatment of patients with hemophilia A.

Novoeight was developed for the U.S. market under IND 14059. In Novoeight, the B-domain of the FVIII molecule is truncated to a segment of 21 amino acids including residues ---------(b)(4)---------- of the wild-type B-domain thus preserving the native flanks of the B-domain that are adjacent to the sites of --------(b)(4)-------- of FVIII.

The original BLA was received on 16 October 2012 and reviewed under PDUFA V. In the course of the review, upon FDA requests, the Applicant performed and submitted data from additional viral clearance validation studies; tightened the acceptance criteria for several Specification parameters based on new statistical analyses of manufacturing data; and revised the SOP for the analytical method for the determination of ----------*(b)(4)*----------. The data contained in the original BLA, these additional studies and revisions as well as the Applicant's responses to numerous Information Requests support the consistency and robustness of the manufacturing process for Novoeight.

Novo Nordisk provided data to support the equivalence of Novoeight FVIII potency values determined by the Chromogenic Substrate (CS) and One-Stage Clotting (OC) assays. FDA and Novo Nordisk agreed to the use of the OC assay to assign potency of Novoeight batches distributed in the U.S. based on the general availability of the OC assay in clinical laboratories, and comparable variability of the two assays.

All inspectional issues identified during the facility inspection were satisfactorily addressed. The clinical data demonstrate the safety and efficacy of Novoeight for the proposed indications. Bioresearch Monitoring inspections support the validity of the clinical data.

3. Chemistry, Manufacturing and Controls (CMC)

Manufacturing Process

Drug Substance (DS) for Novoeight is manufactured at the Novo Nordisk A/S facility in ---(b)(4)---, Denmark (------(b)(4)------). The DS manufacturing process is comprised of three stages - cell culture, capture of rFVIII protein from the culture media, and purification of DS.

Recombinant FVIII protein is expressed in a Chinese hamster ovary (CHO) cell line transfected with a vector containing the turoctocog alfa expression cassette. The cells are expanded from ----------(b)(4)----------.

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- ----------(b)(4)--------
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Novoeight Final Drug Product (FDP) is manufactured at the Novo Nordisk A/S Facility in ---(b)(4)---, Denmark (------(b)(4)----------). The FDP manufacturing process consists of the formulation of the --(b)(4)-- DS, sterile filtration (0.22 µm), filling, and lyophilization. Labeling and secondary packaging is performed at the Novo Nordisk A/S facility in ----(b)(4)---, Denmark (-------(b)(4)---------)

Process Validation

Novo Nordisk's validation strategy for the turoctocog alfa DS manufacturing process is consistent with the recommendations in ICH Guidelines Q7, Q8 and Q11, with elements of *Quality by Design*. The strategy included Process Evaluation, Process Performance Qualification, and Continued Process Verification (planned post-marketing monitoring).

Process Evaluation for Drug Substance

Critical Quality attributes (CQAs) and Critical Process Parameters (CPPs) were identified based on comprehensive characterization of turoctocog alfa and risk assessments (severity ranking of quality attributes with respect to risk to patients, and Failure Mode Effects and Criticality Analysis (FMECA) with respect to process parameters at each step). Based on the risk assessments, Process Evaluation studies were performed to establish the acceptance criteria for CPPs with regard to their potential impact on CQAs.

The operational ranges for the CPPs of the cell culture process were established in laboratory-scale, using different combinations of process parameters, and verified under worst-case conditions. The selected ranges were validated for scalability for commercial manufacture by demonstration of comparability of quality characteristics and yields of turoctocog alfa batches produced at different scales. Responding to FDA requests, Novo Nordisk established alert limits for additional in-process control (IPC) parameters, and developed instructions to address aberrant trends in IPC parameters or test results.

Process Evaluation studies for the purification process included single-parameter studies, multi-factorial design-of-experiment studies, and mathematical modeling. Parameter ranges predicted by computer simulation were tested and verified in laboratory-scale experiments performed at set-points and under worst-case conditions. The scalability of the process parameters was confirmed by comparability of quality attributes of products derived from laboratory-scale and manufacturing-scale runs.

All process holding times and storage times for each intermediate are adequately validated in respective stability studies.

Process Performance Qualification for Drug Substance

The Novoeight Process Performance Qualification (PPQ) program is comprised of the ---------(b)(4)----------:

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- ----------(b)(4)----------

- ----------(b)(4)----------.

Based on the results of IPC testing and batch analyses of PPQ batches, the validated manufacturing process performs consistently and produces DS batches that meet the predetermined criteria of quality characteristics.

Process Validation for Drug Product

Process Design experiments established the optimal conditions for the lyophilization process and showed that the filling overage (b)(4) is sufficient to assure that the vial contains the labeled potency for all dosage strengths. The process parameters were justified by the production of (b)(4) manufacturing-scale batches at challenged lyophilization set points.

For PPQ of the manufacturing process, three batches of turoctocog alfa FDP were produced at commercial scale with the highest (3000 IU), lowest (250 IU) and intermediate (2000 IU) dosage strengths. Consistency of the process is supported by IPC and release testing results.

Thus, the manufacturing process for Novoeight is well controlled, adequately validated and performs consistently as evidenced by:

- Identification of CPPs and validation of their operating ranges;
- Identification of IPC and release tests and validation of their acceptance criteria;
- Robustness of the manufacturing process within the design space as demonstrated in Process Evaluation/Design studies by comparable performance of individual steps at both laboratory and commercial scales;
- Extensive characterization of representative DS batches;
- Satisfactory release data for over --------(b)(4)------- batches (commercial scale) spanning (b)(4) fermentation campaigns, including IPC and release test results of all PPQ batches;
- Availability and adherence to SOPs as verified during the Pre-License Inspection.

Final Drug Product: Composition and Presentation

Novoeight is supplied as a white lyophilized powder in single-use glass vials of six nominal dosage strengths: 250, 500, 1000, 1500, 2000 and 3000 IU per vial. Each vial and carton is labeled with the actual FVIII activity determined by a one-stage clotting assay using a reference material calibrated against a World Health Organization (WHO) International Standard for FVIII Concentrate.

Novoeight is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (sterile 0.9% sodium chloride). The reconstituted product contains rFVIII and the following components per mL: 18 mg sodium chloride, 1.5 mg L-histidine, 3 mg sucrose, 0.1 mg polysorbate 80, 0.055 mg L-methionine and 0.25 mg calcium chloride dehydrate.

Each carton contains 1 vial of Novoeight, a syringe pre-filled with the diluent, and a 510(k)-cleared, sterile needleless reconstitution device. The device has a plastic spike for puncturing the stopper of the FDP vial, and a 25-µm in-line filter for particulate filtration and flow aspiration.

Control of Starting Material

No raw materials of animal or human origin are used in the manufacture or formulation of Novoeight other than the CHO cell line. All externally sourced raw materials are purchased from approved suppliers and are control tested according to Novo Nordisk's program for raw materials. -------(b)(4)------ is produced in-house and tested ----------(b)(4)----------.

Cell Bank System
The turoctocog alfa production cell line was created by transfecting a CHO cell line with a vector that contains the turoctocog alfa expression cassette. The expression vector is well-characterized and is based on ----------(b)(4)----------. The turoctocog alfa cDNA was generated from the wild-type human FVIII cDNA sequence by ----------(b)(4)----------. The cDNA sequence of the 21-amino acid truncated B-domain encodes amino acids ----------(b)(4)---------- of the wild-type FVIII B-domain.

Characterization of the Master Cell Bank (MCB) and WCB was performed in accordance with ICH Guideline Q5D: *Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological / Biological Product*, and included specification analyses for Sterility, Mycoplasma, Product Identity, Cell Growth, and Cell Viability. Evaluation of the cell bank system for safety with regard to adventitious viruses was performed in accordance with ICH Guideline Q5A(R1): *Guideline for Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.*

Genetic characterization confirmed the same integration pattern in genomic DNA isolated from MCB, WCB and End-of-Production (EOP) cells (by --------(b)(4)--------), the same size of expressed mRNA (by ----------(b)(4)----------), and expression of the correct turoctocog alfa coding DNA sequence in all sample types. Stable protein expression is maintained from start to end of production as supported by constant FVIII levels measured by a validated --(b)(4)--.

Anti-FVIII Monoclonal Antibody
The immunoaffinity step employs a recombinant anti-FVIII mAb expressed in another transfected CHO cell line cultured in a ---(b)(4)--- process. The antibody is purified by a (b)(4) process which includes ----------(b)(4)----------.

----------(b)(4)----------. The manufacturing process for anti-FVIII mAb was qualified according to FDA Guidance: *Monoclonal Antibodies Used as Reagents in Drug Manufacturing*, March 2001. Process consistency was demonstrated by producing (b)(4) anti-FVIII mAb batches that met release specifications, and analysis of three batches for consistent removal of process-related impurities ----------(b)(4)---------- and product-related impurities ---(b)(4)---.

Characterization of rFVIII Structure and Function

The active ingredient in Novoeight is a rFVIII with a molecular mass of 166 kDa, calculated excluding post-translational modifications. This rFVIII molecule is a glycoprotein containing a heavy chain (HCh) of (b)(4) and a light chain (LCh) of -(b)(4)-, with 21 of the 908 amino acids of the B-domain of endogenous FVIII connected to the C-terminus of the heavy chain. Once activated, the resulting rFVIIIa has a comparable structure to the endogenous FVIIIa.

The Novoeight characterization program utilized an extensive panel of analytical methods to evaluate the structure and function of the rFVIII product.

The primary structure of turoctocog alfa was confirmed by ----------(b)(4)----------.

The biological activity of Novoeight was demonstrated by its ability to support Factor X activation in the CS assay and to promote blood clotting in the OC assay. Based on the data from (b)(4) DS batches and (b)(4) FDP batches, the Applicant showed that the activity values of Novoeight determined by the CS and OC assays are very similar. The OC/CS ratio of FVIII activity values for the Reference Material is ----(b)(4)---- using both the 7th and the 8th WHO International FVIII Standard for assay calibration, and those for DS and FDP batches are -----(b)(4)-----, respectively. The OC/CS ratio was close to 1 in a field study.

Evaluation of Safety Regarding Adventitious Agents

Novo Nordisk manufactures the Novoeight FDP according to cGMP regulations. The potential contamination with non-viral adventitious agents such as bacteria, fungi, and mycoplasma is well controlled through the use of validated cleaning/sanitization procedures, in-process controls, and filtration steps including 0.2 µm sterile filtration. The Novoeight FDP is release tested for sterility, endotoxins, and particulate matter.

Turoctocog alfa is produced in a transfected CHO cell line. The potential risk of contamination with transmissible spongiform encephalopathy agents and viruses is minimized because no animal-derived raw materials are used in the establishment of the MCB, WCB, or manufacture and formulation of turoctocog alfa. The anti-FVIII mAb used in the purification process is also expressed in CHO cells, and produced without any animal-derived raw materials. In accordance with ICH Guidelines Q5A and Q5D, all tests performed on MCB, WCB, EOP cells and unprocessed bulks were found negative for the presence of virus, mycoplasma, bacteria and fungi. The tests only revealed the expected presence of non-infectious endogenous retrovirus-like particles detected in ----------(b)(4)----------. These results demonstrate that the cell bank system is adequately controlled, and the safety of the cell culture is ensured for up to (b)(4) harvests used in commercial production.

The risk of virus contamination is further mitigated by the inclusion of two dedicated viral clearance steps in the purification process: detergent treatment for virus inactivation (----------(b)(4)----------) and 20 nm filtration for virus removal. In addition, the immunoaffinity -------(b)(4)------- chromatographic steps also contribute to viral clearance. Novo Nordisk has evaluated these steps for viral clearance using ----------(b)(4)----------

----------(b)(4)----------. These model viruses represent a wide range of size and physico-chemical properties and the results support the effectiveness of the manufacturing process to clear viruses from Novoeight.

Release and Shelf-Life Specifications

The specifications for DS and FDP are established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from the CQAs to ensure consistency of identity, purity, biological activity (potency, content, specific activity), and safety. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. As requested by FDA during the review process, additional parameters were included and acceptance criteria for some parameters were tightened to represent manufacturing experience. These changes are summarized below and presented in **bold** in Tables 1 and 2.

For Drug Substance:

- ----------(b)(4)----------.
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- ----------(b)(4)----------.

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----(b)(4)----

-----(b)(4)-----

For Final Drug Product:

- The parameter "*FVIII Activity*" determined by the OC assay was included in FDP Specification, in addition to the parameter "*Potency*" determined by the CS assay. The acceptance ranges for the two assays are similar as supported by the data in the BLA.
- The parameter "*Specific Activity*" was included in DP Specification, with the established limit of ----(b)(4)----.
- The Specification limit for "*Purity*" at release was revised from -------(b)(4)--------, and the shelf-life limit from ------(b)(4)------, based on statistical analyses of release and stability data for batches produced from 2010 to present.
- ----------(b)(4)----------. This limit relates to product handling after reconstitution as reflected in the Prescribing Information: "Use Novoeight within 4 hours after reconstitution when stored at room temperature."
- Acceptance limits for Bacterial Endotoxin were revised based on the release and stability data for the highest dosage strength (3000 IU). The limit of ---(b)(4)--- is calculated according to ---(b)(4)--- for the lowest dosage strengths (250 IU) and is used for all dosage strengths, consistent with manufacturing experience.
- The Applicant committed (in a Postmarketing Commitment) to establish the methods for quantitative measurement of the excipients calcium chloride and sucrose in the FDP, and will include these parameters with acceptance criteria in the FDP Specification when the assays are validated (please refer to section 14).

TABLE 2: SPECIFICATIONS FOR DRUG PRODUCT

Test Parameter	Analytical Procedure	Acceptance Criteria
Solid state		
Appearance of powder	Visual inspection	Complies[1]
Reconstitution time / Solubility	Visual inspection	Complies[2]

Water content	----------(b)(4)----------	----------(b)(4)----------
Liquid state		
Appearance of solution	Visual inspection	Complies[4]
(b)(4)	------(b)(4)-----	----(b)(4)----
Identification	------(b)(4)-----	Complies[5]
Potency, IU/vial [6,7]	Chromogenic Substrate assay	----------(b)(4)---------- ----------(b)(4)--------
		----------(b)(4)---------- ----------(b)(4)-------
		----------(b)(4)---------- ----------(b)(4)-------
		----------(b)(4)---------- ----------(b)(4)--------
		----------(b)(4)---------- ----------(b)(4)--------
		----------(b)(4)---------- ----------(b)(4)--------
FVIII Activity, IU/vial [6,7]	One-Stage Clotting assay	**----------(b)(4)----------**
		----------(b)(4)----------
		----------(b)(4)----------
		----------(b)(4)----------
		----------(b)(4)----------
		----------(b)(4)----------
Content, mg/vial[7]	**----------(b)(4)----------**	**----------(b)(4)----------**
		----------(b)(4)----------
		----------(b)(4)----------
		----------(b)(4)----------
		----------(b)(4)----------
		----------(b)(4)----------
Specific Activity	Calculated from Potency and Content	**----------(b)(4)----------**
Purity	**--------(b)(4)-------**	**----------(b)(4)----------** **----------(b)(4)----------**
--------(b)(4)-------	**--------(b)(4)-------**	**----------(b)(4)----------** **----------(b)(4)----------**
--------(b)(4)------- **--------(b)(4)-------**	**--------(b)(4)-------**	**----------(b)(4)----------** **----------(b)(4)----------** **----------(b)(4)----------**
Antioxidant (L-Methionine)	**--------(b)(4)-------**	**----------(b)(4)----------**
Polysorbate 80	**--------(b)(4)-------**	**----------(b)(4)----------**
Particulate matter, particles per container	**--------(b)(4)-------**	**----------(b)(4)----------** **----------(b)(4)----------**
--------(b)(4)-------	**--------(b)(4)-------**	**----------(b)(4)----------**
Bacterial Endotoxins	**--------(b)(4)-------**	**----------(b)(4)----------**
Sterility	**--------(b)(4)-------**	Complies[8]

[1] A white or slightly yellow powder or friable mass
[2] The lyophilized powder dissolves within (b)(4) minutes at 20-25°C, giving a clear or slightly opalescent solution
----------(b)(4)----------

[4] Clear or slightly opalescent solution
[5] Comparable to reference
[6] The mean of three separate measurements
[7] The units IU/vial and mg/vial refer to IU or mg per withdrawable volume, (per 4 mL volume), and reflect what is available for the patient
[8] The product meets the requirement of test for sterility in --------**(b)(4)**------- 21 CFR.610.12

The current specifications for DS and FDP are adequate to control the identity, purity, biological activity, and safety of Novoeight.

Batch Analyses and In-Support Testing

The BLA contains results of batch analyses for --------**(b)(4)**------- lots of commercial-scale FDP and includes three PPQ batches of three dosage strengths - ----------(b)(4)----------. The results for all PPQ batches are within FDP Release Specification.

The Laboratory of Analytical Chemistry and Blood Related Products of the Division of Biological Standards and Quality Control (DBSQC) performed in-support testing of the 3 PPQ batches for the following parameters:

- Appearance of the lyophilized powder, and solution after product reconstitution with 0.9% sodium chloride
- Reconstitution Time
- Water Content by Karl Fischer Coulometry
- Purity and ----------(b)(4)---------- procedure as specified in the application
- Endotoxin by the Gel Clot and the Kinetic Turbidimetric test methods

DBSQC test results of the above tests for these lots met the respective specifications and were comparable to those reported by the Applicant. However, in the testing of Potency and Content and -------(b)(4)---------, DBSQC had the following observations:

- Potency
  Potency was determined for four lots of Novoeight: ----------(b)(4)---------- using both the CS and OC assays. DBSQC results were within ±20% of the Applicant's results. The values obtained by the CS method were 12-23% higher than those obtained by the OC method. The difference was ascribed to the use of different standards and aPTT reagents.

- Content and --------(b)(4)--------
  In performing the assay, DBSQC identified consistent difficulties in meeting the Criteria for System Suitability ----------(b)(4)----------. As a result of discussion at the Late-Cycle Meeting, Novo Nordisk sent technical experts to DBSQC on August 12-16, 2013 to exchange experience in ---(b)(4)--- analysis. The issue was resolved satisfactorily by revising the procedure to include recommendations from DBSQC and more specific procedural details. The current version of the procedure is found suitable for its intended use. DBSQC results on the three PPQ lots are comparable to those of the Applicant and are within the Specifications.

In conclusion, in-support testing confirmed the results of batch analyses for PPQ lots reported in the BLA and suitability of test methods for their intended use.

Exemption from CBER Lot Release

Novoeight is a recombinant product, and as such, alternatives to official lot release are allowed under the provision described in Federal Register (FR) 58:38771-38773. In 60 FR 63048-63049 published on 8 December 1995, FDA announced that routine lot-by-lot release by CBER is no longer required for licensure of this class of products. Novo Nordisk has demonstrated its ability to adequately control the manufacturing process, and consistently produce product lots of established quality. Therefore, exemption of Novoeight from CBER Lot Release is justified.

Stability Studies

The stability program for Novoeight includes studies under long-term storage conditions (refrigerated, and combination of refrigerated and room temperatures) and accelerated conditions and is adequate. The available stability data for the low (250 IU) and high (2000 IU and 3000 IU) dosage strength batches indicate that no unfavorable trends are observed during storage under long-term conditions. The data support the proposed shelf-life of Novoeight of 24 months when stored at 2 – 8ºC (36 – 48ºF). The data also support product storage at room temperature (≤ 30°C or 96ºF) for a single period of up to 6 months not to exceed the expiration date. The reconstituted product is stable for up to 4 hours at room temperature. The storage conditions and handling of reconstituted Novoeight are accurately described in the labeling.

As a Post Marketing Commitment (PMC), Novo Nordisk committed to include commercial batches of intermediate dosage strengths (500 IU, 1000 IU, and 1500 IU) in their stability study, which will be performed under real-time and accelerated conditions, and the results will be reported to FDA as specified in section 14.

Review of Manufacturing Facilities

The manufacture of Novoeight is performed at -(b)(4)- Novo Nordisk A/S facilities in Denmark ----------(b)(4)----------.

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Inspection of the Manufacturing Facilities

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----------(b)(4)----------.

At the conclusion of the inspection, CBER issued Form FDA 483 with four objectionable observations. The issues cited included (i) deficiencies in following the aseptic techniques in the seed laboratory; (ii) insufficient control over the cell culture process in ----(b)(4)---- in terms of addressing potential aberrant trends in process control parameters; (iii) lack of quantitative criteria in the qualification of chromatographic columns; and (iv) inadequate cleaning validation of critical process equipment, with set acceptance limits that do not reflect process capabilities.

In their August 16th, 2013 response, Novo Nordisk described the corrective actions that were implemented to address the 483 items. The corrective actions were reviewed and found to be adequate. All inspectional issues are considered resolved satisfactorily.

Environmental Assessment

The BLA included a request for a categorical exclusion from an Environmental Assessment under 21 CFR § 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally

occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

Recommendation

The manufacturing process for Novoeight, Antihemophilic Factor (Recombinant), is validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the product that meets release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents. Inspectional issues were adequately addressed in Novo Nordisk's responses dated 16 August 2013. The reviewers from the Division of Hematology and the Division of Manufacturing and Product Quality conclude that Novo Nordisk has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of Novoeight.

4. Non-Clinical Pharmacology/Toxicology

a) Pharmacological/Toxicological

The nonclinical program for Novoeight consisted of a series of Good Laboratory Practices (GLP)-compliant and non-GLP studies to demonstrate the safety and effectiveness of Novoeight in animals. Completed studies included safety pharmacology (rats and dogs), effectiveness including pharmacology (monkeys), proof-of-principle (hemophilic mice and dogs), dose range-finding studies (mice), acute toxicity (monkeys, with toxicokinetics), repeat-dose toxicity (rats with toxicokinetics and monkeys with toxicokinetics), immunogenicity (rats), and pharmacokinetics (mice and dogs). Activity of Novoeight for the proposed indication was tested in FVIII-deficient mice and dogs.

Overall, the nonclinical safety profile of Novoeight showed no unexpected findings, and did not identify any specific or novel, treatment-related toxicities. Novoeight was tested in animals at acute doses up to 5000 IU/kg (50 times the intended clinical dose of 100 IU/kg for each perioperative dose). Novoeight dosed animals were followed for a 24-hour recovery and observation period, during which time no adverse events were reported before the animals were euthanized at study termination. After repeated administration, the nonclinical safety profile for Novoeight raised no specific concerns and findings were related to exaggerated pharmacologic effects of FVIII. Repeat-dose toxicity studies were completed with daily dosing of up to 5000 IU/kg/day for 14 days (166 times the intended clinical dose of 30 IU/kg per dose for prophylactic use), and the product was well-tolerated. In the repeat-dose setting adverse events, including thromboembolic events, local reactions at the treatment site, and re-bleeding were noted in rats and monkeys at cumulative doses of 50 to 100-fold greater (i.e., 1250 IU-5000 IU/kg Novoeight) than the proposed maximum, single clinical dose of 150 IU/kg. With the exception of the thromboembolic events these adverse findings were predictive for human use of the product, as confirmed by the adverse events reported in the clinical trials. Pharmacokinetic profiles demonstrated a linear dose-dependent increase in the levels of FVIII, followed by a time-dependent decrease in product levels coincident with formation of anti-FVIII antibody and decreased FVIII activity. Previous nonclinical experience with similar recombinant FVIII products suggests that Novoeight dosing has the potential to elicit thromboembolic events, local irritation, hypersensitivity and neutralizing antibody formation following administration to animals. These potential safety issues, with the exception of the thromboembolic events observed

only in animal studies, are appropriately described in the clinical adverse event section of the Novoeight package insert.

The Applicant has not completed animal studies for carcinogenicity, mutagenicity, fertility, reproductive toxicity or teratogenicity: these studies are not required in support of this product class and indication as per the current ICH S6 (R1) guidance, and there were no special toxicity concerns identified for this product regarding impurities or unexpected toxic effects. An assessment of the carcinogenic potential of Novoeight was completed, and no carcinogenic risk from product use has been identified.

A toxicological risk assessment analysis was completed on potential leachables and extractables associated with Novoeight manufacturing and container closure system components. The results of this risk analysis indicated that the levels of potential leachable/extractable impurities appear acceptable, as they are significantly lower than the maximally allowed daily exposure levels based on extensive clinical and nonclinical experience.

Recommendation

The safety profile determined for Novoeight in the non-clinical program is sufficient to support its use in the proposed indications for the on-demand treatment and prophylaxis of bleeding episodes and the perioperative management of patients with hemophilia A.

5. Clinical Pharmacology

a) Mechanism of Action

When administered in a hemophilia A patient, Novoeight replaces the missing endogenous FVIII that is needed for effective hemostasis or prevention of bleeding. Upon activation by thrombin, FVIIIa acts as a cofactor for activated Factor IX triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen results in the formation of the fibrin clot that stops the bleeding.

b) Pharmacokinetics

The clinical pharmacology program included four studies. In all studies, blood samples for pharmacokinetic analysis were collected pre-dose, then at regular intervals up to 48 hours post administration of trial product(s). Pharmacokinetic assessments were based on FVIII activity which was determined using a one-stage clotting assay and a chromogenic substrate assay.

Study NN7008-3522: A multi-center, multi-national, open-label, single-dose sequential trial comparing pharmacokinetics and safety of Novoeight and a recombinant full length FVIII product (rFL FVIII product) in subjects with hemophilia A (FVIII activity <1%). There were 23 male patients (22 Caucasians and one Hispanic) in this trial and the mean age was 22 years (13-54 years). Two patients were below the age of 18 years (13 and 17 years). The patients received rFL FVIII product at a dose of 50 IU/kg body weight in the first period and subsequently (following a washout period of 4 days) Novoeight at a dose of 50 IU/kg body weight in the second period. Pharmacokinetic parameters were estimated by non-compartmental analysis. Overall, pharmacokinetics of Novoeight were comparable with the pharmacokinetics

of rFL FVIII product. The ninety percent confidence interval on log transformed AUC was within 0.80 to 1.25, indicating that the two products were bioequivalent (Table 3).

Table 3: Pharmacokinetic parameters for Novoeight and rFL FVIII product estimated by clotting and chromogenic assays (adjusted for actual dose and product strength)

Parameters	Clotting Assay		Chromogenic Assay	
	Novoeight	**rFL FVIII**	**Novoeight**	**rFL FVIII**
AUC (IU*hr/mL)	13.6 ± 4.1	12.7 ± 4.3	18.7 ± 5.1	14.9 ± 4.0
CL (mL/hr)	295 ± 115	316 ± 106	210 ± 67	264 ± 88
Half-life (hrs)	11 ± 5	11 ± 3	12 ± 9	12 ± 4
V_{ss} (mL)	3984 ± 775	4428 ± 818	3149 ± 1773	4037 ± 991
Incremental recovery	0.019 ± 0.004	0.018 ± 0.003	0.028 ± 0.006	0.023 ± 0.004

Study NN 7008-3600: Multi-center, open-label, non-randomized single dose trial investigating the pharmacokinetics of Novoeight in Japanese patients (n = 6, males) with severe hemophilia A, with a mean age of 33 years (19 to 46 years). The mean body weight was 67 kg (40 to 107 kg). The patients received a single intravenous Novoeight dose of 50 ± 5 IU/kg. Although the half-life of Novoeight was comparable between the Japanese and the Caucasian patients with hemophilia A, the clearance of Novoeight was slower (almost 45%) in Japanese patients.

Study NN7008-3543: A multi-center, open-label, uncontrolled trial on safety and efficacy of Novoeight in prevention and treatment of bleeds in previously treated patients (n = 22; 20 adults and 2 adolescents >12 years of age) with severe hemophilia A. This study compared the pharmacokinetics of Novoeight after the first dose (50 IU/kg body weight as in Study NN7008-3522) and after prophylactic dosing for 3-6 months (36-65 doses of Novoeight prior to the assessment of pharmacokinetics). The results of the study indicated that the pharmacokinetics of Novoeight were comparable between the first dose and after 3-6 months of dosing, i.e. there is no accumulation of Novoeight after multiple dosing.

Study NN7008-3545: A multi-center, multi-national, open-label, uncontrolled trial on safety and efficacy of Novoeight in previously treated pediatric patients with hemophilia A (0-<12 years) who had at least 50 exposure days (EDs) to their previous FVIII product. The pharmacokinetic study consisted of two age groups: 0-6 years (n = 14) and 6-<12 years (n = 14), with the mean age of the younger children 3.7 years (1-5 years) and the mean age of the older children 8.2 years (6-11 years). The children received a single dose of Novoeight. The results indicated that the clearance of Novoeight increased with increasing age requiring dose adjustment in younger and older children as compared to adults. The clearance in younger children (1-5 years), older children (6-12 years), and adults was 79, 117, and 210 mL/hr, respectively. The half-life of Novoeight was comparable between younger and older children but it was about 2 hours shorter in children than adults. This difference may not be of any clinical significance.

Recommendation

The design for pharmacokinetic studies is adequate, and the results and conclusions are acceptable. The clinical pharmacokinetic data indicate bioequivalence of Novoeight and a licensed recombinant full-length FVIII product.

6. Clinical/Statistical

a) Clinical Program

The clinical development program to support licensure of Noveight consisted of three Phase 3 trials that were designed as multi-center, open-label, uncontrolled, single-arm trials in previously treated patients (PTPs) with severe hemophilia A to evaluate the safety including immunogenicity, efficacy and pharmacokinetic parameters of Novoeight:

Trial ID (type of study)	No of subjects	Study title and design	Regimen
NN7008-3543	*Total (including sub-trial):* 150 adolescents and adults Surgery sub-trial: 9 PK: 22 subjects (same as in Trial 3522)	Pivotal trial A multi-center, multi-national, open label, safety, efficacy, single-arm trial in patients with severe hemophilia A investigating Novoeight when used for prevention and treatment of bleeds. Sub-trial: safety and efficacy when used for perioperative management.	Routine Prophylaxis: 20–40 IU/kg every second day or 20–50 IU/kg three times weekly. Treatment of acute bleeds: initial dose as per treatment guidelines Surgery: based on individual PK PK: In the first period rFL FVIII product at a dose of 50 IU/kg was given, followed by a washout period of 4 days. Then Novoeight at a dose of 50 IU/kg was given in the second period. Followed by prophylactic dosing for 3−6 months
NN7008-3545	*Total:* 63 children <12 years PK: 28	A multi-center, open-label, uncontrolled safety and efficacy trial of Novoeight in previously treated pediatric patients with hemophilia A.	Routine Prophylaxis: 25–50 IU/kg every second day or 25–60 IU/kg three times weekly Treatment of acute bleeds: initial dose as per treatment guidelines Surgery: based on individual PK PK: 50 IU/kg (single dose).
NN7008-3568	*Total (including sub-trial):* 188 pediatric, Adolescent or adults Surgery sub-trial: 2	*Extension trial* A multi-center, multi-national, open label, non-randomized, single-arm, safety and efficacy extension trial in patients with hemophilia A investigating Novoeight when used in a preventative or on-demand treatment regimen. Sub-trial: safety and efficacy when used for perioperative management.	Routine Prophylaxis: 20–50 IU/kg every second day or 20–60 IU/kg three times weekly. Treatment of acute bleeds: initial dose as per treatment guidelines Surgery: based on individual PK

In all of the above mentioned trials, the primary objective was to evaluate safety, especially inhibitor incidence, of Novoeight in patients with severe hemophilia A. The secondary objectives

were to evaluate the efficacy of Novoeight in the treatment of bleeds and the pharmacokinetics (PK) in patients with severe hemophilia A.

A total of 213 subjects, 150 adolescents or adult subjects from the age of 12 years (≥150 exposure days) and 63 pediatric subjects below the age of 12 years (≥50 exposure days) were analysed for efficacy. Safety assessment was performed on a total of 214 subjects. One subject only had PK assessment and did not participate in the pivotal efficacy trial.

b) Review of Clinical Data (Pivotal Trial NN7008-3543)

Pediatric data are discussed under PREA section below. The efficacy results of the extension study are not discussed here as the study is ongoing.

Study Design

The trial is a multi-center, multi-national, open-label, safety, efficacy, single-arm trial in subjects with hemophilia A. The subjects were recruited at 48 sites in 15 countries. The trial included three parts: Part A included subjects who completed the pharmacokinetic trial (Trial 3522); Part B included all other subjects, i.e., those receiving Novoeight for prevention or treatment of bleeding; Part C included subjects from Part A or Part B undergoing surgical procedures. The treatment period was 20-28 weeks per subject.

Subjects in Parts A and B received either 20-40 IU/kg body weight (BW) every other day or 20-50 IU/kg BW three times per week of Novoeight for at least 75 days. A total of 125/150 (83%) subjects were treated with the three times per week regimen. Subjects received 20-50 IU/kg for mild/moderate bleeds and doses of up to 200 IU/kg per day for up to 14 days for treatment of severe bleeds. Doses for surgery were calculated based on the recovery of Novoeight that was measured in the individual subject prior to the surgical procedure, and were adjusted to maintain a trough level of about 0.50 IU/mL.

Patient Characteristics

A total of 150 subjects were enrolled and treated with at least one dose of Novoeight, including 24 adolescents 12 to <18 years of age (16 subjects were ≥12 to <16 years). All subjects were males with severe hemophilia A (FVIII ≤1%) and > 150 previous exposure days (ED) to FVIII therapies. The median age was 25 years (mean 28 years; range 12-60 years). Among the 24 adolescents, the mean age was 14 years old (ranging from 12 to 17 years old).

A total of 91 subjects (60%) were previously treated with prophylactic regimens for an average of 79 months (range 2-480 months). Sixty-nine (69) subjects (46%) were previously treated with recombinant FVIII products. The majority of the subjects were White (81%); the second-largest group was Asian (13%). Nineteen percent (19%) of the subjects were from the US, 13% were from Serbia and 11% were from Brazil; the remaining 57% of the subjects were from 12 other countries.

A total of 4 subjects (3 adults and 1 adolescent) withdrew from the trial for the following reasons:

- -(b)(6)-: adverse event (fatigue for 24 hours after infusion)
- -(b)(6)-: treatment with another FVIII containing product
- -(b)(6)-: lost to follow-up
- -(b)(6)-: considered ineligible after it was determined that the adolescent subject had a history of a positive inhibitor test of 1 BU at another medical facility

Endpoints

The primary objective of this study was to determine the incidence rate of FVIII inhibitors (activity-neutralizing antibodies) associated with the use of Novoeight. The ----------(b)(4)---------- of the Bethesda inhibitor assay was used for inhibitor detection. A subject was considered to have developed an inhibitor if the titer was ≥0.6 Bethesda Units (BU)/mL. Any positive inhibitor with a titer of ≤5 BU/mL was considered as a low-titer inhibitor.

The secondary objectives were to assess the clinical efficacy of Novoeight for reducing the number of acute bleeding events per year on prophylactic treatment when compared to on demand treatment and for treatment of breakthrough bleeds using the following endpoints:

- Annualized bleeding rate (ABR; bleeds/patient/year) of prophylactic vs on-demand treatment
- Hemostatic effect for intra- and post-operative management and for treatment of spontaneous and traumatic bleeding episodes using a pre-specified four-point rating scale
- The number of infusions required per bleeding episode
- Novoeight consumption (international units/kg)

The safety of Novoeight was assessed using the following endpoints:

- Frequency of adverse events
- Vital signs (blood pressure, pulse, temperature, and respiratory rate)
- Clinical laboratory tests

EFFICACY AND SAFETY STATISTICAL METHODS

Analysis for efficacy and safety were done on the full analysis set (FAS), which included all subjects who were treated with Novoeight.

Primary Safety Analysis

The incidence rate for FVIII inhibitors was calculated and a one-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. For the calculation of the rate, the numerator included all subjects with inhibitors while the denominator included all subjects with a minimum of 50 EDs. If a subject did not complete 50 EDs but had inhibitor, he would also be included in the safety analysis. Safety endpoint with regard to inhibitors would be met if the upper one-sided 97.5% confidence limit was below 6.8%.

Secondary Efficacy Analysis

(1) The annualized bleeding rate was estimated in total and by cause of bleed (spontaneous, traumatic or other) based on a Poisson model allowing for overdispersion. No formal statistical testing was performed. The estimated mean bleeding rates were presented for all subjects and separately for adolescents and adults. The annualized bleeding rate was also estimated by country and by compliance group.

(2) Hemostatic efficacy for treatment of acute bleeds was evaluated according to a pre-specified four-point scale of “excellent”, “good”, “moderate”, or “none” (Appendix I). The treatment of the bleed was considered as a success with a response rating of “excellent” or “good”. As a conservative approach, the missing ratings were included as treatment failures. Hemostatic effect was further summarized by cause of bleed (spontaneous, traumatic or other), site of the bleed (central nervous system, joint, gastrointestinal, subcutaneous, muscular or other), classification of the bleed (mild/moderate or severe), time of the bleed (the day was divided into six time intervals, each of four hours), and compliance (good compliance or less compliance).

(3) Hemostatic efficacy both intra- and post-operatively was evaluated according to a pre-specified four-point scale of “excellent”, “good”, “moderate”, or “none” and was analyzed using descriptive statistics (Appendix I).

RESULTS

Safety
A total of 148 subjects had at least 50 EDs. There were no confirmed inhibitors reported for any subject. The one-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 2.46%, thus the primary safety endpoint (upper confidence limit below 6.8%) was met.

EFFICACY ANALYSES

Control and Prevention of Bleeding
A total of 499 acute bleeds were reported in 105 subjects. The median dose for treatment of a bleed was 27 IU/kg/dose (range 9.8 to 61.1 IU/kg). By site and causality for all bleeds, 373 (75%) were joint bleeds, 332 (66%) were spontaneous, 124 (25%) traumatic, and 43 (9%) were of unknown cause. Ninety percent were of mild severity (uncomplicated joint, muscular or subcutaneous bleeds). Sixty-seven percent (67%) of the 46 severe bleeds, defined as major bleeds which require hospitalization, occurred in the joint. A total of 357 bleeds (71%) were treated with one infusion, 89 (18%) were treated with two infusions and the remaining 11% required more than three infusions. One subject required 26 infusions to treat a muscle bleed caused by trauma. The duration of the bleed was 304 hours and the hemostatic response was rated as good.

The hemostatic response was rated as “excellent” (n=140) or “good” (n=263) for 81% of the bleeds. There was no treatment effect for 2.4% of the bleeds, and an additional 4.4% were not rated. A total of 300/373 (80%) joint bleeds and 22/25 (88%) muscle bleeds were treated successfully. For treatments of gastrointestinal bleeds (n=3), the success rate was 67%.

Perioperative Management
Data from nine surgeries (eight major and one minor; defined in Appendix II) in nine subjects were assessed. The surgery indications included arthropathy and chronic pain (n=1), synovitis (n=1), semi-impacted tooth and removal of tooth root (n=1), arthropathy (n=4), circumcision (n=1) and recurrent hemarthosis (n=1). Hemostasis was rated as “excellent” or “good” in all surgeries. Transfusion support of three units of red blood cells was required for one subject who underwent surgery for arthropathy.

Routine Prophylaxis
Of the 150 subjects dosed with Novoeight, 142 (95%) subjects had at least 75 EDs, and 148 (97%) had at least 50 EDs. The median dose per prophylactic infusion was 21 IU/kg (range 12.8-97.4 IU/kg).

The hemostatic efficacy of Novoeight for prophylaxis was evaluated against historical controls who received on-demand therapy. The control bleeding rate was calculated using data from nine publications. Trial data were weighted by the number of patients in each trial. The calculated mean ABR was 22 bleeds/patient/year for historical controls treated with on-demand therapy, and for subjects treated with routine Novoeight prophylaxis, it was estimated as 6.9 bleeds/patient/year. This represents a 68% reduction in the bleeding rate for subjects treated with Novoeight prophylaxis as compared to on-demand therapy historical controls.

The ABR for the year prior to study enrollment was calculated for subjects previously treated with on-demand therapy based on the average number of bleeds per month that was reported from each subject's memory in the prior year. For the 49 adults and 9 adolescent subjects treated with on-demand regimens only, the calculated mean ABR was 53 (median 36; range 12-216). When these subjects switched to prophylaxis treatment with Novoeight, the estimated ABR was 5.3 for adults and 6 for adolescents, resulting in a greater than 80% reduction in their ABR.

Efficacy Conclusion:

The outcomes of the study support the efficacy of Novoeight in adults with hemophilia A for control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

7. Safety

a) Safety Summary

Data from the three efficacy and safety trials and from the three PK studies were pooled to allow for an integrated review of the safety profile of Novoeight. A total of 214 PTPs received at least one infusion of Novoeight as part of either on-demand treatment of bleeding episodes, peri-operative management, routine prophylaxis, or PK evaluation. These subjects had a total of 54,957 EDs during prevention or treatment of bleeding episodes. The mean age was 21.5 years (range of one to sixty years). The mean age for 14 subjects undergoing surgery was 28.4 years (range of 14–55 years). These subjects had a total of 222 EDs Novoeight (average of 17.1 EDs per patient).

There was one unrelated death reported during the extension trial of a 27-year old who experienced a fatal subdural hemorrhage after an assault. The subject was brought to the hospital bleeding from the scalp and unconscious with a Glasgow coma scale score of 7. An emergency right decompressive craniectomy and evacuation of the clot was performed. The subject received Novoeight peri-operatively, including two days post-operatively before he was pronounced dead.

b) Adverse Reactions

There were 783 adverse events (AEs) reported in 179 (84%) subjects (data lock date of September 2012), of which 31 were considered serious adverse events (SAEs). Most of the SAEs described above were not considered related to the product both by the investigator and the FDA reviewer. Four SAEs of hypertension, insomnia and tachycardia reported in one subject and increased hepatic enzymes in another were considered to be related to Novoeight by the investigator. No SAEs were recorded during surgery.

Table 4: Serious Adverse Events from Novoeight Clinical Trials as Reported by the Investigators and Confirmed by Applicant

Preferred Term	Trial	EDs	Severity	Relationship to Novoeight
Melena	3543	60	Severe	Not related
Melena	3543	11	Mild	Not related
Upper GI hemorrhage	3543	86	Severe	Not related
Hypertension	3543	28	Moderate	Related (Same subject for these 3 SAEs)
Sinus tachycardia				
Insomnia				
Road traffic accident	3543	17	Severe	Not related
Suicide attempt	3543	90	Severe	Not related
Fall	3543	66	Moderate	Not related
Hepatic enzyme increased	3543	84	Moderate	Related
Soft tissue injury	3545	46	Moderate	Not related
Gastroenteritis viral	3545	35	Moderate	Not related
Device related infection	3545	57	Mild	Not related
Injury	3568	324	Moderate	Not related (Same subject for these 2 SAEs)
Psychotic disorder		368		
Scrotal pain	3568	237	Mild	Not related
Fall	3568	190	Severe	Not related (Same subject for these 3 SAEs)
Femur fracture			Severe	
Hand fracture			Moderate	
Muscle hemorrhage	3568	124	Severe	Not related
Intestinal hemorrhage	3568	133	Severe	Not related
Skin injury	3568	99	Moderate	Not related
Road traffic accident	3568	244	Moderate	Not related
Subdural hemorrhage	3568	137	Severe	Not related
Staphlococcal infection	3568	125	Severe	Not related
Bipolar I disorder	3568	266	Severe	Not related
Pancreatitis	3568	133	Severe	Not related
Cholelithiasis	3568	252	Severe	Not related
Cholelithiasis	3568	?	Severe	Not related
Radial nerve palsy	3568	?	Severe	Not related
Forearm fracture	3568	?	Severe	Not related
Hepatitis C	3568	?	Severe	Not related

The two cases described below were considered related to the product by the investigators but FDA reviewers considers them unrelated:

Mild hypertension and sinus tachycardia were detected in one patient who also reported insomnia for two days. The subject was admitted for observation, and blood pressure and heart rate normalized without medical intervention. This subject later experienced the fatal subdural hemorrhage described above.

The subject with increased hepatic enzymes had a history of HCV, HIV, and a mildly elevated aspartate aminotransferase at baseline. Elevations in hepatic enzymes were noted after 84 EDs, and persisted after Novoeight was discontinued. A liver biopsy showed findings consistent with chronic hepatitis, including lobular inflammation and mild portal fibrosis. The clinical reviewer finds that the elevations in hepatic enzymes were unlikely to be related to Novoeight.

Adverse drug reactions that occurred in >0.5% of subjects are shown in Table 5 below.

Table 5: Summary of Adverse Drug Reactions

System Organ Class	Preferred Term	Number of ARs	Number of Subjects (N=214) n (%)
General disorders and administration site conditions	Injection site reaction	5	5 (2.3)
Investigations	Increased hepatic enzyme	4	3*(1.4)
General disorders and administration site conditions	Pyrexia	2	2 (0.9)

Four AEs of fatigue, schizophrenia, (fatal) subdural hemorrhage and increased hepatic enzymes resulted in withdrawal of the subjects.
* One subject described above
The other two subjects had Hepatitis C; the observation of increased hepatic enzymes in these subjects was not considered related to the product

c) Immunogenicity

In all trials, subjects were monitored for neutralizing antibodies to FVIII by the ---(b)(4)--- assay and binding antibodies to CHO and murine protein by validated --(b)(4)--.

No subjects developed confirmed neutralizing antibodies to FVIII in any trial. In the pediatric trial (NN7008-3545, N=63), one 22- month old child developed a low-titer inhibitor (1.3 BU using the Bethesda assay) after 15 exposure days that was not present when checked at a later time point, and was therefore considered transient. In vivo recovery was normal for this child and no clinical adverse findings were observed.

Nineteen subjects were positive for anti-CHO antibodies at one or more time points. Two of these subjects changed from anti-CHO negative to anti-CHO positive, and 6 subjects changed from anti-CHO positive to anti-CHO negative. The remaining 11 subjects were either positive throughout the trials (n=6), negative at baseline and end-of trial but with transient positive response during the trial (n=2), or positive at baseline and end-of trial but negative during the trial (n=3). No clinical adverse findings were observed in any of these subjects. No patients developed de novo anti-murine antibodies.

Safety Conclusion

The safety profile of Novoeight has been adequately demonstrated for the proposed population and indications.

Orphan Product Designation

Novoeight does not have orphan product designation.

Financial Disclosure Information

Financial disclosure forms have been submitted for all investigators.

Bioresearch Monitoring (BIMO)

BIMO inspections of four clinical sites were performed in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The four clinical sites enrolled 28 subjects that represented 22% of the total subjects enrolled in the pivotal clinical trial NN7008-3543.

Table 6: Inspection of clinical sites and outcome

Study site / Site # / Time of Inspection	Location	Number of subjects	Form FDA 483 issued	Final classification
Oregon Health and Science University / 861 / March 11-25th, 2013	Portland, OR	6	Yes	VAI*
University of Iowa Hospitals and Clinics / 868 / March 25 – April 1st, 2013	Iowa City, IA	6	Yes	VAI
Instituto Estadual Arthur de Siqueira Cavalcanti, HEMORIO/351 / July 15 – 19th, 2013	Rio de Janeiro, Brazil	6	Yes	VAI
Universidade Estadual de Campinas/352 July 22 – 26th, 2013	Campinas,SP, Brazil	10	Yes	VAI

** VAI- Voluntary Action Indicated*

Form FDA 483's notifying the company's management of objectionable conditions were issued at the sites outlined a number of deviations from protocol adherence and data discrepancies between the source documents and the data reported in the BLA. However, the inspections did not reveal significant problems that would impact the clinical data submitted in the BLA.

8. Pediatric Research Equity Act (PREA)

PREA requirements were triggered as a new indication was being sought.
The safety and efficacy of Novoeight in children was established in a multi-center, multi-national, prospective, open-label, uncontrolled safety, efficacy and PK trial in children <12 years of age. A total of 63 subjects were enrolled and treated with at least one dose of Novoeight, including 31 children 0 to <6 years of age and 32 children 6 to <12 years. The median age was 6 years (range 1-11 years). All were males with severe (FVIII≤1%) hemophilia A who had > 50 EDs with previous FVIII products at the time of enrollment. The majority of the subjects were White (84%); the second-largest group was Asian (10%). A total of 48 subjects (76%) were previously treated with prophylactic regimens for an average of 34 months (range 1-110 months). Sixty-nine (69) subjects (46%) were previously treated with recombinant FVIII products.

Table 7: Pediatric Trial Characteristics

Study type	Safety/Efficacy/PK

Study Design	Prospective, open-label, uncontrolled
Ages Studied	0 to <12 years of age
Subject (n) Small children (0 - <6) Older children (6 - <12)	63 31 32
Centers (n)	26
Countries (n)	11
Countries (centers, n)	Brazil (3), Italy (1), Lithuania (1), Macedonia (1), Malaysia (1), Poland (2), Russia (2), Serbia (1), Taiwan (1), Turkey (3) and the US (10)
Race, N (%) White Asian Other	63 53 (84%) 6 (10%) 4 (6%)

Subjects were treated with prophylactic regimens of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly for 18-22 weeks (at least 50 EDs). The primary endpoint was the incidence rate of FVIII inhibitors (≥0.6 BU/mL) measured at 10-14 EDs and approximately every 28 days. Secondary efficacy endpoints included ABR, hemostatic effect using a four-point scale of "excellent", "good", "moderate", or "none", number of infusions required per bleeding episode, and time to control of bleeding after the first dose. All main descriptions and analyses of safety, efficacy and PK data were based on the full analysis set (FAS).

Results

- There were no confirmed neutralizing antibodies to FVIII. One 22- month old child developed a transient low-titer inhibitor (1.3 BU) after 15 exposure days. In vivo recovery was normal for this child and no clinical adverse findings were observed.
- Hemostatic efficacy for the treatment of acute bleeds in 41 subjects was successful for 116/126 (92%) of bleeds treated. A total of 102/126 (81.0%) were stopped with one infusion and eighteen (14.3%) were stopped with 2 infusions. These findings are consistent with the results of the pivotal trial.
- Hemostatic efficacy for two minor surgeries (dental extraction and central line removal) in two subjects was rated as "excellent".
- The ABR (95% CI) was 5.62 (4.16, 7.59) with an average prophylactic dose of 36.8 IU/kg (range 3.2-73.9 IU/kg). The mean ABR for the twelve months prior to trial enrollment for subjects previously treated with on-demand therapy was 34.
- The pharmacokinetic parameters were comparable between younger (0 to < 6 years) and older (6 to < 12 years) children. The mean clearance of Novoeight in younger and older children was 67% and 34% higher (based on per kg body weight) than in adults (3.74 mL/h/kg) when using the clotting assay, and 60% and 29% higher than in adults (2.87 mL/h/kg) when using the chromogenic substrate assay. As clearance (based on per kg body weight) is higher in children, higher or more frequent dosing may be needed.

PeRC ASSESSMENT

Data from the pediatric trial and pediatric patients in the pivotal trial were presented to the FDA Pediatric Review Committee (PeRC) on September 11th, 2013. In these two studies the safety and efficacy of Novoeight was evaluated in 79 children between 0 and <16 years, including 4 from 0 to <2 years, 27 from 2 to <6 years, 32 from 6 to <12 years, and 16 from 12 to <16 years of age. No confirmed inhibitors were reported in any subject. As expected, hemostatic response in 54 subjects was excellent or good for 210/244 (86%) of bleeding episodes. The ABR (95% CI) for the 79 subjects treated with prophylaxis was 4.8 (3.74, 6.15). Based on these data, PeRC agreed with the review determination that Novoeight is safe and efficacious for children with hemophilia A. These findings are accurately reflected in the Pediatric Use section of the Package Insert.

9. Advisory Committee Meeting

The Division of Hematology in the Office of Blood Research and Review recommended that referral to the Blood Products Advisory Committee (BPAC) prior to approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

1. The new molecular entity provision (NME) does not apply to Novoeight as Novoeight belongs to an existing product class. Recombinant FVIII products have been licensed in the U.S. since 1992, and have been used to control and prevent bleeding in Hemophilia A patients. The first product in this class, Recombinate, manufactured by Baxter, was approved by FDA in 1992. There are currently several full-length (Kogenate FS, Advate) and B-domain-deleted (Xyntha) recombinant FVIII products licensed in the U.S.

2. The mechanism of action of FVIII and its function in blood coagulation is well studied and understood. Upon activation by thrombin, FVIIIa acts as a cofactor for activated Factor IX triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen resulting in the formation of the fibrin clot that stops the bleeding. When infused into a Hemophilia patient, FVIII products temporarily replace the missing endogenous FVIII.

3. Novoeight is identical to human plasma-derived FVIII in heavy and light chain amino acid sequence and major post-translational modifications, but it is distinct in having a truncated 21 amino acid B-domain. Thrombin-activated Novoeight has the same structure as plasma-derived activated FVIII. *In vitro* and *in vivo* physico-chemical, biochemical and functional characterization of Novoeight demonstrates that its structure and hemostatic activities are comparable to those of human plasma-derived FVIII.

4. The manufacturing process for Novoeight includes two viral clearance steps - detergent treatment for virus inactivation and nanofiltration for virus removal.

5. The proposed indications for Novoeight are identical or similar to those of other U.S. licensed recombinant FVIII products.

6. The clinical pharmacokinetic data indicate bioequivalence of Novoeight product and a licensed full-length recombinant FVIII.

7. The design of pivotal clinical studies to evaluate safety and efficacy of Novoeight was adequate and the results of the studies did not raise any concerns.

8. Evaluation of the safety data for Novoeight (214 subjects) did not reveal any safety concerns. No confirmed inhibitors (neutralizing antibodies to FVIII), hypersensitivity/allergic reactions, or thromboembolic events were reported for any subject in any trial.

9. Review of information submitted in the BLA for Novoeight did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

10. Pharmacovigilance

Pharmacovigilance data are not available as this product is not currently marketed anywhere in the world.

There were no new safety signals identified during the clinical trials for Novoeight. The clinical development program included 214 treated subjects and no confirmed inhibitor development, severe allergic reactions, thrombotic events, or other unexpected events were observed. One 22-month old subject developed a low-titer transient inhibitor and 19 additional subjects were positive for anti-CHO antibodies during the trials. However, these were not associated with adverse events. Data for 79 pediatric subjects <16 years supports the safety and efficacy for use of Novoeight in children; however, there are insufficient safety data for use in elderly

The submitted pharmacovigilance plan to monitor the safety of Novoeight post-marketing is adequate and includes:

- Quarterly periodic adverse event reports for four years
- 15-day expedited reports for serious, unlabeled adverse events
- Completion of the ongoing trial in pediatric previously untreated patients for efficacy and safety
- Completion of the trial evaluating long-term treatment of hemophilia A patients

The potential risks are outlined in the package insert under Contraindications and Warnings and Precautions sections. The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) or the need for a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of Novoeight outweigh its risks.

11. Labeling

a) Proprietary Name

The proposed proprietary name, Novoeight, for Antihemophilic Factor (Recombinant) was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective. The initial reviews were performed on March 13, 2012 under IND

14059 and on November 16, 2012 under BLA 125466/0, and the proprietary name was found acceptable.

On July 31, 2013 APLB performed a re-evaluation of the proposed proprietary name, Novoeight, to determine if any new products had been approved since the previous review on November 16, 2012. APLB found that no new products have been approved that would change their previous recommendation. APLB found the proposed proprietary name, Novoeight, to be acceptable.

b) Prescribing Information
The Full Prescribing Information (FPI) was reviewed by the BLA committee, including APLB, during the labeling review meetings on July 2, 2013 and August 9, 2013. The comments regarding product labeling were conveyed to Novo Nordisk on August 15 and September 9, 2013. The final labeling was submitted by Novo Nordisk on September 19, 2013 and was found acceptable.

c) Carton Labeling
Carton and container labels submitted to the BLA were considered acceptable.

d) Patient Labeling/Medication Guide
Patient Information is appropriately provided in Section 17 of the Full Prescribing Information (FPI).
A copy of the FPI is attached as Appendix 1.

12. Recommendation/Risk Benefit Assessment

There were no new safety signals identified during the clinical trials for Novoeight. The clinical development program included 214 treated subjects and no confirmed inhibitor development, severe allergic reactions, thrombotic events, or other unexpected events were observed. One 22-month old subject developed a low-titer transient inhibitor and 19 additional subjects were positive for anti-CHO antibodies during the trials. However, these were not associated with adverse events. Data for 79 pediatric subjects <16 years supports the safety and efficacy for use of Novoeight in children; however, there are insufficient safety data for use in elderly.

The CBER review committee recommends approval of this BLA. The manufacturing process for Novoeight, Antihemophilic Factor (Recombinant), is validated and adequately controlled. Efficacy and safety clinical data for Novoeight were found adequate to make a favorable decision concerning potential risk/benefit balance and to support its use for the proposed indications.

13. Post Marketing Requirement

The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) or REMS.

14. Post Marketing Commitments

As stated in Amendment STN 125466/0.26 dated 29 July 2013 and Amendment STN 125466/0.34 dated 19 September 2013, Novo Nordisk commits to the following:

1. To develop the methods for quantitative measurement of excipients calcium chloride and sucrose in the Final Drug Product, and include these parameters with acceptance criteria in Drug Product Specification. The results will be submitted as a post-marketing commitment (PMC) Submission – Final Study Report by October 16, 2014.

2. To include at least one commercial batch each of 500 IU, 1000 IU, and 1500 IU dosage strengths in their stability study, and these batches should be monitored under the referenced storage conditions as described on page 4 of 11 in the BLA section 3.2.P.8.2 Stability Protocol and Stability Commitment for PPQ and Confirming Batches for Drug Product (novoDOCS: 001161237). The interim stability data from these batches will be submitted as annual updates (PMC Submission – Status Update) through the dating period, and the final report will be submitted within 3 months of completion of the study (PMC Submission – Final Study Report).

3. To complete the ongoing trial NN7008-3809, *Safety and efficacy study in prevention and treatment of bleeds in paediatric previously untreated patients with Haemophilia A*, with the following milestones:
    - First Patient First Visit: September 25, 2012
    - Last Patient Last Visit: September 30, 2016
    - Submission of Final Study Report: March 31, 2017

4. To complete the trial NN7008-3553, *Non-interventional safety and efficacy study during long term treatment of severe and moderately severe Haemophilia A*, with the following milestones:
    - First Patient First Visit: September 30, 2014
    - Last Patient Last Visit: September 30, 2018
    - Submission of Final Study Report: March 31, 2019

Appendix I. Hemostatic Efficacy Rating Scales

Definition of Hemostatic Response (Acute Bleeds):

- **Excellent**: abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion
- **Good**: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than one infusion for complete resolution
- **Moderate**: probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion
- **None**: no improvement, or worsening of symptoms

Definition of Hemostatic Response (during Surgery):

- **Excellent:** blood loss less than expected in this type of patient and procedure
- **Good:** blood loss as expected
- **Fair/Moderate:** blood loss more than expected
- **None:** uncontrolled bleeding.

Definition of Hemostatic Response (after Surgery):

- **Excellent:** good or better than expected in this type of patient and procedure;
- **Good:** minimal negative impact on quality of hemostasis;
- **Fair/Moderate:** less than optimal for the type of procedure, maintained without change of treatment regimen;
- **None:** bleeding due to inadequate therapeutic response with adequate dosing; change of regimen required.

Appendix II. Classification of Surgery

Major Surgery

Major surgery was defined as any invasive operative procedure where any one or more of the following occurred:

- A body cavity was entered
- A mesenchymal barrier (e.g., pleura, peritoneum or dura) was crossed
- A fascial plane was opened
- An organ was removed
- Normal anatomy was operatively altered

These procedures could have been performed using general anesthesia, spinal anesthesia, epidural anesthesia, conscious sedation or with a combination of these modalities.

Minor Surgery

Minor surgery was defined as any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue was manipulated. Examples of minor surgery included vascular cutdown for catheter/fistula placement, implanting pumps or ports in subcutaneous tissue, biopsies or placement of probes, leads, or catheters requiring the entry into a body cavity only through a needle/guidewire. Dental surgery was classified as minor or major based on above definitions.