

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Review:	July 24, 2018
Requesting Office or Division:	Center for Biologics Evaluation and Research (CBER)
Application Type and Number:	BLA 125671
Product Name and Strength:	Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII)
Product Type:	Combination Product
Device Constituent:	Delivery System
Rx or OTC:	RX
Applicant/Sponsor Name:	Novo Nordisk
FDA Received Date:	February 27, 2018
OSE RCM #:	2018-632

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1 REASON FOR REVIEW

Novo Nordisk submitted a Biologics License Application (BLA 125671), on February 27, 2018 for Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII). The Center for Biologics Evaluation and Research (CBER) requested a Human Factors (HF) consultative review of the HF validation study results submitted under BLA 125671.

1.1 PRODUCT BACKGROUND

Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII) is indicated to prevent and control bleeding in patients with Hemophilia A, as well as, for perioperative management of these patients.

Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII) is a lyophilized powder for intravenous infusion after reconstitution with 0.9% sodium chloride solution; it will be available in single-use vials containing 500, 1,000, 1,500, 2,000, or 3,000 International Units (IU) per vial, and supplied with a pre-filled diluent syringe and vial adapter, see Figure 1.1.1. The identical drug delivery system is approved for NovoSeven RT, Novoeight and REBINYN.

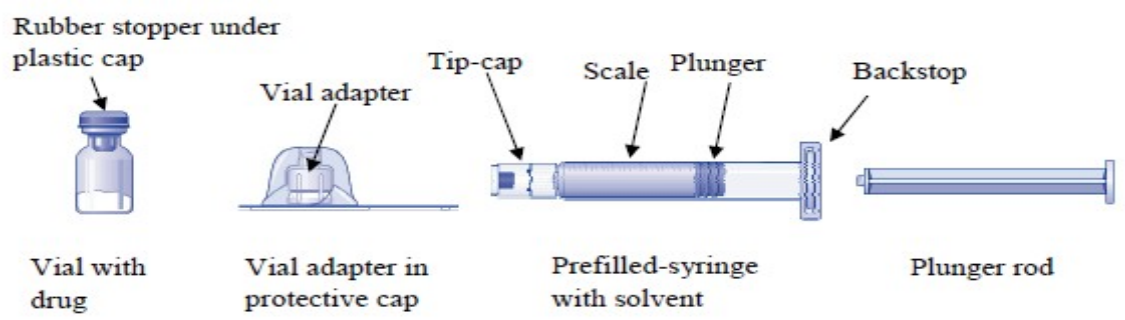


Figure 1.1.1 Device Constituents Parts

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews & Information Requests	B
Summative Usability Test Report, Differentiation Tasks	C
Human Factors Validation Test Conclusive Report	D

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Novo Nordisk submitted a HF validation results report and a differentiation study report^a. The Sponsor concluded that the combination product design for Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII) is safe and effective for use by the intended users, for the intended uses and use environments as indicated. We reviewed the HF validation study report results to determine if adequate mitigation of potential medication use errors have been implemented and for alignment with the Sponsors conclusion.

3.1 Human Factors Validation Results Report

Novo Nordisk conduct a HF validation study to evaluate the safe and effective use of the delivery system (including the instructions for use (IFU)) for Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII). The delivery system is used for reconstitution and administration of Turoctocog alfa.

The test involved 76 participants, with at least 15 participants in each of the 5 intended user groups, these include children (from age 10), adolescents and adults with hemophilia A, caregivers and healthcare practitioners (HCP) (hemophilia HCPs and ER nurses). All participants were trained in full dose and calculated dose preparation techniques, with the exception that

^a DMEPA has not been involved previously. If we were involved, we would have identified opportunities to guide the sponsor to leverage from other similar marketed products.

emergency room nurses who do not specialize in the treatment of patients with Hemophilia did not receive training. An untrained patient/caregiver group was not included in the study. On May 24, 2018, we sent an Information Request (IR) for the rationale for not including an untrained user group. On May 30, 2018, the Applicant responded stating the reason for not using untrained user groups is specific to the standard management of hemophilia. Training must be provided to patients/caregivers prior to use of the product as it is administered intravenously. Intravenous injections should not be administered by untrained patients/caregivers (see Appendix B.2). We agree with this approach.

All test participants were able to refer to the IFU as they would and independently performed the tasks. We reviewed the critical task steps, participant responses and mitigation strategies outlined in the HF validation results report (Appendix D) and agree they are comprehensive and appropriate for the proposed product. The HF validation results show that no close calls and one use-error was observed (see Table 1). Root-cause analysis, and participant feedback, of the single use-error, attributed it to be a test artifact as the participant did not adhere to the scenario instruction due to stress induced by the testing situation. We agree with the Sponsor's analysis that no further mitigation is warranted.

Table 1. List of tasks where failures occurred and the assessment of these failures				
Study Task	Use Error	Sponsor' Root Cause Analysis	Sponsor' Mitigation	Additional Analysis from DMEPA
Draw out the mixed solution into the pre-filled syringe	1 error by HCP The participant drew out the full amount of the mixed drug instead of the calculated dose in the specified.	The participant reported being nervous and reverted to original training of never wasting drug. In subsequent scenario the participant withdrew the correct amount of the calculated dose.	The Sponsor concluded this was a study artifact and no further mitigation was necessary.	Failure to draw out the appropriate amount of mixed drug may potentially result in an under-dose or over-dose. However, based on the root cause of this failure, we agree that no further mitigation is necessary.

3.1 Summative Usability Test Report, Differentiation Tasks

A summative differentiation usability test was conducted to evaluate that intended users can differentiate Turoctocog alfa pegol (Recombinant, glycopegylated human coagulation factor VIII) product cartons from cartons of other, similar products and against various Turoctocog alfa pegol product strengths.

The Applicant analyzed the risks associated with the critical tasks in product differentiation, see Appendix C, and we agree that the tasks evaluated are comprehensive and appropriate for the proposed product.

No participants encountered any use errors, close calls, operational difficulties, nor required test administrator assistance when performing differentiation tasks.

4 CONCLUSION & RECOMMENDATIONS

We find the Human Factors validation studies acceptable. We have no recommendations at this time.

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On 06/4/2018, we searched DMEPA's previous reviews using the terms, BLA 125671 and IND 014410. Our search identified no previous review relevant for this review.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS (Information Request)

On May 24, 2018, we sent an Information Request (IR) requesting that the Applicant submit their rationale for omission of an untrained patient/caregiver study group. May 30, 2018, the Applicant responded as follows:

Novo Nordisk acknowledges that the Human Factors Validation study presented to give evidence for the adequate ability to handle the device did not include an arm of untrained patients/caregivers. The reason for not using untrained patient and caregiver groups is specific to the standard management of hemophilia. As discussed in UT 84, (M 5.3.5.4), Human Factor Validation Test Conclusive Report (section 1.6.1) patients and caregivers are trained in the preparation and administration of their product before being allowed to self-administer. This prior training is necessary since the therapy is given intravenously. Intravenous injections should not be administered by an untrained patient/caregiver. The ability to deliver a drug intravenously is acquired through training and practice, which is why Novo Nordisk states that "It is the Hemophilia HCPs responsibility to judge when caregivers or patients are ready to perform the treatment at home" in the UT 84, (M 5.3.5.4), DV0297 Usability Specification.

Novo Nordisk therefore judges that the most realistic scenario for its Human Factors Validation handling study is to include hemophilia patient and caregiver user groups with prior experience in administering treatment.

The Novo Nordisk blood factor products Novoeight® (BLA 125466), NovoSeven® RT (BLA 103665) and REBINYN® (BLA 125611) use the same delivery system as is being proposed for Turoctocog alfa pegol. At Novo Nordisk, post-marketing surveillance for devices is

done to identify and investigate any unforeseen residual risks associated with the use of marketed medical devices (including the delivery system in use for the blood factor products). Post-marketing surveillance analysis of these products has been performed and the data analyses included any post-marketing reports received between Q4 2012 up to November 2017. At present, the number and nature of the reported and identified handling-errors do not raise safety concerns for the delivery system. Therefore, it is concluded that the delivery system proposed for Turoctocog alfa pegol, which has been in use for several years in Novoeight® and NovoSeven® RT, has instructions for use adequate for caregivers and patients. Further, the post-marketing surveillance supports the rationale for not including untrained patients and caregivers in the handling study.

APPENDIX C. SUMMATIVE USABILITY TEST REPORT, DIFFERENTIATION TASKS



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The test involved 47 participants representing the following three user groups:

- 16 child/adolescent patients (age 11–17 years) with hemophilia, using factor treatment, who self-administer hemophilia treatments to themselves at home
- 15 adult/elderly patients (age 18+ years) with hemophilia, using factor treatment, who self-administer hemophilia treatments to themselves and retrieve their own medication at home
- 16 healthcare professionals (HCPs), including physicians and nurses, who specialize in hemophilia and are familiar with the preparation of hemophilia products, provide hemophilia treatment in clinics, and train hemophilia patients and caregivers, as well as pharmacists with experience dispensing hemophilia medication

Of these 47 total participants, one adolescent participant was disqualified for having participated in a previous hemophilia differentiation study within the past six months. As such, this participant's data was excluded from all test report findings.

Prior to administering the tasks, the test administrator gave each patient participant the opportunity to become comfortable with the Turoctocog alfa pegol carton in the assigned product strength. The test administrator presented patient participants with a carton in the assigned product strength. The test administrator then instructed participants that they have just received the new hemophilia medication, and to take whatever steps necessary to become comfortable with the new product until it is time for their first infusion later that week. The test administrator instructed the participant to state when s/he felt generally comfortable with the new product. After the participant stated s/he was comfortable, the test administrator removed the carton from the table and out of the participant's view.

HCP participants did not have the opportunity to become comfortable with the product because HCPs are not expected to become comfortable with the product before retrieving the carton.

All participants performed two differentiation (i.e., carton retrieval) tasks during the test session. For each task, all participants were randomly assigned a specific product strength. To initiate each task, the test administrator presented a task card containing specific task instructions to the participant (see Table 1). Each participant was asked to retrieve a Turoctocog alfa pegol carton in an assigned product strength from a refrigerator (see Figure 1). No patient participants were assigned the same product strength for both tasks; two HCP participants were randomly assigned the same product strength during both tasks. Participants read the task instructions aloud and then performed the tasks.

Before each task, test personnel arranged the prescribed Turoctocog alfa pegol carton randomly among the distractor products' cartons in the refrigerator. During patient sessions, the refrigerator contained

two Turoctocog alfa pegol cartons in different product strengths and two distractor cartons. The refrigerator for patients also contained sample food items that might be found in a patient's refrigerator at home (See Figure 1).

During HCP sessions, the refrigerator contained five Turoctocog alfa pegol cartons in different product strengths and 16 – 18 distractor cartons, for a total of 21 – 23 cartons. The cartons were grouped by brand and organized from lowest to highest product strength (e.g., all Turoctocog alfa pegol cartons were grouped together in stacks, with the 500 IU carton on the top of the left stack and the 3000 IU carton on the bottom of the right stack) to replicate the way refrigerator contents are most likely organized in a clinical environment (See Figure 1).



Figure 1 Example refrigerator setup for patients (left) and HCPs (right)

Table 1 Task instructions

User group	Task instructions (presented on a printed card)
Patients	Please select the medication in the strength you saw a few moments ago. Bring back the carton to the table.
HCPs	Go to the refrigerator and retrieve a [product strength] IU carton.

APPENDIX D. HUMAN FACTORS VALIDATION TEST CONCLUSIVE REPORT



hf-validation.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b we reviewed the following labeling submitted by Novo Nordisk Pharmaceuticals.

- Prescribing Information (Image not shown) received on 02/27/2018

G.2 Label and Labeling Images

Prescribing Information

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Instructions for Use

(b) (4)

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.