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## Memorandum

**DATE:** November 29, 2018

**TO:** Seameen (Jean) Dehdashti MSc., RPM, CBER/OTAT/DRPM/RPMBI  
Andrey Sarafanov, Ph.D., Committee Chair, CBER/OTAT/DPPT/HB  
Najat Bouchkouj M.D., Clinical Reviewer, CBER/OTAT/DCEPT/CHB

**FROM:** Kristine T. Khuc, Pharm.D.  
Consumer Safety Officer  
Advertising and Promotional Labeling Branch (APLB)  
Division of Case Management (DCM)  
Office of Compliance and Biologics Quality (OCBQ)

**THROUGH:** Lisa L. Stockbridge, Ph.D.  
Branch Chief  
APLB/DCM/OCBQ

**SUBJECT: ESPEROCT [antihemophilic factor (recombinant), glycoPEGylated- exei]  
BLA: 125671/0  
Sponsor: Novo Nordisk, Inc.**

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## Background

The sponsor submitted:

New Approval  
 Changes Being Effected (CBE) supplement  
 Prior Approval Supplement (PAS)  
 Major Amendment

Submission contains:

Prescribing Information (PI)  
 Patient Package Insert (PPI)  
 Package and/or container labels  
 Other

Submission Date: February 27, 2018

PDUFA Action Date: **February 27, 2019**

## **APLB Comments/Recommendations**

This review is for an original BLA submission by Novo Nordisk for ESPEROCT (antihemophilic factor (recombinant), glycoPEGylated- exei). APLB reviewed the draft labeling dated February 27, 2018. The following comments are from a promotional and comprehension perspective.

### **GENERAL**

- Use active voice and command language whenever possible throughout the PI.
- Replace “TRADENAME” with your approved proprietary name “ESPEROCT”. In addition, add the suffix “-exei” to your proper name.
- Revise the approval date to the BLA approval date. Delete the revision date at the end of the HIGHLIGHTS section.
- Do not bullet single items. Overuse of bulleting in sections and subsections reduces readability.

### **HIGHLIGHTS**

#### **PRODUCT TITLE**

Present the proper name in small case lettering within parentheses. In the second row, present the dosage form then the route of administration of the product. For example,

**ESPEROCT<sup>®</sup> [antihemophilic factor (recombinant), glycoPEGylated-exei]  
lyophilized powder for solution, for intravenous use**

#### **INDICATIONS AND USAGE**

- Present the established pharmacologic class of the product in the first sentence of this section. Also, add the adolescent group in the indication. For example,

ESPEROCT (antihemophilic factor (recombinant), glycoPEGylated – exei) is a coagulation Factor VIII concentrate indicated for use in adults, adolescents, and children with hemophilia A for...
- Leave space between the indications and usage statement and the limitations of use statement.

## DOSAGE AND ADMINISTRATION

- Bold the directive directly beneath this header to provide emphasis, and make this a sentence (add a period at the end). If the decision is to have this directive also included in a subsection, the statement should be the same: **For intravenous infusion after reconstitution only.**
- Present the dosing information in the same order as the indications to enhance readability.
- In the fourth bullet, provide a numerical cross reference to the FPI.

## ADVERSE REACTIONS

Delete the bullet if there is just one comment underneath a section header.

## USE IN SPECIFIC POPULATIONS

Please refer to the comment above when there is only one concept presented.

## FULL PRESCRIBING INFORMATION: CONTENTS

Ensure any changes in the table of contents is consistent with the FULL PRESCRIBING INFORMATION.

## FULL PRESCRIBING INFORMATION

### INDICATIONS AND USAGE

- Add the adolescent age group to the indication statement.
- Present the bulleted indications in the same order as the presentation in the HIGHLIGHTS.

## DOSAGE AND ADMINISTRATION

- To maintain consistency with other drug class labels, revise subsection header 2.1 “Dosing Guidelines” to “Dosing.”
- For readability, present the dosing information in the same order as the indications.
- Underneath subsection 2.2:
  - Revise the third bullet to “If the *dose* requires more than one vial of [Tradename] per infusion, reconstitute each vial according to the following instructions.
  - Delete the statements “The instructions below serve as a general guideline for preparation and reconstitution of [Tradename]. For full instructions, refer to the FDA-approved patient information and Instructions for Use.” The instructions

- provided in this section should be sufficiently informative and complete to allow for the safe and effective use of this product. Information in this section should not imply that there are more instructions elsewhere.
- Step 12 contains information relating to administration. Please move step 12 to the Administration subsection.
  - Underneath subsection 2.3:
    - Delete the practice of medicine statements regarding accidental needle sticks.
    - Revise the parenteral product regulatory statement to “Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.”
    - Delete the Novo Nordisk phone number at the end of this subsection. The phone number belongs and is already listed in the package label.

## **WARNINGS AND PRECAUTIONS**

- For the hypersensitivity reaction relating to hamster proteins, please provide a cross reference to section 11 DESCRIPTION.
- For consistency with other factor VIII class labeling, revise the subsection header in 5.2 from “Inhibitors” to “Neutralizing Antibodies.”
- Also, in subsection 5.2, relate the risk of neutralizing antibodies to ESPEROCT. Currently, the statement “The formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of Factor VIII products,” minimizes the fact that this is a risk for using ESPEROCT.

## **ADVERSE REACTIONS**

Underneath subsection 6.1, delete the promotional term “unique.”

## **USE IN SPECIFIC POPULATIONS**

Under subsection 8.5 Geriatrics, please revise this subsection using the following regulatory wording:

Clinical studies of “Tradename” did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the (dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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## **CLINICAL PHARMACOLOGY**

Under the Pharmacokinetic (PK) subsection 12.3, consider deleting the PK information for the standard Factor VIII product. This subsection should contain only the PK data for this product, ESPEROCT.

## **NONCLINICAL TOXICOLOGY**

Information in this section belongs in regulatory subsections. The lack of data, as described, should be in subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

## **CLINICAL STUDIES**

- Avoid using research terminology (i.e., phase 3). Instead, just describe the studies.
- Please ensure that the quality of life assessment information is validated for inclusion in this section.

## **HOW SUPPLIED/STORAGE AND HANDLING**

Consider adding the color scheme identifying the different dosages to the “How Supplied” table.

## **PATIENT COUNSELING INFORMATION**

- Reference the appended FDA-approved product labeling directly beneath the section heading, using the following regulatory statement:

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

- Delete the fourth and fifth bullet directing the patient to consult with their provider prior to travel and to discard all equipment in an appropriate container. The patient labeling (PPI) contains that information and is the first bullet of this section.

## **PATIENT PACKAGE INSERT**

- Underneath the header, “What is Tradename?” revise the sentence stating “Tradename is used to treat and prevent bleeding in people with hemophilia A” to “Tradename is used to treat and *reduce* the number of bleeding episodes in people with hemophilia A.”
- Underneath the header, “What are the Tradename dosage strengths?” add the color scheme identifying the different dosages to the table.

## **INSTRUCTIONS FOR USE**

- Please list the proper name alongside the proprietary name.
  - Avoid the overuse of bolding as this decreases readability.
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**PACKAGE AND CONTAINER LABELS**

Please list latex information in the package labels.

If you have any questions regarding this review, please contact Kristine T. Khuc, Consumer Safety Officer at 240-402-8982.