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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
From:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Novo Nordisk, Inc.
Product:	Esperoct [Antihemophilic Factor (Recombinant), GlycoPEGylated-exei]
STN:	125671/119
Indication:	For use in adults and children with hemophilia A for: (1) on-demand treatment and control of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to reduce the frequency of bleeding episodes
Meeting Date:	Pediatric Advisory Committee Meeting, April 2022

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review is the February 19, 2019 approval of Esperoct for use in children and adults with hemophilia A.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

Esperoct is a recombinant analogue of human coagulation Factor VIII (FVIII) conjugated with a 40-kDa polyethylene glycol (PEG) molecule. The addition of a PEG moiety to the active molecule is used to extend the plasma half-life for Esperoct. The FVIII protein in Esperoct is produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology, and contains a truncated B domain, which is O-glycosylated.

1.3 Regulatory History

FDA approved Esperoct original BLA 125671/0 on February 19, 2019 for use in children and adults with hemophilia A for: (1) on-demand treatment and control of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to reduce the frequency of bleeding episodes.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Esperoct during February 19, 2019 to October 22, 2021
- Manufacturer's Submissions
    - Esperoct U.S. package insert (USPI), updated October 30, 2019
    - Applicant response to information request regarding dose distribution data
    - Risk Management Plan, version 0.1, dated August 15, 2017
    - Periodic safety reports
- FDA Documents
    - BLA 125671/0 Esperoct Approval Letter, dated February 19, 2019
    - BLA 125671/0 OBE/DE Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA[1]

The U.S. and worldwide distribution data for Esperoct for the time period of February 19, 2019 to October 31, 2021 are provided in table below.

Period	Volume of Esperoct® (IU)		
	U.S.	Worldwide (excluding the US)	Total
19 Feb 2019 – 31 Dec 2019	0	5,979,500	5,979,500
01 Jan 2020 – 31 Dec 2020	7,392,500	64,565,000	71,957,500
01 Jan 2021 – 22 Oct 2021[a]	17,084,000	156,288,500	173,372,500
Total	24,476,500	226,833,000	251,309,500

[a] The distribution data of Esperoct® reflected in the table is through 31 Oct 2021 as the database allows retrieval with the input of month and year only.

Note: The data represent volumes distributed to external customers. The IBD of Esperoct® is 19 Feb 2019.

Abbreviations: IBD = international birth date; IU = international unit(s).

Based on certain assumptions, as well as an assumed average patient weight 50kg in the pediatric population and 70kg in the adult population, the patient exposure in the time period 19 Feb 2019 – 22 Oct 2021 was estimated by the sponsor as patient-years of exposure (PYE):

- U.S. patient exposure: 33 PYE in pediatric patients and 51 PYE in adults
- Worldwide (excluding U.S.) patient exposure: 159 PYE in pediatric patients and 579 PYE in adults

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP), is the Risk Management Plan, version 0.1, dated August 15, 2017, which lists the important identified risks and missing information displayed in Table 1.

[1] Distribution data is protected as confidential commercial information and may require redaction from this review.

Table 1: Esperoct safety concerns

Important Identified Risks
• Inhibitor development • Allergic/hypersensitivity reactions
Important Potential Risks
• None
Missing Information
• Previously untreated patients • Patients with HIV with high viral load and low CD4 T cell count • Patients with history of FVIII inhibitors • Patients with history of thromboembolic events • Patients on ITI regimen

CD4 T cells= Cluster of differentiation 4 T lymphocytes; FVIII = factor VIII; HIV = human immunodeficiency virus; ITI = immune tolerance induction

The identified risks for Esperoct listed in table 1 are common to the factor VIII product class, and these risks are labeled events. The risk of inhibitor development with formation of neutralizing antibodies, and hypersensitivity reactions are included in the USPI under *section 5 Warnings and Precautions*.

A potential risk of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues and organs has been described based on findings from animal studies with other products from PEGylated coagulation factor product class. Of note, the label for Esperoct states that, “No evidence of polyethylene glycol accumulation was detected by immunohistochemical staining of brain tissue, including the choroid plexus” (USPI, section 13.2 Animal Toxicology and/or Pharmacology).

The sponsor is also conducting a post-authorization safety study (PASS) in EU countries based on an EU regulatory requirement. The primary objective of the study is to investigate the safety of Esperoct during long-term routine use in patients with hemophilia A. The study will include assessment of FVIII inhibitors and allergic-type hypersensitivity reactions, and it is planned to include safety follow-up assessments at routine comprehensive care visits for up to 50 patients for at least 4 years.

The identified and potential risks for Esperoct are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no ongoing or planned additional pharmacovigilance activities for Esperoct, such as safety-related postmarketing requirement/commitment (PMR/PMC) studies or Risk Evaluation and Mitigation Strategy (REMS).

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Esperoct received between February 19, 2019 (PAC trigger) to October 22, 2021 (data lock point for this review period). FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of adverse event reports for Esperoct during the review period are listed in Table 2. There was only 1 US report and 6 foreign reports.

Table 2: FAERS reports for Esperoct (February 19, 2019 to October 22, 2021)

Age (years)	Serious non-fatal, US	Serious non-fatal, foreign	Deaths, US	Deaths, foreign	Total, US	Total, Foreign
<18	0	1	0	0	0	1
≥18	0	4	0	1	0	5
Unknown	1	0	0	0	1	0
All	1	5	0	1	1	6

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

6.2.1 Deaths

There was one adult death (foreign report) involving a 66-year-old man with hemophilia (type not reported) and past medical history that included hepatitis, cirrhosis, portal hypertension, esophageal varices, and thrombocytopenia who experienced fatal gastrointestinal hemorrhage.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 6 serious non-fatal reports, one of which involved a pediatric patient.

The pediatric report involved a 3-year-old male with hemophilia A who experienced flushing, erythema, breathlessness, lightheadedness, and abdominal pain. Esperoct was discontinued and symptoms resolved.

The most frequently reported preferred terms (PTs) occurring in >1 serious report are shown in the table below. Note that a report may have one or more PTs.

Table 3: Top PTs for serious reports

Preferred Term (PT)	Number of reports	Label status
Coagulation factor VIII level decreased	2	Unlabeled
Haemorrhage	2	Unlabeled

Esperoct USPI, updated October 30, 2019

The unlabeled PT for *Coagulation factor VIII level decreased* is not an adverse event and represents results of laboratory testing. This PT is related to the labeled event of neutralizing antibodies, which may lead to decreased levels of Factor VIII. The label also includes information on Monitoring Laboratory Tests (section 5 Warnings and Precautions) to monitor Factor VIII activity levels in plasma. The PT for Hemorrhage is confounded by indication (hemorrhage associated with underlying hemophilia).

6.2.3 Non-serious Reports

There were no non-serious reports during the reporting period.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Esperoct were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis as of October 29, 2021. Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

A query of Empirica Signal using the Product Name (S) run did not identify any PTs with a disproportional reporting alert.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Esperoct covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the U.S. National Library of Medicine's PubMed.gov database on November 17, 2021, for peer-reviewed literature, with the search term "Esperoct" and published dates between February 19, 2019 and November 15, 2021, retrieved 9 articles. Titles and abstracts were reviewed for relevance to safety information for Esperoct, and 5 articles relevant to safety were identified and are summarized below. No new safety concerns were identified.

Table 5: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Šaulytė Trakymienė S, Economou M, Kenet G, Landorph A, Shen C, Kearney S. Long-term safety and efficacy of N8-GP in previously treated pediatric patients with hemophilia A: Final results from pathfinder5. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):15-25. doi: 10.1111/jth.15036. PMID: 32940955; PMCID: PMC7540298.	Presents findings from a multi-center, open-label, single-arm, non-randomized, non-controlled trial in previously treated male patients <12 years old with severe hemophilia A. Sixty-eight patients were exposed to N8-GP (Esperoct) for a median time of ~4.9 years on regimen. No FVIII inhibitors or other safety concerns were detected. The authors concluded that overall, data from the completed trial showed that long-term (median 4.9 years) N8-GP treatment was efficacious and well tolerated in previously treated pediatric patients with severe hemophilia A.
Matsushita T, Mangles S. An overview of the pathfinder clinical trials program: Long-term efficacy and safety of N8-GP in patients with hemophilia A. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):26-33. doi: 10.1111/jth.14958. PMID: 32558236; PMCID: PMC7540506.	Presents an overview of the pathfinder clinical development program and summarizes data from the completed clinical trials. The authors concluded that study results have confirmed the long-term efficacy and safety of N8-GP in previously treated patients (children, adolescents, and adults). N8-GP was well tolerated, and there were no unexpected safety concerns reported.
Giangrande P, Abdul Karim F, Nemes L, You CW, Landorph A, Geybels MS, Curry N. Long-term safety and efficacy of N8-GP in previously treated adults and adolescents with hemophilia A: Final results from pathfinder2. J Thromb Haemost. 2020 Sep;18 Suppl 1(Suppl 1):5-14. doi: 10.1111/jth.14959. PMID: 32544297; PMCID: PMC7540590.	Presents findings from a multi-center, open-label trial of N8-GP in previously treated adolescent and adult patients with severe hemophilia A. Overall, 186 patients were exposed to N8-GP for up to 6.6 years (median 5.4 years). No safety concerns were detected. The authors concluded that data from the completed trial demonstrated the efficacy and safety of N8-GP in previously treated adolescent and adult patients.

Article	Authors' safety conclusion
Klamroth R, Hampton K, Saulyte Trakymienė S, Korsholm L, Carcao M. Illustrative Cases from the Pathfinder Clinical Trials of Patients with Hemophilia A Treated with Turoctocog Alfa Pegol (N8-GP). Patient Prefer Adherence. 2021 Nov 4;15:2443-2454. doi: 10.2147/PPA.S326282. PMID: 34764641; PMCID: PMC8575374.	Presents selected patient cases from the pathfinder clinical trial program, which included clinical studies in adults (pathfinder 2 and 3) and children (pathfinder 5). There were improvements in treatment adherence, bleeding rates, and overall physical activity levels in two adult cases from the pathfinder 2 trial. N8-GP demonstrated good or excellent hemostatic coverage in three adult patients undergoing multiple major surgeries. The benefits of N8-GP for joint health and in support of children and adolescents with evolving active lifestyles were reported for several pediatric cases. The authors concluded that these patient cases highlighted the benefits of N8-GP, for patients with severe hemophilia A.
Benson G, Morton T, Thomas H, Lee XY. Long-Term Outcomes of Previously Treated Adult and Adolescent Patients with Severe Hemophilia A Receiving Prophylaxis with Extended Half-Life FVIII Treatments: An Economic Analysis from a United Kingdom Perspective. Clinicoecon Outcomes Res. 2021 Jan 18;13:39-51. doi: 10.2147/CEOR.S280574. PMID: 33500640; PMCID: PMC7822074.	Applies pharmacokinetic/pharmacodynamic modeling to estimate FVIII levels for four extended half-life FVIII treatments (turoctocog alfa pegol [Esperoct®], rurioctocog alfa pegol [Adynovi®], efmoroctocog alfa [Elocta®], and damoctocog alfa pegol [Jivi®]) to predict comparative annual bleeding rates (ABRs). The authors concluded that turoctocog alfa pegol prophylaxis was associated with fewer cumulative bleeds, as well as lower product and resource costs related to resolving a breakthrough bleed and most quality-adjusted life years (QALYs) versus comparators.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Esperoct does not indicate any new safety concerns. The PAC review was initiated due to the February 19, 2019 approval of Esperoct for use in children and adults with hemophilia A. Overall there were very few reports, and only a single pediatric report. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Esperoct.