

FILING MEETING AGENDA/SUMMARY

Application type and number: BLA 125671
Product name: Antihemophilic Factor (Recombinant), GlycoPEGylated
Proposed indication: For use in adults and children with hemophilia A for: on-demand treatment and control of bleeding episodes; perioperative management; and routine prophylaxis
Applicant: Novo Nordisk, Inc.
Meeting date & time: **April 13, 2018; 3 – 4 PM EST**
Meeting Chair: Andrey Sarafanov, PhD
Meeting Recorder: Jean Dehdashti, MSc, RAC

Background: Sponsor has submitted an original BLA for Antihemophilic Factor (Recombinant), GlycoPEGylated, for use in adults and children with hemophilia A. The drug product is a lyophilized powder for intravenous infusion, after reconstitution with 0.9% sodium chloride solution. The clinical development program for this product is under IND 14410.

Table 1: Review Committee and Discipline Filing Decision Summary

Discipline/Organization	Name [with credentials (not title)]	Attended meeting	Fileable	RTF	Deficiencies Identified
Regulatory Project Manager	Jean Dehdashti, MSc, RAC	X	Y		
Chair/CMC Reviewer	Andrey Sarafanov, PhD	X	Y		
Clinical Reviewer	Najat Bouchkouj, MD	X	Y		
CMC Reviewer	1. Alexey Khrenov, PhD	X	Y		
	2. Mikhail Ovanesov, PhD	X	Y		
	3. Ze Peng, PhD	X	Y		
	4. Yideng Liang	X	Y		
CMC Inspector	Andrey Sarafanov, PhD	X	Y		
Animal Pharmacology /Toxicology Reviewer	Gaya Hettiarachi, PhD	X	Y		
Clinical Pharmacology	Iftexhar Mahmood, PhD		Y		
OCBQ/DMPQ RPM	Ekaterina Allen, PhD		Y		

Discipline/Organization	Name [with credentials (not title)]	Attended meeting	Fileable	RTF	Deficiencies Identified
OCBQ/DMPQ Reviewer	Hector Carrero	X	Y		
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	X	Y		
OCBQ/DMPQ/Lead Inspector	Hector Carrero	X	Y		
Statistical Reviewer of clinical data	Lin Huo		Y		
Postmarketing Safety Epidemiological Reviewer	Ohenewa Ahima, MD	X	Y		
OCBQ/APLB Reviewer (Proprietary Name Review [PNR])	Oluchi Elekwachi, PharmD	X	Y		
OCBQ/APLB Reviewer (Labeling)	Kristine Khuc, PharmD	X	Y		
OCBQ/BIMO Reviewer	Anthony Hawkins, M.S.	X	Y		
OCBQ/DBSQC Reviewer	1. Marie Anderson, PhD	X	Y		
	2. Parmesh Dutt, PhD	X	Y		
	3. Karla Garcia, M.S.	X	Y		
	4. Jing Lin, PhD	X	Y		
	5. Tao Pan, PhD	X	Y		
	6. Charlene Wang, PhD	X	Y		
CDER/OSE/OMEPRM/DMEPA (Usability Studies) Consult	1. Idalia Rychlik, PhD 2. Hina Mehta, PhD				
<u>Other Attendees:</u>					
OTAT	Rachael Anatol, PhD	X			
OTAT	Kim Benton, PhD	X			
OCBQ/DBSQC	Suzanne Carter, PhD	X			
OCBQ/DIS	Dennis Cato	X			
OBE/DB	Wambui Chege, MD	X			
OTAT/DPPT	Mahmood Farshid, PhD	X			
OTAT/DCEPT	Bindu George, MD	X			
OTAT/DCEPT	Ilan Irony, MD	X			
OTAT/DCEPT	Tejashri Purohit-Sheth, MD	X			
OTAT/DPPT	Tim Lee, PhD	X			
OCBQ/DMPQ	Tony Lorenzo	X			
OCBQ/DIS	Carla Jordan	X			

Discipline/Organization	Name [with credentials (not title)]	Attended meeting	Fileable	RTF	Deficiencies Identified
OTAT/DCEPT	Iwen Wu, PhD	X			
OTAT/DCEPT	Lei Xu, MD	X			
OBE/DB	Renee Rees, PhD				

ADMINISTRATIVE ITEMS

1. Filing checklist for all disciplines has been uploaded to SharePoint.
2. A note to all review committee members to please log into eMRP on a regular basis, daily when possible, and review/complete tasks as appropriate, to make certain that all subsequent time-sensitive tasks are triggered in the system to the appropriate review committee members.
3. The compiled BLA 125671 Submission Matrix Excel document, with assigned review committee members has been uploaded to SharePoint. Review committee was asked to review the document, to ensure that all sections of the submission are appropriately assigned.

REGULATORY CONCLUSIONS / DEFICIENCIES

1. **Does the application, on its face, appear to be suitable for filing or is the application unsuitable for filing and will require a RTF letter?**

Yes, the committee members from assigned disciplines (Chemistry, Manufacturing and Controls [CMC], Pharm/Tox, Clinical, Clinical Pharmacology, DMPQ, Biostatistics, Epidemiology, APLB, BIMO, and DBSQC) unanimously agreed that the application, on its face, appears to be suitable for filing.

2. **If fileable, list any substantive deficiencies or issues that have significant impact on the ability to complete the review or approve the application:**

- a. CMC stated that there are either missing or misplaced documents in Module 3 (and corresponding CMC sections in Module 5); however CMC stated that these documents are not substantive deficiencies, and can be requested, if needed, through an information request (IR).

3. **If RTF, list any substantive deficiencies or issues that would make this application unsuitable for filing:**

N/A, no substantive deficiencies or issues identified.

FILING MEETING DISCUSSION, IF FILED:

4. Indicate any comments on the status of the proprietary name review (PNR).

PNR - APLB has accepted the sponsor submitted proprietary name, ESPEROCT. The review Office, OTAT, had no objections to APLB's decision, and a PNR approval letter was issued to the sponsor on April 11, 2018.

Proper name 4-letter suffix - APLB has issued an information request (IR) to the sponsor providing them the option to submit 4-letter suffix(s) for FDA review by Friday, April 27, 2018.

5. Indicate whether the product should/would be subject to lot release, surveillance, or exempt from lot release. Verify sample availability.

OCBQ/DBSQC issued a sample and reagent request from sponsor on April 03, 2018, requesting that the samples be provided by close of business (COB), Friday, April 27, 2018.

6. Confirm review schedule of this application.

Review committee confirms that this application is subject to a standard review (12 month) cycle.

7. Indicate the decision regarding the need for an Advisory Committee.

The review committee unanimously agreed that an Advisory Committee (AC) was not required for this application.

8. Indicate whether the submission triggers PREA; if yes, a PeRC meeting is needed.

Submission triggers PREA. PeRC meeting will be scheduled after the Mid-Cycle Meeting. RPM will work with Clinical and Statistical reviewer on identifying a date in either August or September 2018 for the PeRC meeting.

9. Is a comprehensive and readily located list of all clinical sites included or referenced in the application?

Yes, the sponsor has provided a comprehensive and readily located list of all clinical sites, because of an historical IR issued by the BIMO and Clinical reviewers.

10. Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?

Yes, a comprehensive and readily located list of all manufacturing facilities included in the application.

11. Indicate any updates since the First Committee Meeting on pre-license inspection, pre-approval inspection, or BIMO sites requiring inspections (Is the establishment(s) ready for inspection?)

- a. A Pre-License Inspection (PLI) will be conducted for the drug substance (DS) manufacturing facility in (b) (4), the week of (b) (4).
- b. BIMO stated that they are working closely with the Clinical reviewer, and that BIMO will conduct an inspection of the pivotal study, consisting of several sites within UK and US. A finalized selection within the group will be made, where 3-4 sites will ultimately be inspected.

12. If the application is affected by the Application Integrity Policy (AIP), has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A, the application is not affected by the API.

13. Is the product an Original Biological Product or a New Molecular Entity (NME) for an NDA?

Yes, the product is an Original Biological Product.

FOR APPLICATIONS IN THE PDUFA PROGRAM (NME NDAs/Original BLAs), IF FILED

14. Confirm that any late submission components were submitted within 30 days. List any late submission components that arrived after 30 days.

N/A, no major submissions were submitted within the last 30 days.

15. Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?

Yes, the application was complete upon submission.

ADMINISTRATIVE DETAILS, IF FILED:

16. Review the Milestone Schedule and indicate if there are any issues with the schedule. Note: This is a confirmation to capture any changes made since the First Committee Meeting.

- **PDUFA 60-Day Filing Date – April 27, 2018**

- **PDUFA 74-Day Deficiencies Letter – May 11, 2018**
- **90-Day PNR for “ESPEROCT” – APLB accepted, Approval letter issued April 11, 2018.**
- Mid-Cycle Internal Meeting – July 27, 2018; 1 – 2 PM EST
- Mid-Cycle External Communication (Teleconference)– August 8, 2018; 3 – 4 PM EST
- PLI – Week of August 20, 2018
- Late-Cycle Meeting Internal – November 2, 2018; 3 – 4 PM EST
- Late-Cycle External Communication (Face-to-Face) – November 29, 2018; 3 – 4 PM EST
- PeRC Meeting – August 1, 2018, 9:00 – 12:00 PM (exact time-slot TBD one week prior to scheduled meeting).
- Weekly Labeling Meetings – Initiated 2 months prior to FDA reviewed draft package insert (PI) is sent to sponsor (projected goal date – January 15, 2018)
 - *December 7, 2018 – First labeling meeting for all review committee members*
 - *December 14, 2018 – Sections and meeting required attendees to be determined*
 - *December 21, 2018 – Sections and meeting required attendees to be determined*
 - *December 28, 2018 – Sections and meeting required attendees to be determined*
 - *January 4, 2018 – Sections and meeting required attendees to be determined*
 - *January 11, 2018 – Sections and meeting required attendees to be determined*
 - *January 18, 2018 – Sections and meeting required attendees to be determined*
 - *January 25, 2018 – Sections and meeting required attendees to be determined*
- **Soft due date – February 15, 2018**
- **PDUFA Action Due Date – February 27, 2019**
- Post-approval de-briefing – April 12, 2019; 2 – 3 PM EST

Review schedule:

BLA Standard 12 Month Review	
STN:	BLA 125671/0
Applicant:	Novo Nordisk
Product:	Antihemophilic Factor (Recombinant), GlycoPEGylated
Short Summary:	Original BLA for Antihemophilic Factor (Recombinant), GlycoPEGylated for use in adults and children with hemophilia A for: On-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes
RPM:	Jean Dehdashti
Chairperson:	Andrey Sarafanov

Review Schedule	Target Date
DCC Receipt Date	Feb 27, 2018
Complete regulatory filing review; Assign review committee	Mar 9, 2018
Acknowledge receipt; Establish review schedule	Mar 13, 2018
First Committee Meeting	Mar 20, 2018
30 Day Late Components Due	Mar 29, 2018
AOM and Dataset Walk-through	Apr 11, 2018
Filing Meeting	Apr 13, 2018
Send Filing Determination Letter	Apr 27, 2018
Deficiencies Identified Letter	N/A
Proprietary Name Review	April 11, 2018
Request initial labeling review	Jul 30, 2018
Mid-Cycle Review Meeting	July 27, 2018
MidCycle Communication with Applicant	Aug 8, 2018
Send Information Requests as needed	
Complete Discipline Reviews (Primary)	Oct 3, 2018
Complete Discipline Reviews (Secondary Review)	Oct 17, 2018
Send Discipline Review Letters as completed	Oct 30, 2018
Send Late Cycle / Advisory Comm briefing package	N/A
Late-Cycle Meeting (Internal)	Nov 2, 2018
External Late-Cycle Meeting	November 29, 2018
Advisory Committee Meeting, if needed	N/A
Promotional labeling review (APLB)	Nov 29, 2018
Complete inspection reports	Dec 28, 2018
PeRC Meeting	August 1, 2018
Circulate draft press release	Jan 28, 2019
Complete PMC Study, Labeling Review, Review Addenda	Jan 28, 2019
Complete Supervisory Review	Jan 28, 2019
Request Compliance Check, Lot Release Clearance	Feb 13, 2019

Send Press Release to OCOD	Feb 13, 2019
<i>T-minus date</i>	<i>Feb 13, 2019</i>
Send FDA Action Letter	Feb 27, 2019
Post-Action Debrief Meeting	Apr 12, 2019