

Mid-Cycle Meeting Agenda/Summary

Application number: STN 125611/0
Applicant: Novo Nordisk Inc.
Product name: Coagulation Factor IX (Recombinant), GlycoPEGylated
Proposed Indication: Indicated for use in adults and children with hemophilia B for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis

Meeting date & time: December 1, 2016 from 3 PM to 5 PM
Committee Chair: Chava Kimchi-Sarfaty
RPM: Edward Thompson

Attendees:

Discipline	Name	Attended meeting?
Regulatory Project Manager (RPM)	Edward Thompson	X
Chair/CMC Reviewer	Chava Kimchi-Sarfaty	X
Clinical Reviewer	Megha Kaushal	X
CMC Reviewer	Aikaterini Alexaki	X
CMC Reviewer	Nobuko Katagiri	X
Clinical Pharmacology Reviewer	Iftekhar Mahmood	X
Pharm/Toxicology Reviewer	La’Nissa Brown-Baker	X
OCBQ/DMPQ Team Lead	Ellen Huang	X
OCBQ/DMPQ Reviewer	Jeremy Wally	X
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	
Statistical Reviewer of clinical data	Judy Li	X
Statistical Reviewer of non-clinical data	Judy Li	X
Postmarketing Safety Epidemiological Reviewer	Ravi Goud	X
OCBQ/APLB Reviewer	Kristine Khuc	X
OCBQ/BIMO Reviewer	Anthony Hawkins	X
OCBQ/DBSQC Representative	Marie Anderson	X
OCBQ/DBSQC Reviewer	Kouassi Ayikoe	X
OCBQ/DBSQC Reviewer	Simleen Kaur	X
OCBQ/DBSQC Reviewer	Grainne Tobin	X
OCBQ/DBSQC Reviewer	Hsiaoling Wang	X
PNR Reviewer	Oluchi Elekwachi	
Division Director Product	Basil Golding	X
Division Director Product	Michael Kennedy	X
Product Chief (Acting)	Timothy Lee	X
Statistical Team Lead	Renee Rees	X
OCBQ/DBSQC	Lokesh Bhattacharyya	X

Discipline	Name	Attended meeting?
OCBQ/BIMO Chief	Patricia Holobaugh	X
Pharm/Toxicology Chief (Acting)	Becky Robinson	X
Pharm/Toxicology Team Lead	Mercedes Serabian	X
Clinical Chief	Ke Liu	X
Clinical Team Lead	Maura O’Leary	X
Postmarketing Safety Epidemiological Team Lead	Deepa Arya	X
OBE/DE Division Director	Scott Proestel	X
OTAT Office Director	Wilson Bryan	X

Discussion Summary:

The mid-cycle meeting addressed the status of the BLA review. Each discipline reviewer briefly presented his or her review focus and findings. The Pharmacology/Toxicology (P/T) and clinical reviewers presented and discussed data related to the PEG accumulation in the CNS/choroid plexus in nude rats and immune competent nonhuman primates (NHPs). The need for presentation of the BLA at an advisory committee meeting was not determined during this mid-cycle meeting. Further discussion of the review findings will be conveyed to Novo Nordisk in the mid-cycle communication teleconference, to specifically inform the sponsor of the concern regarding the accumulation of PEG in various tissues including the choroid plexus, observed in both the rats and the NHPs. A decision was made not to request a CDRH consult since the Hemophilia community is very familiar with the syringe device attached to this vial.

Report and Discuss:

1. Summary of Reviewer Reports

Chemistry, Manufacturing, and Controls (CMC)

CMC presented the main manufacturing process, specifically the enzymatic reaction utilized to attach the 40 kDa PEG molecule to the sugar molecules. Additionally CMC illustrated the major changes made to the manufacturing process since Phase 3. Pending: Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements.

No CMC major deficiencies were identified.

Clinical

- The median ABR was 2.04 for adolescents/adults (2.93 in the 10 U/kg arm and 1.04 in the 40 U/kg arm) and 1.44 for pediatric subjects.
- The majority of bleeds resolved with one injection of REBINYN in the adolescent/adult study and pediatric study (86% and 97%, respectively).
- None of the subjects developed anti-FIX inhibitory antibodies.
- There were no deaths reported.
- REBINYN was safe and well tolerated for perioperative management in nine major and four minor surgeries in 13 subjects.
- Efficacy was rated as good or excellent for perioperative management.

Clinical Pharmacology

No substantive issues were identified.

Nonclinical P/T

Vacuolization was observed in the choroid plexus of NHPs and nude rats at a 50- to 100-fold tentative safety factor (tSF) of the clinical dose level; however, this microscopic finding did not result in clinically meaningful adverse effects. There were no other notable histopathology changes observed in either animal species in repeat-dose toxicity studies resulting from presence of the vacuoles. In addition, this finding did not interfere with the pharmacokinetics/toxicokinetics of the 40 kDa PEGylated product. Additional internal analysis to determine the potential significance and impact of the vacuolization findings in the animals to the clinical scenario is warranted. There are no P/T post-marketing commitments or requirements that have been identified. From the P/T reviewer's perspective, the submitted nonclinical data appear to be sufficient to continue the review of the submission.

Epidemiology

Concern for possible PEG accumulation in the brain - depending on the conclusions of the P/T and clinical reviewers, and a CDER consult, it will be determined if more than routine pharmacovigilance is required. It will be necessary to determine if there is anything significantly different with this PEGylated product compared to other approved pegylated products, and whether there is sufficient concern that we need a PMR/PMC, or if we have confidence that this product is adequately safe, and routine pharmacovigilance is justified. Another possibility is to limit the indication to adults only, so that the possibility of accumulation is reduced.

Nephrotic syndrome following ITI – sponsor identifies this as an important potential risk. This is listed as a warning and precaution for another FIX product, and maybe considered for this product as well.

Statistics

No major statistical issues were identified.

Bioresearch Monitoring (BIMO) Inspections

No substantive BIMO issues to report at this time.

Division of Manufacturing and Product Quality (DMPQ) Facility/CMC

An inspection waiver memo for the Novo Nordisk manufacturing facilities has already been completed and is in the EDR. A second waiver memo for the (b) (4) manufacturing facilities will also need to be completed (the included facilities will be determined based upon the response to the pending Information Request [IR]).

No key finding(s) or substantive issues have thus far been identified.

Division of Biological Standards and Quality Control (DBSQC)

No lot release protocol (LRP) template was required as this is a recombinant product and not subject to CBER lot release. A test plan has been written, reviewed by the chair (15 Sep 2016), and has been routed to Integrated Quality System (IQS) reviewers.

Simleen Kaur Laboratory of Microbiology, In-Vivo Testing and Standards (LMIVTS) (DBSQC) completed her review of the Bioburden, Sterility and Endotoxin Test Method Qualifications. The review memo was completed on 24 Oct 2016.

Quality- FIX Potency by One Stage Clotting Assay and (b) (4) by the (b) (4) Assay:

The applicant used a FIX One Stage Clotting Assay to measure potency of the (b) (4) product. Review of the submission demonstrated that information was lacking with regard to accuracy, repeatability, linearity, and robustness of the assay. This generated a number of IRs, and the responses were received on 30 September 2016 as Amendment 11. The applicant addressed the questions regarding accuracy and robustness; however, further information is required for the repeatability and linearity, and this has generated a further set of IRs, which have been submitted to the applicant.

The applicant also uses an (b) (4) assay to measure the (b) (4) of the (b) (4) drug product. Review of the submission generated a number of IRs, focusing on linearity, limit of quantitation (LOQ) determination, repeatability and robustness of the assay. The sponsor adequately addressed the question on linearity; however, further information is required for repeatability, LOQ determination, and robustness. A further set of IRs have been submitted to the applicant.

DBSQC Quality Control will work with the Chair and CMC Reviewer to come up with an acceptable solution if the IRs are not satisfactorily addressed.

2. For PDUFA V Program submissions, indicate whether discipline review letters will be issued.

The review team and chair confirmed that Discipline Review Letters will not be issued.

3. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

A final decision was not made at this meeting.

4. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

The needs for PMRs or PMCs are in the developmental stage and further discussions will be needed.

5. National Drug Code (NDC) assignments to product/packaging (excludes devices).

0169 is the correct NDC assignment for Novo Nordisk. Each carton and containers are properly assigned.

0169-7905-01	500 IU Carton
0169-7955-11	500 IU Container
0169-7901-01	1000 IU Carton
0169-7911-11	1000 IU Container
0169-7902-01	2000 IU Carton
0169-7922-11	2000 IU Container

6. Proper naming convention.

The committee chair accepts the current naming convention for this product as follows:

Coagulation Factor IX (Recombinant), GlycoPEGylated

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

BIMO is pending receipt and review of three clinical investigator inspection reports covering clinical study protocol NN7999-3747 (requested inspection completion date 11/28/2016):

BIMO:

Clinical Study Site	<u>Status of Inspection</u>
Site #104 - New York, NY	Inspection ended 11/14/2016 - No FDA 483 issued; pending CBER BIMO receipt, review of EIR
Site #106 - Minneapolis, MN	Inspection ended 09/22/2016 - No FDA 483 issued; No action indicated (NAI)
Site #114 - Newark, NJ	Inspection ended 11/10/2016 - No FDA 483 issued; pending CBER BIMO receipt, review of EIR
Site #116 – Houston, TX	Inspection ended 11/03/2016 - No FDA 483 issued; pending CBER BIMO receipt, review of EIR (EIR = Establishment Inspection Report)

DMPQ/CMC:

The facilities are waived for inspection.

Review:

- Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Meeting members confirmed the late cycle meeting and action due date. Further discussion needed for the need on AC meeting.

- Establish a labeling review plan and agree on future labeling meeting activities.

Meeting members agreed that it is too premature on agreeing with a specific date on labeling.

Confirm, as applicable:

- Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

CMC confirms that it will be completed by February 10, 2017.

- New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not complete, indicate date it will be completed.

DMPQ/Facility reviewer confirmed that an inspection will not be performed.

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

Coagulation Factor IX (Recombinant), GlycoPEGylated will be exempt from Lot Release including no requirement for submission of lot release protocols or product samples to CBER as this is a recombinant product. Per the Interim Definition and Elimination of Lot-by-Lot Release For Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products (Federal Register / Vol. 60, No. 236 / Friday, December 8, 1995 / Notices).

A test plan has been prepared and it has been reviewed by the chair (September 15, 2016). The test plan is ready to move through the approval process.

13. Unique ingredient identifier (UNII) code process has been initiated.

RPM acknowledges this deficiency and an IR will be sent.

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/ deferral/ assessment of the PREA decision.

PeRC Meeting Scheduled for January 25, 2017 on PREA assessment and team agreed that the package will be sent 2-weeks prior to the meeting.

15. PeRC is scheduled for January 25, 2017.

See comments in item #14.

16. For applications subject to the PDUFA V Program:

Continued discussion needed for presenting this application to an advisory committee.

END