



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology**

Date: November 14, 2011

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From: Alan C. Ou, MD, MPH
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Subject: Final Review Memorandum

Product: NovoThirteen, Catridecacog [Recombinant Coagulation Factor XIII A-subunit (rFXIII)]

Approval Date: Pending

Application Type/Number: BLA 125398

Applicant/sponsor: Novo Nordisk A/S

Recommendations

Novo Nordisk should proceed with the proposed pharmacovigilance activities for Recombinant Coagulation Factor XIII A-subunit (rFXIII), as described in the document that the sponsor submitted to the BLA on February 23, 2011. As noted in the Pharmacovigilance Plan (PVP), Novo Nordisk should conduct routine monitoring and reporting of adverse events (AEs), including submitting 15-day expedited reports for serious, unlabeled AEs and Periodic Safety Update Reports (PSURs), quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80. In addition, OBE/DE agrees with Novo Nordisk's plan of additional pharmacovigilance activities: 1) to collect more detailed information on AEs of interest (identified and potential important risks) through the use of structured follow-up forms, 2) reporting follow-up outcomes to the FDA in the PSURs, and 3) following a risk-minimization plan for thromboembolic events.

Novo Nordisk should consider measures to expand the safety database, given the limited follow-up and the small number of subjects who were systematically evaluated in the prelicensure study. OBE/DE acknowledges that the pivotal study included approximately 6-10% of the worldwide pool of patients diagnosed with congenital FXIII deficiency.

Novo Nordisk should consider modifying the package insert to make it more internally consistent and to reduce the potential risk of off-label use. OBE/DE specifically recommends adding statements that the product is: 1) not intended for use in elderly adults who are undergoing cardiac surgery, 2) not intended to treat classic hemophilia or Christmas disease, and 3) not intended to treat acute hemorrhage.

The development of neutralizing antibodies in (b) (4) monkeys demonstrates the potential for a serious safety risk. Thus far, the data from clinical trials have not revealed any serious safety signals for the development of neutralizing anti-rFXIII inhibitors in humans with congenital rFXIII deficiency. However, subjects who developed non-neutralizing anti-rFXIII antibodies were withdrawn from the study, and long-term sequelae could not be evaluated. The natural history of repeated exposure to rFXIII in individuals with anti-rFXIII antibodies is unknown. Due to the potential serious risk of neutralizing anti-rFXIII antibody development in humans, a Postmarketing Requirement (PMR) is indicated and authorized under FDAAA Section 505(o)(3). A PMR to evaluate in vitro laboratory safety studies should allow for a clinical evaluation of the significance of inhibitor development, including the development of neutralizing antibodies upon re-exposure. If new safety signals arise during the postmarketing period, then CBER may impose additional PMRs.

Letter-ready Comments Submitted August 30, 2011 to Sponsor

1. Proceed with the proposed pharmacovigilance activities for Recombinant Coagulation Factor XIII A-subunit (rFXIII) as you have previously submitted to the FDA on February 23, 2011. Routine monitoring and reporting of adverse events should be conducted,

including submitting 15-day expedited reports for serious, unlabeled adverse events and Periodic Safety Update Reports, quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80.

2. Measures should be considered to expand the safety database, given the short study duration and the small number of subjects systematically evaluated. The FDA acknowledges, however, that your pivotal study for rFXIII has already included the approximately 6-10% of the worldwide pool of patients diagnosed with congenital factor XIII deficiency.

3. The FDA is aware that non-neutralizing anti-rFXIII antibodies have developed in (b) (4) monkeys which were repeatedly exposed to rFXIII in study NN205255. The FDA notes that in your pivotal clinical trial F13CD-1725, for the 3 of the 4 patients who developed non-neutralizing antibodies of uncertain clinical significance, treatment was discontinued due to the discovery of non-neutralizing antibodies and usually after about two to three doses. In these cases, the natural history following further repeated doses to rFXIII was not allowed to develop and be characterized. At present, the data from your studies raise concerns that the development of neutralizing anti-rFXIII antibodies in humans after repeated exposure to rFXIII is a potential serious risk and cannot be ruled out as one possible sequela. Therefore, a post marketing requirement is indicated and authorized under FDAAA Section 505(o)(3). The post marketing requirement should utilize in vitro laboratory safety studies of rFXIII inhibitor development and should allow for a clinical evaluation of the significance of inhibitor development, including the development of neutralizing anti-rFXIII antibodies upon re-exposure. If new safety signals arise for rFXIII during the postmarketing period, then the FDA may impose additional PMRs.

The first two issues above have been resolved in Amendment 0.4 to the original BLA as follows:

1) “Novo Nordisk commits to routine monitoring and reporting of adverse events, including submitting 15-days alert reports for serious, unlabeled adverse events and Periodic adverse experience reports quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80. In addition, reporting of antibodies to rFXIII and reports of allergic reaction will be reported on an expedited basis regardless of source of report, seriousness and expectedness.”

2) “Novo Nordisk is expanding the safety database by including additional (naïve to rFXIII) subjects into the F13CD-3720 according to a protocol amendment no 8, September 2010. In addition, a trial in pediatric (1 to less than 6 years) patients (F13CD-3760) and a follow-on trial (F13CD-3835) in the same patients are ongoing and will also expand the safety database.”

“Additionally as described in the Risk Management Plan and the observational study protocol submitted with the original BLA, Novo Nordisk is committed to conducting a post marketing observational study in order to expand the safety database. The

observational study protocol describes the proposed study duration to be a maximum of 5 years, with a treatment period of 2-5 years per patient, depending on the time of enrolment [sic] of each individual patient. The study will observe approximately 40 patients for a total of 1000 exposures to rFXIII.”

“Novo Nordisk welcomes the opportunity to further discuss the study protocol with the Agency.”

The third letter-ready comment was not submitted to NovoNordisk in FDA CBER’s Information Request dated August 30, 2011. On September 19, 2011, Dr. Charles Maplethorpe, the Clinical Reviewer for OBRR, stated that the approval letter will provide specific details about the Post-Marketing Requirement.