CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208751Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

COMPLETE RESPONSE

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated and received December 8, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin aspart injection, 100 units/mL.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

For convenience, the proposed proprietary name, (b) (4) is used throughout this letter. This name was found to be conditionally acceptable. As stated below, resubmit the proposed proprietary name when you respond to the application deficiencies.

CLINICAL PHARMACOLOGY

The bioanalytical method used to (b) (4) (for the purpose of primary pharmacokinetic analyses) is deemed unreliable because of the issues listed below. As a result, the reliability of the pharmacokinetic data for all clinical pharmacology studies that used this method is called into question.

1. (b) (4)
2.

3. (b) (4)

4.

5.

Our recommendations are as follows:

6. Develop and validate a new analytical method where (b) (4) We recommend you use the validation acceptance criteria outlined in the draft "Guidance for Industry - Bioanalytical Method Validation," September 2013. If the analytical method meets the validation acceptance criteria, we recommend that (b) (4) reported in this NDA, we recommend that you submit this information

to the Investigational New Drug Application (IND) to facilitate further discussion, before you resubmit this NDA.

7. (b) (4)

8.

9. If quantification of total insulin aspart concentrations were to be planned, then this needs to be done for the key clinical pharmacology studies data intended to inform sections of labeling. For this approach, assurance of stability data of the retained test samples needs to be provided in the NDA. Utilizing total insulin aspart concentrations from only 3 studies (NN1218-3978, NN1218-3891, NN1218-3852), as you proposed in your email correspondence dated September 12, 2016, is not an acceptable approach. An extensive clinical program was carried out for this NDA to establish different aspects of the PK/PD profile of (b) (4) including pharmacokinetic/pharmacodynamic (PK/PD) difference from NovoLog, dose-response relationship, injection site variation, (b) (4).

   Therefore, proposing to quantify total insulin aspart concentrations from 3 studies has a number of limitations (listed below) which limits a comprehensive understanding of the PK/PD of (b) (4) and restricts the information that can be included in relevant sections of the proposed label. The limitations of quantifying total insulin aspart concentration from 3 studies are:

   a. The data from select studies where total insulin is characterized for PK as a secondary measurement limits the comprehensive review of the clinical pharmacology data.

   b. No data pertaining to the total insulin aspart concentrations from the meal challenge studies (mealtime, postmeal) will be assessed. We consider these studies as an integral part of comprehensive assessment of the PK/PD of (b) (4)

   c. (b) (4)

IMMUNOGENICITY

There are multiple deficiencies regarding the validation of the radioimmunoprecipitation assay (RIA) for the detection of insulin aspart-specific and cross-reactive anti-human insulin anti-drug antibodies as listed below.

10. Validation Report 215373 describes the QC3 suitability control as a guinea pig polyclonal anti-human insulin (GPα Insulin). Table 1-6 of Section 2.7.1 of the NDA (Summary of biopharmaceutic studies and associated analytical methods) describes QC3 as a polyclonal anti-insulin aspart antibody. Explain the discrepancy between the two descriptions of QC3 and indicate what immunogen was used to raise the QC3 antibodies used during the testing of clinical samples.

11. It is not clear whether the patient samples were diluted prior to testing. If patient samples are diluted prior to testing, provide data demonstrating the suitability of the minimum required dilution.

12. Serum samples were tested in three parallel conditions: D, E, and F. Conditions E and F involved competition with unlabeled insulin aspart and human insulin respectively. However, the concentrations of unlabeled insulin aspart and human insulin used in the assay are not provided. Indicate the concentrations of unlabeled insulin aspart and human insulin used in the assay as well as the rationale for the selected concentrations.

13. You did not provide data demonstrating the tolerance of the assay to on-board insulin aspart. The tolerance of the assay to human insulin was determined during assay development but supporting data was not provided. Provide data demonstrating the assay tolerance of insulin aspart and human insulin to ensure that on-board levels of these proteins will not interfere with assay performance.

14. The levels of total anti-drug antibodies (ADA), insulin aspart-specific antibodies, and antibodies cross-reactive with human insulin are quantitated using the percentage of total radiolabeled tracer (insulin aspart) that is co-precipitated with Ig (%B/T). However, there is insufficient data in the Validation Reports to demonstrate that the assay is quantitative. One approach to address this deficiency and support the use of the %B/T value as a quantitative measure of antibodies in patient samples would be to demonstrate that there is a linear relationship between the positive control antibody concentration and the %B/T signal. Include a graphical and tabular analysis for each series (D, E, F) and the subtracted (D-E, D-F, F-E) values.

15. Section 2.7.1 Table 1-6 indicates that the two positive suitability controls used for analysis of clinical samples were QC2 (monoclonal anti-insulin aspart, 560 ng/ml) and QC3 (guinea pig polyclonal anti-human insulin antibody, 23-230 ng/ml). The sensitivity analysis described in Validation Report 215373 indicates that both QC2 and QC3 are toward the upper limit of quantitation of the assay. This raises concerns that your suitability controls are inadequate to ensure the detection of low levels of ADA. Low positive controls should be set to have a 1% failure rate based on the assay cutpoint. Indicate how the detection of low levels of ADA was demonstrated during clinical

testing. For guidance refer to the draft "Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products," April 2016.

16. Some of the assay parameters, such as intra-assay precision, inter-assay precision, and robustness, were validated by analyzing only the D-E series. However, the clinical samples were evaluated using the D-F and F-E series. Therefore, assay parameters validated using only the D-E conditions need to be validated using the D-F and F-E series.

17. You did not provide data demonstrating the stability of the positive control antibodies used during the testing of clinical samples. In order to demonstrate that the X14-6F34 and GPa Insulin antibodies remain stable under normal testing conditions assess the performance of the antibodies under long-term storage, freeze-thaw, and benchtop conditions.

18. The acceptance criteria used for the QC2 and QC3 suitability controls were calculated from a nominal value for each control +/- 20%. It is unclear how the nominal values for QC2 and QC3 indicated in Table 1-6 of Section 2.7.1 were calculated or what the upper and lower acceptance limits were for each series. Provide a description of how the calculations were done to establish the acceptance criteria for the suitability controls (including the QCneg) used during testing of clinical samples.

19. Validation data for the labeling efficiency, batch-to-batch consistency, and stability of the radiolabeled insulin aspart tracer were not provided. Provide data validating these attributes of the radiolabeled insulin aspart tracer used in the RIA.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

Please refer to correspondence dated July 28, 2016, which addresses the proposed proprietary name, (b) (4) This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug/product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug/product. Include an updated estimate of use for drug/product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

IV ROUTE OF ADMINISTRATION

In support of intravenous (IV) administration, you have submitted stability data of (b) (4) when diluted in two types of intravenous infusion fluids (0.9% NaCl and 5% glucose) at concentrations of 0.5 U/mL and 1.0 U/mL (Section 1 of Module 3.2.P.8.3). (b) (4) is stable for 24 hours at room temperature post dilution.

We also acknowledge that clinical pharmacology study NN1218-3949 investigated the PK and PD of (b) (4) following IV administration of a relatively low dose of (b) (4) (0.02 U/kg). We do not expect any difference in the PD of (b) (4) vs. NovoLog following IV administration since the active ingredient is insulin aspart. However, there are no data establishing the safety of the drug product (including excipients) for longer-term IV infusion and at higher doses that are likely to be used in the clinical setting.

With regard to nonclinical data, the single-dose rabbit local tolerance study (#212147), which was the only study that included IV dosing, was adequate to assess toxicity of accidental exposure or very short-term exposure, but was not adequate to support long term repeated IV exposure. The nonclinical study that you conducted to support clinical studies with SC dosing was a 4 week local tolerance study (#212251) in rats.

You should clarify how you plan to address the safety of longer-term infusion and higher doses of (b) (4) that are likely to occur in the clinical setting, specifically with regards to the excipients, nicotinamide and arginine. We recommend that you submit your plan to the IND before you resubmit this NDA.

IMMUNOGENICITY

Regarding the analysis of clinical data from Study NN1218-3852, Section 2.7.1 of the NDA notes that most patients were positive for ADA at baseline and that no cut-points were established to evaluate treatment-boosted ADA responses. In order to compare the immunogenicity of (b) (4) and Novolog, the frequency of patients with treatment-emergent and treatment-boosted ADA should be determined. Indicate how treatment-emergent and treatment-boosted patients were mathematically defined in your analysis as well as the frequency of patients in each treatment group with treatment-induced or treatment-boosted ADA.

(b) (4)

(b) (4)

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110 . If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
10/07/2016