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APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

COMPLETE RESPONSE

Novo Nordisk Inc.
Attention: Robert Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) dated and received September 11, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL

We acknowledge receipt of your amendments for Ryzodeg dated October 5 (2), 24, and 25, and December 2 and 22, 2011, and January 10, 13, and 27, February 15, March 16 and 23, April 4, 18 (2), and 24, May 11, 16 (2), 21, 23, and 25, July 9, August 10 (2), 15, and 17, October 11 and 22, November 1, 6, 26, and 29, and December 11, 14, and 17, 2012.

We acknowledge receipt of your amendments for Tresiba dated October 5 (2) and 24, and December 2, 13, and 22, 2011, and January 10, 13, and 27, February 15, March 16 and 23, April 4, 18 (2), and 24, May 3, 11, 16 (2), 21, 23, and 25 (2), July 9, August 10 (2), 15, and 17, October 11 and 22, November 1, 2, 6, 26, 29, and 30, and December 11, 14, 17, and 20, 2012.

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.

CLINICAL

1. Cardiovascular Safety

A consistent and persistent signal of excess cardiovascular (CV) risk associated with insulin degludec and insulin degludec/aspart relative to comparators is observed across multiple analyses.

You were informed on February 24, 2009, at your End-of-Phase 2 meeting, to collect and analyze the CV data from your clinical trials as outlined in the December 2008 *FDA Guidance for Industry Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf). You submitted your statistical analysis plan (SAP) for evaluation of CV risk on February 19, 2010, to IND 073198 and IND 076496, stating that all confirmatory Phase 3a trials AND their planned extensions would be combined and that these combined data would be considered as one data set for the purpose of CV risk assessment. Under Section 4.2.2 of the SAP you stated that "the combined data set will be the basis for summaries, analyses and presentation of MACE."

At the time of NDA submission, your CV meta-analysis did not include data from these planned extensions with the exception of Study 3645. A total of 16 studies were included in the meta-analysis referred to as "the original meta-analysis." This analysis, based on 80 CV events including CV death, nonfatal stroke, nonfatal myocardial infarction (MI), or unstable angina pectoris (hereafter referred to as MACE+), yielded a HR (95% CI) of 1.10 (0.68-1.77). Your analysis excluded three additional events in the insulin degludec treatment groups which occurred 9, 11, and 18 days after last day of treatment even though your SAP did not specify exclusion of such events. Our analysis including these three events yielded a HR (95% CI) of 1.17 (0.73, 1-87). Both analyses suggested an unfavorable risk signal leading to a request for additional information on April 27, 2012.

As a result of this request, you submitted an updated analysis on May 11, 2012. This analysis was based on 17 trials and included data from seven controlled extensions as specified in your original SAP. The one additional trial (Study 3896) was a 26-week trial comparing insulin degludec/aspart to glargine in patients with type 2 diabetes mellitus (T2DM) on other background oral anti-diabetic therapies. In this trial, the process of CV event collection and adjudication was similar to that of the trials included in the pre-planned meta-analysis and it was therefore deemed appropriate to include this trial in the updated meta-analysis. The endpoint was a composite of MACE+ individual components. The updated meta-analysis provided 60% additional CV events and increased the total patient-years of exposure (PYE) from 5444 to 7716 PYE. We carefully reviewed the characteristics of the study population originally randomized and compared these to characteristics of the population continuing into the planned extensions. Patient demographics as well as disease characteristics remained balanced between treatment groups and between those originally randomized and those who continued into the extension phases. Furthermore, no evidence of selection bias for continued participation in either treatment groups was noted when discontinuation rates or reasons for discontinuation were examined. As a result, we concluded that this updated database provided reliable and robust data to assess CV risk and accordingly conducted an updated meta-analysis on these data. Despite the increased exposure and additional events, the original signal of CV risk was not attenuated. The following table summarizes the results for MACE+ and MACE, which includes only CV death, nonfatal MI, and nonfatal stroke. While your SAP identified MACE+ as the primary composite endpoint, inclusion of unstable angina introduces events which are less objective in their evaluation and may be less specific to an underlying atherosclerotic process. Inclusion of less objectively evaluated events, and those that may be less specific, in a planned comparison pre-specified to

rule out an excess amount of risk (i.e., non-inferiority comparison) increases the likelihood of showing no treatment difference (i.e., bias to the null). This point is exemplified in Tables 1 and 2 below wherein the hazard ratio is consistently greater in analyses of MACE than MACE+ leading us to conclude that in the face of a potential CV signal, a more rigorous assessment should be based on MACE endpoints.

Table 1. CV Meta-analyses of Original Database and Updated Database on both MACE+ and MACE Endpoints

	Original Database		**Updated Database**	
	IDeg/IDeg-Asp N=5647 (PYE 3569.9)	**Comparator N=3312 (PYE 1873.9)**	**IDeg/IDeg-Asp N=5794 (PYE 5153.6)**	**Comparator N=3461 (PYE 2562.7)**
MACE+	53 (14.8)	27 (14.4)	95 (18.4)	37 (14.4)
MI	20 (5.6)	7 (3.7)	34 (6.6)	9 (3.5)
Stroke	11 (3.1)	4 (2.1)	24 (4.6)	6 (2.3)
CV Death	8 (2.2)	4 (2.1)	12 (2.3)	6 (2.3)
UAP	14 (3.9)	12 (6.4)	25 (4.8)	16 (6.2)
MACE+ HR (95% CI)	1.10 (0.68, 1.77)		1.30 (0.88, 1.93)	
MACE	39 (10.9)	15 (8.0)	70 (13.6)	21 (8.2)
MI	20 (5.6)	7 (3.7)	34 (6.6)	9 (3.5)
Stroke	11 (3.1)	4 (2.1)	24 (4.6)	6 (2.3)
CV Death	8 (2.2)	4 (2.1)	12 (2.3)	6 (2.3)
MACE HR (95% CI)	1.39 (0.76, 2.57)		1.67 (1.01, 2.75)	

We also conducted a meta-analysis of all clinical trials and their planned extensions as **you proposed** in your statistical analysis plan. The results are summarized in the following table.

Table 2. CV Meta-analysis based on Novo Nordisk's Statistical Analysis Plan

	Degludec/Degludec-Asp	**Comparator**
MACE+ Events	93	36
HR (95% CI)	1.29 (0.87, 1.91)	
MACE Events	68	20
HR (95% CI)	1.65 (0.99, 2.75)	

The data summarized in both Tables 1 and 2 support the conclusion of a consistent and persistent signal of excess CV risk associated with insulin degludec and insulin degludec/aspart relative to comparators observed across multiple analyses.

You have de-emphasized the findings in the updated meta-analysis citing decreasing sample size and unexplained changes in hazard rates in the comparator group after Week 52. However, we note that even in Table 1 the original meta-analysis, which would have excluded all but one planned extension phase, did not show a favorable effect of insulin degludec and insulin degludec/aspart on CV risk.

2. Hypoglycemia Risk Reduction

We were unable to identify a unique benefit of insulin degludec and insulin degludec/aspart over existing insulin therapies to offset a potential adverse CV effect. Although you have presented data and analyses to NDA 203314 (insulin degludec) in support of a hypoglycemic risk reduction, we do not agree with your conclusion that insulin degludec provides a clinically meaningful reduction in the risk of developing hypoglycemia over other available once-daily basal insulin for the following reasons:

a. The reliability and generalizability of the estimates are limited due to reliance on point of care derived data obtained from trials with an open-label design and due to exclusion of populations of patients at increased risk of developing hypoglycemia.

b. There was not a consistent trend to suggest a hypoglycemia benefit across definitions of hypoglycemia and in particular for specific, objective, definitions of hypoglycemia (i.e., severe hypoglycemia).

c. A clear hypoglycemia benefit was not seen in the population most susceptible to developing hypoglycemia (i.e., type 1 diabetes mellitus [T1DM]) in analyses of individual trials and in the meta-analysis of glargine comparator trials. In fact, subjects with T1DM randomized to insulin degludec in the three pivotal T1DM trials were three times more likely to withdraw due to hypoglycemia than subjects randomized to comparators; were numerically more likely to experience at least one event of hypoglycemia; and had more numerous events of hypoglycemia per exposure time. These findings were found to be inconsistent with the observation that at the trial end, subjects with T1DM randomized to insulin degludec in all three pivotal trials used on average numerically lower total units of insulin per day compared to subjects randomized to comparators.

d. Although you stated in your advisory committee briefing material that "hypoglycemia is the primary limiting factor to achieving glycemic control with insulin"[1] and repeated this position in your advisory committee meeting presentations, you were not able to demonstrate that the purported hypoglycemic risk reduction associated with insulin degludec use led to better glycemic control based on HbA1c reduction from baseline or

[1] Novo Nordisk November 8, 2012 Advisory Committee Briefing Materials for NDA 203313, page 32.

proportion of individual patients achieving HbA1c target. In four trials comparing glycemic efficacy of insulin degludec to insulin glargine in a basal-only insulin regimen (Studies 3579, 3672, 3586, and 3668), the LS mean treatment difference in HbA1c reduction consistently favored insulin glargine.

e. The presumed benefit of insulin degludec on confirmed nocturnal hypoglycemia may have been confounded by differences in pharmacodynamic profiles between insulin degludec and insulin glargine. You captured events for this subgroup analysis as those occurring between midnight and 0600. The Tmax for glucose lowering is approximately 12 hrs for insulin degludec and 4 hrs for glargine. Because insulin degludec was administered only in the evenings (with evening meal or before bedtime), its peak affect and risk for hypoglycemia may not have been captured within the time band specified for identifying nocturnal hypoglycemia. Although glargine could be administered anytime of the day in these trials, its administration in the evening might result in a biased ascertainment not favoring glargine. You did not capture information on time of day for glargine administration in your trials; however, an exploratory analysis by FDA in which the time band for collecting nocturnal hypoglycemic events was extended by two hours showed an attenuated reduction in hypoglycemic risk associated with degludec suggesting that a treatment difference may be related to time of insulin injection, not inherent qualities of the insulin products.

Path Forward

To address the above cardiovascular safety deficiencies, you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be discussed with the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate. We encourage you to seek Agency feedback regarding trial design and statistical analysis plan before trial initiation.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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.

FACILITY INSPECTIONS

During a recent inspection of the Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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 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 the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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. Include an updated estimate of use for drug marketed in other countries.

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

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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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's "Guidance for Industry - Formal Meetings Between the 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 Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
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/

CURTIS J ROSEBRAUGH
02/08/2013