CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203314Orig1s000

Trade Name:	Tresiba, Injection
Generic Name:	Insulin degludec
Sponsor:	Novo Nordisk, Inc.
Approval Date:	September 25, 2015
Indication:	Tresiba (insulin degludec injection) to improve glycemic control in adults with diabetes mellitus.

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203313Orig1s000
203314Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203314

NDA APPROVAL

Novo Nordisk Inc.
Attention: Shawn Hoskin
Senior Director, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Hoskin:

Please refer to your New Drug Application (NDA) dated and received September 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tresiba (insulin degludec injection) 100 units/mL and 200 units/mL.

We acknowledge receipt of your amendments 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, and February 15, March 1, April 18, and May 1, 2013, and January 2, February 17, March 26(3), April 23 and 29, May 14, 21, and 22, June 5, 16, and 30, August 3, 19, 26, and 28, and September 4, 8, 11, 21, 22, 24, and 25, 2015.

The March 26, 2015, submission constituted a complete response to our February 8, 2013, action letter.

This new drug application provides for the use of Tresiba (insulin degludec injection) to improve glycemic control in adults with diabetes mellitus.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, instructions for use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs*

and As, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203314**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRY DATING PERIOD

A shelf life of 30 months is granted for Tresiba (insulin degludec injection) 100U/mL and 200U/mL, when stored at 5°C ± 3°C. An in-use period of 56 days at up to 30°C is granted for Tresiba.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for type 1 diabetes mellitus in ages 0 to < 1 year and type 2 diabetes mellitus in ages 0 to < 10 years because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with diabetes mellitus to study.

We are deferring submission of your pediatric study for ages 1 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarket study. The status of this study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2954-1 An open-label, 26-week, randomized, controlled efficacy and safety trial comparing Tresiba (insulin degludec injection) with insulin detemir in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive) using insulin aspart at each meal, followed by a 26-week safety extension.

Final Report Submission: June 2016

Submit the protocol(s) to your IND 073198, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) OR FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

A signal of a serious risk of cardiovascular events was identified from a meta-analysis of data from clinical trials evaluating insulin degludec and insulin degludec and insulin aspart, and available data have not definitively excluded the potential for this serious risk with Tresiba (insulin degludec injection).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with Tresiba (insulin degludec injection).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with Tresiba (insulin degludec injection).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2954-2 Conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3.

The timetable you submitted on September 11, 2015, states that you will conduct this trial according to the following schedule:

Trial Completion:	December 2016
Final Report Submission:	September 2017

Submit the protocol(s) to your IND 073198, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)**," "**Required Postmarketing Final Report Under 505(o)**," "**Required Postmarketing Correspondence Under 505(o)**."

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2954-3 To develop and validate an assay to assess for the presence of anti-degludec antibodies that has a sensitivity consistent with FDA guidance. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for

parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

The timetable you submitted on September 11, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2016

2954-4 To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with Tresiba (insulin degludec injection) in Tresiba (insulin degludec injection) clinical trials and determine whether they are associated with differences in pharmacokinetics parameters (e.g. exposure), efficacy (e.g. hemoglobin A1c, insulin dose), and safety (e.g. hypoglycemia and hypersensitivity). The clinical samples should not be tested until the results from the PMC for anti-degludec antibody assay development and validation have been submitted to and reviewed by the Agency.

The timetable you submitted on September 11, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2017
Study Completion: July 2017
Final Report Submission: October 2017

Submit clinical protocols to your IND 073198 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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

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

Enclosures:
Content of Labeling
Carton and Container Labeling

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
09/25/2015