

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203313Orig1s000

Trade Name: Ryzodeg, Injection 70/30

Generic Name: Insulin degludec and insulin aspart

Sponsor: Novo Nordisk, Inc.

Approval Date: September 25, 2015

Indications: Ryzodeg 70/30 (insulin degludec and insulin aspart injection) to improve glycemic control in adults with diabetes mellitus.

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203313Orig1s000

203314Orig1s000

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 203313

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 Ryzodeg 70/30 (insulin degludec and insulin aspart injection) 100 units/mL.

We acknowledge receipt of your amendments 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, 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, 21, 26, and 28, and September 4, 8, 11, 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 Ryzodeg 70/30 (insulin degludec and insulin aspart 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 203313.**” 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 24 months is granted for Ryzodeg 70/30 (insulin degludec and insulin aspart injection) 100 units/mL when stored at 5°C ± 3°C. An in-use period of 28 days at up to 30°C is granted for Ryzodeg 70/30.

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 postmarketing 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.

- 2955-1 An open-label, 16-week, randomized, controlled efficacy and safety trial comparing Ryzodeg 70/30 (insulin degludec and insulin aspart injection) administered once daily with a main meal and insulin aspart for additional meals to insulin detemir, in combination with mealtime insulin aspart at each meal, in pediatric patients with type 1 diabetes mellitus ages 1 to 17 years (inclusive).

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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2955-2 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

- 2955-3 To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with Ryzodeg 70/30 (insulin degludec and insulin aspart injection) in Ryzodeg 70/30 (insulin degludec and insulin aspart 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