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APPLICATION NUMBER:

22-341

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022341

NDA APPROVAL

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your March 23, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Victoza (liraglutide [rDNA origin]) injection, solution for subcutaneous use.

We acknowledge receipt of your submissions dated May 23, June 18, July 8 and 11, August 14 and 25, September 17 and 23, October 3, 7, and 14, November 6 and 14, and December 17, 19, 23 (2), and 24, 2008, January 14, 16, and 21, February 11, 13 (2), 20, 25, and 26, March 27 and 30, April 17 and 22, May 8, 18, 22, and 28, June 22 and 25, July 8, 17, 20, and 29, August 5, 6, 11, 12, 25, 27, and 28, September 2, 4 (2), 11, 16, 17, 22, 23, 25, 29, and 30, October 5, 7, 8, 13, 21, and 26, November 3, 11, 16, 23 (2), and 25, and December 1, 3, 4 (2),10, 21, 22 (2), and 28, 2009, and January 4, 7, 11, 21, and 22, 2010.

This new drug application provides for the use of Victoza (liraglutide [rDNA origin]) injection), solution for subcutaneous use, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 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, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be identical to the submitted labeling (package insert submitted January 22, 2010, and Medication Guide submitted January 21, 2010). The content of labeling should be provided by submitting a link to your SPL file submitted to the drug establishment registration and labeling system. The drug establishment and labeling system will transmit the labeling to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022341.**"

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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 titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. 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 022341.**" Approval of this submission by FDA is not required before the labeling is used.

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

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impractical. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 16 years (inclusive) until May 17, 2013, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

> **1583-1**: A phase 1 pharmacokinetic pediatric study to determine doses for the subsequent phase 3b study that will be conducted under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.

The timetable you submitted on **January 7, 2010**, states that you will submit this study report according to the following schedule:

Study Completion Date:	**June 30, 2010**
Final Report Submission:	**October 31, 2010**

1583-2: A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months.

This study must not be initiated until at least 1 month after you have submitted the complete study report for your postmarketing requirement **1583-5** (13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection [RET] proto-oncogene activation).

The timetable you submitted on **January 7, 2010**, states that you will submit this study report according to the following schedule:

Final Protocol Submission:	**July 31, 2012**
Study Completion Date:	**November 30, 2015**
Final Report Submission:	**March 30, 2016**

Submit all final study reports to NDA 022341. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the 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 (section 505(o)(3)(A)).

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 the signal of a serious risk of medullary thyroid carcinoma, a signal of a serious risk of cardiovascular events, and the signal of a serious risk of acute pancreatitis, including necrotizing pancreatitis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

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

1583-3: A 2-year study in mice to determine if 26 weeks of liraglutide treatment increases the lifetime risk of thyroid C-cell tumors. The study must include a 26-week interim sacrifice group to determine the incidence of focal C-cell hyperplasia and tumors at the end of the treatment period.

The timetable you submitted on **January 7, 2010**, states that you will submit this study report according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**January 31, 2013**
Final Report Submission:	**July 31, 2013**

1583-4: A 3-month study of the effects of liraglutide on the exocrine pancreas in a rodent model of insulin-resistant type 2 diabetes mellitus. This study must include monitoring biomarkers for pancreatitis (amylase, lipase) and glucose-lowering efficacy (HbA1c) during the treatment period and a thorough assessment of macroscopic and microscopic pathology of the pancreas including pancreatic exocrine cell and ductal cell proliferation/metaplasia. Reversibility of any effects on the pancreas must also be determined.

The timetable you submitted on **January 14, 2010**, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**May 30, 2011**
Final Report Submission:	**July 31, 2011**

1583-5: A 13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid glucagon-like peptide-1 (GLP-1) receptor and rearranged-during-transfection (RET) proto-oncogene activation. Autoradiographic ligand binding in thyroid tissue sections can be used to determine GLP-1 receptor localization in mice with and without focal C-cell hyperplasia. RET activation and downstream signaling must be assessed in normal C-cells and focal hyperplastic C-cells from mouse thyroid tissue sections.

The timetable you submitted on **January 14, 2010** states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**May 30, 2011**
Final Report Submission:	**July 31, 2011**

1583-6: A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza (liraglutide [rDNA origin]) Injection and patients with type 2 diabetes not exposed to Victoza (liraglutide [rDNA origin]) Injection, as

well as the incidence of serious hypoglycemia, pancreatitis, hypersensitivity, and overall malignant neoplasms.

The timetable you submitted on **January 7, 2010** states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**April 30, 2010**
Study Completion Date:	**July 31, 2015**
Final Report Submission:	**January 31, 2016**

1583-7: A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Victoza (liraglutide [rDNA origin]) Injection into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Victoza (liraglutide [rDNA origin]) Injection.

The timetable you submitted on **January 7, 2010** states that you will conduct this study according to the following schedule:

Final Protocol Submission:	**July 31, 2010**
Study Completion Date:	**September 15, 2025**
Final Report Submission:	**September 15, 2026**

1583-8: Submission of the complete final study report for Study 1797, a head-to-head efficacy and safety comparison of Victoza (liraglutide [rDNA origin]) Injection and exenatide.

The timetable you submitted on **January 7, 2010** states that you will submit this trial report according to the following schedule:

Final Report Submission:	**February 26, 2010**

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Victoza (liraglutide [rDNA origin]) Injection. 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 cardiovascular events with antidiabetic medications, including Victoza (liraglutide [rDNA origin]) injection. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1583-9: A randomized, double-blind, controlled trial evaluating the effect of Victoza (liraglutide [rDNA origin]) injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of Victoza

(liraglutide [rDNA origin]) injection on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects of Victoza (liraglutide [rDNA origin]) injection on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms.

The timetable you submitted on **January 7, 2010** states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	**March 14, 2010**
Trial Completion Date:	**September 14, 2015**
Final Report Submission:	**April 30, 2016**

Submit the protocols to your IND, with a cross-reference letter to NDA 022341. Submit all final reports to NDA 022341. 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on January 21, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

A. Evaluation of patients' understanding of the serious risks of Victoza (liraglutide [rDNA origin])

B. Evaluation of healthcare providers' understanding of the serious risks of Victoza (liraglutide [rDNA origin])

C. An assessment of healthcare providers' awareness of:

   a. appropriate patient population characteristics, and
   b. the potential risk for medullary thyroid carcinoma
   c. the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis

D. Evaluation of healthcare providers' identification and treatment of:

   a. medullary thyroid carcinoma after initiation of Victoza (liraglutide [rDNA origin])
   b. acute pancreatitis after initiation of Victoza (liraglutide [rDNA origin])

E. Evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed

F. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

G. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

H. An assessment of the number of Victoza (liraglutide [rDNA origin]) prescribers identified to receive the Dear Health Care Provider (DHCP) Letter and the number of DHCP letters mailed

I. An assessment of the percentage of targeted physicians who are presented with the Highlighted Information for Prescribers via Sales Specialists, the website, or medical information department

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022341 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022341
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022341
REMS ASSESSMENT
PROPOSED REMS MODIFICATION *(if included)*

If you do not submit electronically, please send five copies of REMS-related submissions.

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications, see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

We request that for a period of two years, you submit all cases of pancreatitis as 15-day alert reports and that you provide analyses of clinical trial and post-marketing reports of pancreatitis as adverse events of special interest in your periodic safety update reports.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to NDA 022341.

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-ACTION FEEDBACK MEETING

New molecular entities and important new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process throughout drug development and marketing application review. The purpose is to learn from successful aspects of the process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, contact the Division of Metabolism and Endocrinology Products.

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
Package Insert
Medication Guide
Pen Carton Labels (1 variable dose pen (0.6-1.2-1.8 mcg), 2 variable dose pens (0.6-1.2-1.8 mcg), 3 variable dose pens (0.6-1.2-1.8 mcg)), Pen Container Labels (1 variable dose pen (0.6-1.2-1.8 mcg), 2 variable dose pens (0.6-1.2-1.8 mcg), 3 variable dose pens (0.6-1.2-1.8 mcg))
Patient Instructions for Use
REMS and REMS-related documents

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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
01/25/2010