CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206321Orig1s000

Trade Name:	Saxenda Injection, 3 mg.
Generic Name:	Liraglutide [rDNA origin]
Sponsor:	Novo Nordisk, Inc.
Approval Date:	December 23, 2014
Indication:	Use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obese), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

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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 206321

NDA APPROVAL

Novo Nordisk, Inc.
Attention: Michelle Thompson
Senior Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. Thompson:

Please refer to your New Drug Application (NDA) dated and received December 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Saxenda (liraglutide [rDNA origin] injection), 3 mg.

We acknowledge receipt of your amendments dated January 10, February 6, 13, and 14, March 4 and 21, April 2(3), 11, 15, 18, and 29, May 1, 2(2), 23, and 27, June 6, 16, 18, and 26, July 1, 3, 8, 9, 11, 14, and 15(2), August 14(2), 20, 28, and 29, September 24, 26, and 29(2), October 1(2), 2, 3(2), 6, 7, 9, 15, 17(2), 18, 20 and 24, November 10(2), 18, and December 12,16, 17, 18, and 2014.

This new drug application provides for the use of Saxenda (liraglutide [rDNA] injection), as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obese), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

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, medication guide, and 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.

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 *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 206321**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the products 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to 6 years (inclusive) because necessary studies are impossible or highly impracticable. This is because weight maintenance, not weight loss, is the clinical goal for obese children 2 to 6 years of age. Weight loss is not recommended in children less than 2 years of age because of the requirement for adequate growth and development and optimal deposition of lipids in the developing nervous system.

We are deferring submission of your pediatric studies for ages 7 to 17 years (inclusive) for this application 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.

2802-1 A juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity.

Final Report Submission: December 2014

2802-2 A clinical pharmacology study (Trial NN8022-3967) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive).

Final Report Submission: December 2014

2802-3 A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).

Final Protocol Submission August 2015
Study Completion: August 2019
Final Report Submission: August 2020

2802-4 A clinical pharmacology study to assess pharmacokinetic and pharmacodynamics parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive).

Final Protocol Submission September 2015
Study Completion: August 2017
Final Report Submission: February 2018

2802-5 A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). The trial may not be initiated until results from the Saxenda adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission April 2020
Study Completion: October 2023
Final Report Submission: August 2024

Submit the protocols to your IND 073206, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are

warranted based on the data derived from these studies. 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 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.

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 medullary thyroid carcinoma associated with Saxenda (liraglutide [rDNA origin] 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.

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

2802-6 A medullary thyroid carcinoma registry-based case series 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 Saxenda (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 Saxenda (liraglutide [rDNA origin] injection).

The timetable you submitted on December 16, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 2015
Study Completion:	September 2030
Final Report Submission:	September 2031

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 breast cancer associated with Saxenda (liraglutide [rDNA origin] injection).

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

2802-7 To assess the risk of breast cancer associated with liraglutide in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular

Outcome Results) cardiovascular outcomes trial. To assess this risk, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

The timetable you submitted on December 16, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2015
Trial Completion:	September 2015
Final Report Submission:	April 2016

2802-8 To assess the risk of breast cancer associated with liraglutide in Trial 1839. To assess this risk, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

The timetable you submitted on December 16, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2015
Trial Completion:	March 2015
Final Report Submission:	August 2015

Submit the protocols to your IND 073206, with a cross-reference letter to this NDA. Submit all final reports 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.

We also remind you that the following requirements under section 505(o)(3) of the FDCA, as stated in the approval letter for NDA 022341 for Victoza (liraglutide [rDNA origin] injection) dated January 25, 2010, also apply to NDA 206321:

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.

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

Please cross-reference NDA 206321 when you submit your final report for requirement 1583-9 to NDA 022341.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2802-9 A study evaluating gallbladder ejection fractions in liraglutide-treated subjects to further characterize the effect of liraglutide on gallbladder motility.

The timetable you submitted on December 16, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2015
Study Completion:	January 2017
Final Report Submission:	September 2017

Submit clinical protocols to your IND 073206 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**."

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)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Saxenda (liraglutide) to ensure the benefits of the drug outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on December 17, 2014, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Saxenda (liraglutide) into interstate commerce.

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

a. An evaluation of the implementation of REMS Communication Plan activities:
    i. Product launch date
    ii. Number of healthcare providers and professional societies targeted by the REMS.
    iii. REMS Letter: Number of REMS letters sent to healthcare providers and Professional Societies via US mail (or email if this method is added) and the dates the letters were sent. Number of letters that were undeliverable will be included. Provide a list of names of professional societies with date of confirmed REMS letter receipt, along with any actions taken (e.g., posting on societies website, other outreach to members regarding REMS letters).
    iv. REMS Factsheet: number of healthcare providers detailed and provided the REMS Factsheet through the detail.

v. REMS Slides: number of presentations employing the REMS Slides during the reporting period and cumulatively and number of attendees (including targeted physicians).

vi. Scientific meetings: list of scientific meetings where Novo Nordisk Medical Information has a presence (e.g., booth) in which the SAXENDA® REMS Factsheet was made available.

vii. REMS website: Date when the REMS website went live and number of unique site visits during the assessment period and cumulative.

b. Evaluation of healthcare providers' knowledge:

i. An evaluation of healthcare providers' knowledge of the potential risk for medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis). Stratify results by type of healthcare provider.

ii. An evaluation of healthcare providers' awareness of REMS materials.

iii. An evaluation of healthcare providers' sources of knowledge about the risks associated with SAXENDA.

c. Safety Surveillance and Utilization Data for the reporting period and cumulatively:

i. SAXENDA total prescription data by healthcare providers target in SAXENDA call plan.

ii. A summary and analysis of all SAXENDA postmarketing case reports of (a) pancreatitis and b) medullary thyroid carcinoma.

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

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 the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 206321 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

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

NDA 206321 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 206321
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 206321
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 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
Office of Prescription Drug Promotion
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. 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.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

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

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
- Content of Labeling
- Medication Guide
- Instructions for Use
- Carton and Container Labeling
- REMS

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

/s/

JAMES P SMITH
12/23/2014