CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206321Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

NDA/BLA #s:	NDA 206321
Products:	SAXENDA (liraglutide [rDNA origin] injection), solution for subcutaneous use
APPLICANT:	Novo Nordisk
FROM:	Jennifer Rodriguez Pippins, M.D., M.P.H.
DATE:	October 10, 2014

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

SAXENDA (liraglutide) is a subcutaneous injection for chronic weight management in addition to a reduced-calorie diet and physical activity. It will be approved for use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition such as hypertension, type 2 diabetes, or high cholesterol (dyslipidemia). Liraglutide received initial U.S. approval in 2010 at a lower dose (1.8 mg vs 3.0 mg) as VICTOZA, a second-line therapy for the treatment of type 2 diabetes mellitus. VICTOZA (liraglutide) has in place a REMS (communication plan and a timetable for submission of assessments) that addresses the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis associated with VICTOZA (liraglutide).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for SAXENDA (liraglutide) to ensure that the benefits of the drug outweigh:

- The potential risk of medullary thyroid carcinoma identified in non-clinical studies of SAXENDA (liraglutide) and other glucagon-like peptide (GLP)-1 receptor agonists; and

- The risk of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, identified in the post-marketing reports for liraglutide. Cases of acute

pancreatitis have also been described in association with SAXENDA (liraglutide) during clinical trials. In reaching this determination, we considered the following:

A. In 2011-2012 the prevalence of obesity in the United States was 34.9% in adults, and more than two-thirds of adults are either overweight or obese.[1] In 2011, approximately 2.74 million patients used antiobesity drugs; the most commonly used product was phentermine, which is approved for short-term weight loss.[2]

B. Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, and type 2 diabetes mellitus.

C. The benefit of SAXENDA (liraglutide) is expected based on significant weight loss over lifestyle modification and modest improvements in weight-related co-morbidities. The effect of pharmacological weight-loss on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

D. The expected duration of therapy is over a patient's lifetime.

E. In addition to the most serious risks of medullary thyroid carcinoma and acute pancreatitis, SAXENDA (liraglutide) also has the following risks: acute gallbladder disease, heart rate increase, hypoglycemia when used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, renal impairment, and hypersensitivity.

F. SAXENDA (liraglutide) is a not a new molecular entity.

The REMS will consist of a communication plan and a timetable for submission of assessments of the REMS.

[1] Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Childhood and Adult Obesity in the United States, 2011-2011. *JAMA*. 2014; 311(8): 806-814.
[2] Hampp C, Kang EM, Borders-Hemphill V. Use of prescription antiobesity drugs in the United States. *Pharmacotherapy*. 2013; 33(12):1299-1307.

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/s/

JENNIFER R PIPPINS
12/22/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	December 11, 2014
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Oswell, MA, Health Communications Analyst DRISK
Team Leader:	Naomi Redd, Pharm.D, Acting Team Leader DRISK
Division Director	Cynthia LaCivita, Pharm.D, Acting Director DRISK
Subject:	FDA's comments to Novo Nordisk regarding their proposed amendment (October 10, 2014) to the Saxenda REMS
Drug Name(s):	Saxenda (liraglutide [rDNA] injection)
Therapeutic Class:	Glucagon-like peptide -1 (GLP-1) receptor agonist
Dosage and Route:	Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg/ml, 2.4 mg/ml, 3 mg/ml (6 mg/ml 3 ml)
Application Type/Number:	NDA 206321/Amendment
Submission Number:	Seq. No. 0054
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2014-77 and 2014-79
TSI #:	TSI 894

1 INTRODUCTION

This review documents the joint decision by the Division of Risk Management (DRISK), the Division of Metabolism and Endocrinology Products (DMEP), and the Office of Chief Counsel to revise the Saxenda REMS document for the purpose of clarifying the REMS requirement involving the distribution of a REMS Factsheet to healthcare providers.

The November 10, 2014 amendment (Seq. No. 0054) to the Saxenda REMS included a revised version of the REMS, REMS Supporting Document, REMS Letters for Healthcare Providers, REMS Letter for Professional Society, REMS Factsheet, REMS Website, REMS Slides, and the REMS Changes Table. DRISK recommended approval of the Saxenda REMS as submitted on November 10, 2014. See DRISK's review dated November 14, 2014.

Upon further discussions between DRISK, the Division of Metabolism and Endocrinology Products (DMEP), and the Office of Chief Counsel it has been determined there is a need to clarify a statement in the REMS Document addressing the distribution of the REMS Factsheet.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Saxenda REMS submitted in the original application, the amended REMS received August 20, 2014, MS Word version of all REMS documents received by the FDA via email on September 12, 2014, and amendments received by FDA on October 2, 2014, October 16, 2014, and November 10, 2014.
- DRISK reviews dated September 26, 2014, October 15, 2014, November 5, 2014, and November 11, 2014.
- (b) (5) [redacted]

3 CONCLUSIONS AND RECOMMENDATIONS

As agreed upon by DRISK, DMEP, and Office of Chief Counsel representative, the Saxenda REMS can be approved contingent upon revision of the REMS Document, as follows:

> Communication Plan, section 2) REMS Factsheet: "A REMS Factsheet will be made available to healthcare providers and distributed through Novo Nordisk SAXENDA® field based sales or medical representatives during the initial healthcare provider discussion within the first 18 months after approval of this REMS. (b) (4) [redacted] (b) (4) [redacted] Novo Nordisk SAXENDA® field based sales or medical representatives will verbally review each risk message contained in the Factsheet."

The revised Saxenda REMS Document and REMS Supporting Document are appended to this review.

DRISK request DMEP send Novo Nordisk the comment included in section 4 of this review.

4 COMMENTS FOR THE APPLICANT

FDA determined there is a need for clarification of the requirement for a REMS Factsheet as part of the communication plan included in the Saxenda REMS. FDA requests Novo Nordisk revises the Saxenda REMS Document as follows:

> Communication Plan, section 2) REMS Factsheet: "A REMS Factsheet will be made available to healthcare providers and distributed through Novo Nordisk SAXENDA® field based sales or medical representatives during the initial healthcare provider discussion within the first 18 months after approval of this REMS (b) (4) (b) (4) Novo Nordisk SAXENDA® field based sales or medical representatives will verbally review each risk message contained in the Factsheet."

The revised Saxenda REMS document and REMS Supporting Document are appended.

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/s/

AMARILYS VEGA
12/11/2014

REEMA J MEHTA
12/11/2014
Signed on behalf of Cynthia LaCivita

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Modification Review

Date:	November 14, 2014
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Oswell, MA, Health Communications Analyst DRISK
Team Leader:	Naomi Redd, Pharm.D, Acting Team Leader DRISK
Division Director	Cynthia LaCivita, Pharm.D, Acting Director DRISK
Subject:	FDA's comments to Novo Nordisk regarding their proposed amendment (October 10, 2014) to the Saxenda REMS
Drug Name(s):	Saxenda (liraglutide [rDNA] injection)
Therapeutic Class:	Glucagon-like peptide -1 (GLP-1) receptor agonist
Dosage and Route:	Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg/ml, 2.4 mg/ml, 3 mg/ml (6 mg/ml 3 ml)
Application Type/Number:	NDA 206321/Amendment
Submission Number:	Seq. No. 0054
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2014-77 and 2014-79
TSI #:	TSI 894

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of Novo Nordisk's November 10, 2014 amendment (Seq. No. 0054) to the proposed risk evaluation and mitigation strategy (REMS) for Saxenda (liraglutide) initially received by FDA on December 20, 2013 (Seq. No. 0000) and amended on August 20, 2014 (Seq. No.0033), October 2, 2014 (Seq. No. 0042), and October 16 (email submission).

The November 10, 2014 amendment included a revised version of the REMS, REMS Supporting Document, REMS Letters for Healthcare Providers, REMS Letter for Professional Society, REMS Factsheet, REMS Website, REMS Slides, and the REMS Changes Table.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Saxenda REMS submitted in the original application, the amended REMS received August 20, 2014, MS Word version of all REMS documents received by the FDA via email on September 12, 2014, and amendments received by FDA on October 2, 2014, October 16, 2014, and November 10, 2014.
- DRISK reviews dated September 26, 2014, October 15, 2014, and November 5, 2014.

3 REVIEW RESULTS

The Saxenda REMS documents received by FDA on November 10, 2014 include all the revisions to the REMS materials recommended by DRISK.

4 CONCLUSIONS AND RECOMMENDATIONS

Novo Nordisk revised the Saxenda REMS as recommended by DRISK.

DRISK recommends approval of the Saxenda REMS.

The Saxenda REMS document and REMS materials are appended to this review.

APPENDED MATERIALS:

- REMS Document
- REMS Letter to Healthcare Providers
- REMS Letter for Professional Societies
- REMS Factsheet
- REMS Slides
- REMS Website (landing page)
- REMS Supporting Document

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/s/

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11/14/2014

CYNTHIA L LACIVITA
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Modification Review

Date:	November 5, 2014
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Oswell, MA, Health Communications Analyst DRISK
Team Leader:	Naomi Redd, Pharm.D, Acting Team Leader DRISK
Division Director	Cynthia LaCivita, Pharm.D, Acting Director DRISK
Subject:	FDA's comments to Novo Nordisk regarding their proposed amendment (October 10, 2014) to the Saxenda REMS
Drug Name(s):	Saxenda (liraglutide [rDNA] injection)
Therapeutic Class:	Glucagon-like peptide -1 (GLP-1) receptor agonist
Dosage and Route:	Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg/ml, 2.4 mg/ml, 3 mg/ml (6 mg/ml 3 ml)
Application Type/Number:	NDA 206321/Amendment
Submission Number:	Seq. No. 0042 and Email submission from October 16, 2014
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2014-77 and 2014-79
TSI #:	TSI 894

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of Novo Nordisk's October 2, 2014 amendment (Seq. No. 0042) to the proposed risk evaluation and mitigation strategy (REMS) for Saxenda (liraglutide) initially received by FDA on December 20, 2013 (Seq. No. 0000) and amended on August 20, 2014 (Seq. No.0033), October 2, 2014 (Seq. No. 0042), and October 16 (email submission).

The October 16, 2014 amendment included a revised version of the REMS, REMS Supporting Document, REMS Letters for Healthcare Providers, REMS Letter for Professional Society, REMS Factsheet, REMS Website, REMS Slides, and the REMS Changes Table.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Saxenda REMS submitted in the original application, the amended REMS received August 20, 2014, MS Word version of all REMS documents received by the FDA via email on September 12, 2014, and amendment received by FDA on October 2, 2014.
- DRISK reviews dated September 26, 2014 and October 15, 2014.

3 REVIEW RESULTS

The Saxenda REMS documents received by FDA on October 16, 2014 reflects the most recent changes to the Saxenda label (as of October 16, 2014) and revisions to the REMS materials as recommended by DRISK.

A table included in section 5 of this review includes DRISK's comments to Novo Nordisk's proposed revisions to the REMS.

4 CONCLUSIONS AND RECOMMENDATIONS

Additional revisions to the Saxenda® REMS and REMS appended materials are still required.

DRISK requests that the Division of Metabolism and Endocrinology Products (DMEP) sends Novo Nordisk the comments included in section 5 below and the appended REMS documents with tracked changes.

5 COMMENTS FOR THE APPLICANT

The comments included in the following table address Novo Nordisk's amendment of the Saxenda® REMS (liraglutide, NDA 206321, Submission Number: 0042 and email submission from October 16, 2014). Appended is the revised version of the REMS document, REMS appended material, and REMS Supporting Document.

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APPENDED MATERIALS:

- REMS Document
- REMS Letter to Healthcare Providers
- REMS Letter for Professional Societies
- REMS Factsheet
- REMS Slides
- REMS Website (landing page)
- REMS Supporting Document

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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Modification Review

Date:	October 15, 2014
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Oswell, MA, Health Communications Analyst DRISK
Team Leader:	Naomi Redd, Pharm.D, Acting Team Leader DRISK
Division Director	Cynthia LaCivita, Pharm.D, Acting Director DRISK
Subject:	FDA's comments to Novo Nordisk regarding their proposed amendment (October 10, 2014) to the Saxenda REMS
Drug Name(s):	Saxenda (liraglutide [rDNA] injection)
Therapeutic Class:	Glucagon-like peptide -1 (GLP-1) receptor agonist
Dosage and Route:	Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg/ml, 2.4 mg/ml, 3 mg/ml (6 mg/ml 3 ml)
Application Type/Number:	NDA 206321/Amendment
Submission Number:	0042
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2014-77 and 2014-79
TSI #:	TSI 894

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of Novo Nordisk's October 2, 2014 amendment (Seq. No. 0042) to the proposed risk evaluation and mitigation strategy (REMS) for Saxenda (liraglutide) initially received by FDA on December 20, 2013 (Seq. No. 0000) and amended on August 20, 2014 (Seq. No.0033).

The October 2, 2014 amendment included a revised version of the REMS, REMS Supporting Document, REMS Letters for Healthcare Providers, REMS Letter for Professional Society, REMS Factsheet, REMS Website, REMS Slides, and the REMS Changes Table.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Saxenda REMS submitted in the original application, the amended REMS received August 20, 2014, MS Word version of all REMS documents received by the FDA via email on September 12, 2014, and amendment received by FDA on October 2, 2014.
- DRISK review dated September 26, 2014.

3 REVIEW RESULTS

The Saxenda REMS documents received by FDA on October 2, 2014 do not reflect the most recent changes to the Saxenda label. Revisions to the Saxenda label have resulted in several modifications to the Saxenda REMS Message Map (see Table 1). Also, after further internal discussions, DRISK and Division of Metabolism and Endocrinology Products (DMEP) determined that the risk of duplicative therapy does not need to be included in the REMS and can be communicated via the label.

TABLE 1: REVISED SAXENDA® REMS MESSAGE MAP FOR HEALTHCARE PROVIDERS

	Message 1 **Potential Risk of** **Thyroid C-cell Tumors**	**Message 2** **Risk of Acute Pancreatitis**
Key Message	• Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. • It is unknown whether SAXENDA® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.	• Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide. • In clinical trials studying SAXENDA®, there were more cases of pancreatitis in patients treated with SAXENDA® than in patients treated with comparators.
Supporting Detail 1	• SAXENDA® is contraindicated in patients with a personal or family	• SAXENDA® has not been studied sufficiently in patients with a history

TABLE 1: REVISED SAXENDA® REMS MESSAGE MAP FOR HEALTHCARE PROVIDERS		
	Message 1 **Potential Risk of** **Thyroid C-cell Tumors**	**Message 2** **Risk of Acute Pancreatitis**
Appropriate Patient Selection	history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2).	of pancreatitis.
Supporting Detail 2 HCP Action	• Counsel patients regarding the risk of MTC with use of SAXENDA® and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). • Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with SAXENDA®. • If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. • Patients with thyroid nodules noted on physical examination or neck imaging should be further evaluated.	• After initiation of SAXENDA®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). • If pancreatitis is suspected, SAXENDA® should promptly be discontinued and appropriate management should be initiated. • If pancreatitis is confirmed, SAXENDA® should not be restarted.

Table 2 in section 6 of this review includes DRISK's comments to Novo Nordisk's proposed revisions to the REMS.

4 REMS ASSESSMENT PLAN

Below is a revised version of the REMS assessments plan.

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.

5 CONCLUSIONS AND RECOMMENDATIONS

Additional revisions to the Saxenda® REMS and REMS appended materials are still required to include the most recent changes to the product label and to remove from the REMS the risk of duplicative therapy.

DRISK requests DMEP sends Novo Nordisk the comments included in section 6 below and the appended REMS documents with tracked changes.

6 COMMENTS FOR THE APPLICANT

The comments included in the following table address Novo Nordisk's amendment of the Saxenda® REMS (liraglutide, NDA 206321, Submission Number: 0042). Appended is the revised version of the REMS document and REMS Supporting Document.

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APPENDED DOCUMENTS:

- REMS Document
- REMS Supporting Document

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/s/

AMARILYS VEGA
10/15/2014

CYNTHIA L LACIVITA
10/16/2014
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Modification Review

Date:	September 26, 2014
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Oswell, MA, Health Communications Analyst DRISK
Team Leader:	Doris Auth, Pharm D, Team Leader DRISK
Division Director	Cynthia LaCivita, Pharm.D, Acting Director DRISK
Subject:	FDA's comments to Novo Nordisk regarding their proposed REMS for Saxenda
Drug Name(s):	Saxenda (liraglutide [rDNA] injection)
Therapeutic Class:	Glucagon-like peptide -1 (GLP-1) receptor agonist
Dosage and Route:	Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg/ml, 2.4 mg/ml, 3 mg/ml (6 mg/ml 3 ml)
Application Type/Number:	NDA 206321/Amendment
Submission Number:	0033
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2014-77 and 2014-79
TSI #:	TSI 894

1 INTRODUCTION

This review documents DRISK's evaluation of Novo Nordisk's proposed risk evaluation and mitigation strategy (REMS) for Saxenda (liraglutide) initially received by FDA on December 20, 2013 (Seq. No. 0000) and amended on August 20, 2014 (Seq. No.0033). In this submission, the Sponsor included a revised version of the REMS and REMS Supporting Document to reflect revisions made to the Victoza REMS on July 31, 2014. In addition, at FDA's request, the Sponsor submitted MS Word version of the REMS, REMS appended materials, and REMS Supporting Document via email on September 12, 2014.

Novo Nordisk is seeking approval for liraglutide 3.0 mg for once daily subcutaneous administration, for chronic weight management as an adjunct to a reduced calorie diet and increased physical activity in adults with an initial body mass index (BMI) of ≥30 kg/m^2 (obese) or ≥27 kg/m^2 (overweight) with at least one weight-related co-morbidity such as hypertension, dysglycemia (pre-diabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea.

Liraglutide is marketed worldwide as Victoza with an estimated number of patient years of exposure of over 3.3 million.

1.1 BACKGROUND

Obesity. Obesity is a major public health problem which affects adults and children in the United States. According to a recent publication by the CDC, since 1960, the prevalence of adult obesity in the United States has nearly tripled (13% in 1960–1962 to 36% 2009–2010) and more than tripled among children (5% in 1971–1974 to 17% in 2009–2010).[1] Obesity is associated with major comorbidities, including hypertension, hyperglycemia, type 2 diabetes mellitus, dyslipidemia, certain types of cancer, obstructive sleep apnea and atherosclerosis, as well as with reduced life expectancy.

Alternative Therapies. The treatment of obesity includes lifestyle changes (i.e., dietary and behavioral changes and increased exercise), pharmacotherapy (3 drug products), and surgical interventions. FDA-approved products for obesity include the following warnings:

- Belviq (lorcaserin, approved June 27, 2012) – Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions, valvular heart disease, cognitive impairment, psychiatric disorders, potential risk of hypoglycemia in patients with Type 2 diabetes mellitus (T2DM) on atidiabetic therapy, priaprism, heart rate disease, hematological changes, prolactin elevation, and pulmonary hypertension.
- Qsymia (phentermine/topiramate, approved July 17, 2012) – Teratogenicity, increased heart rate, suicidal behavior/ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, elevation of creatinine, potential risk of hypoglycemia in patients with Type 2 diabetes mellitus (T2DM) on antidiabetic therapy, potential risk of hypotension in patients treated with antihypertensive medications, central nervous system (CNS) depression with concomitant CNS depressants including alcohol, potential seizures with abrupt withdrawal of Qsymia, higher exposure to Qsymia in patients with renal and hepatic impairment, kidney stones, oligohydrosis and hyperthermia, hypokalemia, and the need to monitor

[1] May AL, Freedman D, Sherry B, Blanck HM: Obesity - United States, 1999-2010. MMWR Surveill Summ. 2013 Nov 22;62 Suppl 3:120-8

blood chemistry profile. Qsymia was approved with a REMS comprised of a Medication Guide and elements to assure safe use (ETASU) to address the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy; the importance of pregnancy prevention for females of reproductive potential receiving Qsymia; and the need to discontinue Qsymia immediately if pregnancy occurs.

- Contrave (naltrexone hydrochloride and bupropion hydrochloride, approved September 10, 2014) – suicidal behavior and ideation (Boxed Warning), neuropsychiatric symptoms and suicide risk in smoking cessation treatment (Boxed Warning), seizures, vulnerability to opioid overdose (patients receiving opioid analgesics), precipitated opioid withdrawal (patients receiving opioid analgesics), increased in blood pressure and heart rate, allergic reactions, hepatotoxicity, activation of mania, angle-closure glaucoma, and potential risk of hypoglycemia in patients with T2DM on antidiabetic therapy.

Liragludide. Liraglutide is a Glucagon-like peptide-1 (GLP-1) analog, a hormone released post-prandially. GLP-1 lowers blood glucose by stimulation of insulin secretion and inhibition of glucagon secretion through activation of GLP-1 receptors in the pancreas. Liraglutide is approved by FDA as Victoza as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. GLP-1 delays gastric emptying and regulates appetite and food intake. The mechanism of action for weight loss with liraglutide consists of appetite regulation by modulation of appetite centers of the brain which result in reduced caloric intake.

Victoza was approved with a REMS to address the potential risk of medullary thyroid carcinoma and the risk of pancreatitis. The currently approved REMS consists of a communication plan (CP) and a timetable for submission of REMS assessments. The CP includes: REMS Letters for Healthcare Providers and for Professional Societies, a REMS Factsheet, REMS Slides, REMS website, and a requirement to disseminate REMS-related information at relevant scientific meetings. The Victoza REMS was recently modified (July 2014) to address findings from the most recent REMS assessment report which indicated that healthcare providers' (primary care providers in particular) knowledge about the risks associated to Victoza was below expectations.

Risk Management of Other GLP-1 Agonists. Other approved GLP-1 agonists include Byetta (exenatide), Bydureon (exenatide), Tanzeum (albiglutide) and Trulicity (dulaglutide), all were approved with CP REMS. Byetta was released from the REMS requirement on August 5, 2011. The Bydureon CP REMS is still in place, but has completed all planned communication activities. Both Tanzeum and Trulicity REMS were recent approvals in 2014 and include REMS Letters, REMS Factsheet, REMS website, Timetable for submission of REMS assessments.

1.2 REGULATORY HISTORY:

Following is the regulatory history of liraglutide, in pertinent part,

- **January 25, 2010:** Liraglutide (NDA 022341, Victoza) approved for type 2 diabetes mellitus (up to 1.8 mg/day) with a REMS consisting of a communication plan to address the risks of thyroid medullary carcinoma and pancreatitis.
- **December 20, 2013:** Liraglutide (NDA 206321, Saxenda) received by FDA.
- **July 31, 2014:** Victoza REMS modification approved.
- **September 11, 2014:** Advisory committee meeting. Panel votes in favor of approval of Saxenda for weight management (Yes 14, No 1).

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Saxenda REMS submitted in the original application, the amended REMS received August 20, 2014, and the MS Word version of all REMS documents received by the FDA via email on September 12, 2014.
- Advisory Committee meeting briefing documents and slides.

3 CLINICAL DEVELOPMENT PROGRAM

The clinical development program for liraglutide (3.0 mg) for weight management included six trials that enrolled around 6,000 obese or overweight patients; around 3,300 of these patients were exposed to liraglutide 3.0 mg in phase 2 and 3 trials.

- 1 clinical pharmacology trial (trial 3630)
- 1 phase 2 liraglutide dose-finding trial (trial 1807)
- 4 phase 3a trials (trials 1839, 1923, 1922, and 3970)
- An extension of phase 3 trial (trial 1839) is ongoing, due to complete in 2015.

Table 1 below lists the pre-specified co-primary endpoints in the phase 3 trials.

Table 1. Pre-specified Co-primary Endpoints – Phase 3 Trials

Trial	1st Co-primary endpoint	2nd Co-primary endpoint	3rd Co-primary endpoint
1839	Change in body weight from baseline (% and kg)	Proportion of patients achieving ≥5% reduction of baseline body weight	Proportion of patients achieving >10% reduction of baseline body weight
1923	Change in body weight from baseline (after low calorie diet run-in period) (% and kg)	Proportion of patients that maintained the ≥5% reduction in initial body weight achieved during the low calorie diet run-in period	Proportion of patients achieving ≥5% reduction of baseline body weight
1922	Change in body weight from baseline (% and kg)	Proportion of patients achieving ≥5% reduction of baseline body weight	Proportion of patients achieving >10% reduction of baseline body weight
3970	Change from baseline in apnea-hypopnea index		

Source: Novo Nordisk Advisory Committee Meeting briefing package, page 19.

The assessment of safety is primarily based on pooled data up to 56 weeks from the placebo-controlled phase 2 and 3 clinical trials in the weight management program (trials 1807, 1839, 1923, 1922 and 3970). The focus of the safety assessment was on GLP-receptor activation (e.g., pancreatitis, neoplasms, heart rate increases, gastrointestinal symptoms), on adverse events associated to weight management products (e.g., gallstones, cardiovascular events, psychiatric events), immunogenicity, and

hypoglycemia. Post-marketing reports related to liver and renal safety were also considered in the assessment of safety.

Efficacy

A statistical analysis based on Last Observation Carried Forward (LOCF) showed liraglutide 3 mg reached the required 5% mean placebo-subtracted difference in weight loss described in the FDA draft weight management guidance[Error! Bookmark not defined.] in the largest of the three phase 3 trials and in the pooled analyses [(trial 1839: - 5.39); (trial 1922: -3.95); (trial 3970: -4.15); (trial 1923:-6.06); (trial 1807:-6.08); (phase 3 56-week trials 1839, 1922, and 1923: -5.24); (Total: -5.18)]. Heterogeneity in trial results was attributed to differences in study designs and patient populations.

When compared to placebo, the proportion of patients who achieved 5 and 10% weight loss from baseline at the end of the observation period was statistically significant (5% weight loss: Lira 3 mg 60.3% vs. Placebo 24.4%; 10% weight loss: Lira 3mg 31.2% vs. Placebo 8.7%). However, FDA reanalyzed the data using a different strategy and concluded that the sponsor's primary analysis exaggerates the treatment effect at week 56; statistically significant differences remained but the analysis showed a smaller treatment effect.

All trials met the categorical efficacy standard as outlined in the FDA draft weight management guidance, i.e., proportion of 5% responders in active-treatment group is at least 35% and approximately twice the proportion in the placebo-treatment group.

Liraglutide 3 mg was associated with improvements in the glycemic parameters in patients with and without diabetes, decreases in blood pressure, and modest improvements in lipid parameters commensurate with degree of weight loss.

Safety

Following are the key safety concerns identified in the Saxenda clinical development program:

- Medullary thyroid cancer (MTC) was not observe in clinical trials. MTC cases have been reported postmarketing but the contribution of liraglutide is uncertain.
- Imbalances in the occurrence of pancreatitis and gallstones was observed in clinical trials: both liraglutide and/or weight loss maybe contributing to these findings. Observed pancreatitis events were generally mild and uncomplicated, none were necrotizing or hemorrhagic.
  - Pancreatitis incidence was low but higher in the liraglutide 3 mg group (liraglutide 0.4% vs. placebo <0.1%).
  - Gallbladder-related events: liraglutide 3.0 mg (2.3%) vs. placebo (0.9%).
- Increases in heart rate were observed but the overall cardiovascular risk is uncertain.
- An excess of cases of suicidality was observed in the liraglutide arm; however, most patients were able to continue on treatment.
- An imbalance in breast cancer was observed in clinical trials; however, the available evidence does not support or deny the potential role of liraglutide in cancer promotion or progression.
- If approved, there is a potential risk for duplicity of therapy given liraglutide is already marketed as Victoza.

4 NEED FOR A REMS FOR SAXENDA

The sponsor proposed a boxed warning for the potential risk of thyroid C-cell tumors similar to that included in the Victoza label:

"Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance (b) (4) *Saxenda is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).* (b) (4)

There is a regulatory precedent to manage the potential risk of MTC and the risk of pancreatitis associated with GLP-1 receptor agonists with a CP REMS. A CP REMS proposed by the sponsor is very similar to that recently approved for Victoza. It is likely that primary care providers will be responsible for the largest proportion of Saxenda prescriptions. Although the Victoza CP REMS has not been fully successful at meeting the REMS goal to inform primary care prescribers about the risks associated with the use of Victoza, the most recent REMS modification (July 2014) intended to address this deficiency.

4.1 REMS MESSAGE MAP

Specific REMS messages to communicate to prescribers regarding the serious risks associated to Saxenda are listed in Table 2 below.

TABLE 2: SAXENDA® REMS MESSAGE MAP for HEALTHCARE PROVIDERS

	Message 1 **Potential Risk of Thyroid C-cell Tumors**	**Message 2** **Risk of Pancreatitis**	**Message 3** **Potential Risk of Duplicative Therapy**
Key Message	• Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice • It is unknown whether SAXENDA® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies	• Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide • In clinical trials studying SAXENDA®, there were more cases of pancreatitis in patients treated with SAXENDA® than in patients treated with comparator	• Liraglutide, the active ingredient in SAXENDA®(indicated for weight management), is also the active ingredient in the marketed product VICTOZA® (indicated for type 2 diabetes mellitus) and should not be used together. • There is a strong association between obesity and type 2 diabetes. Therefore, there is a potential for overlap in the patient populations. • If duplicative prescribing occurs there is a potential risk of exceeding the maximum recommended SAXENDA® dose.
Supporting Detail 1 Appropriate	• SAXENDA® is contraindicated in patients with a personal or family	• SAXENDA® has not been studied sufficiently in patients with a history of pancreatitis.	• To be used in adult patients with an initial body mass index (BMI) of 30 kg/m2 or

TABLE 2: SAXENDA® REMS MESSAGE MAP for HEALTHCARE PROVIDERS			
	Message 1 **Potential Risk of Thyroid C-cell Tumors**	**Message 2** **Risk of Pancreatitis**	**Message 3** **Potential Risk of Duplicative Therapy**
Patient Selection	history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2)	It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using SAXENDA®.	greater (obese), or 27 kg/m2 or greater (overweight) in the presence of at least one weight related comorbidity • SAXENDA® has not been studied with other GLP-1 receptor agonists. Use of GLP-1 receptor agonists should be discontinued
Supporting Detail 2 **HCP Action**	• Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. • Although routine monitoring of serum calcitonin is of uncertain value in patients treated with SAXENDA®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation and to rule out thyroid C-cell tumor.	• After initiation of SAXENDA®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting) • Discontinue promptly if pancreatitis is suspected • Do not restart if pancreatitis is confirmed • Consider other anti-obesity medications in patients with a history of pancreatitis	• Review patient medical and prescription history and ensure no concomitant use of SAXENDA® and other GLP-1 receptor agonists

4.2 REMS ASSESSMENT PLAN

The following elements will be included in Saxenda's REMS assessment plan:

a. An evaluation of the implementation of REMS Communication Plan activities:

   i. Product launch date

   ii. Number of HCPs and professional societies targeted by the REMS.

   iii. REMS Letter: Number of REMS letters sent to HCPs 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 HCPs 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 HCPs knowledge:

i. An evaluation of HCPs' knowledge of the potential risk for medullary thyroid carcinoma, the risk of acute pancreatitis (including necrotizing pancreatitis), and avoiding concomitant use of SAXENDA® with VICTOZA® and other GLP-1 agonists. Stratify results by type of HCP.

ii. An evaluation of prescribers' awareness of REMS materials.

iii. An evaluation of prescribers' 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 HCP target in SAXENDA® call plan.
ii. A summary and analysis of all SAXENDA® postmarketing case reports of (a) pancreatitis, b) medullary thyroid carcinoma, and c) duplicity of therapy with Victoza or other GLP-1 agonists.

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.

5 CONCLUSIONS AND RECOMMENDATIONS

The clinical development program demonstrated Saxenda is safe and effective for weight management as an adjunct to a reduced calorie diet and increased physical activity in adults with an initial body mass index (BMI) of $\geq$30 kg/m^2 (obese) or $\geq$27 kg/m^2 (overweight) with at least one weight-related co-morbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea. Management of the risks of MTC, pancreatitis, and the risk for duplicative therapy with other GLP-1 agonists requires the implementation of a REMS similar to that approved for Victoza.

The REMS proposed by Novo Nordisk on August 20, 2014 cannot be approved as submitted. DRISK requests the Division of Metabolism and Endocrinology Products (DMEP) sends Novo Nordisk the comments included in section 6 below.

6 COMMENTS FOR THE APPLICANT

The comments included in the following table address Novo Nordisk's submission for Saxenda® (liraglutide, NDA 206321, Submission Number: 0033). The revised REMS document and REMS Supporting Documents are appended.

SAXENDA REMS - FDA COMMENTS	
Novo Nordisk Submission from 8/20/2014	**FDA's Comments 9/26/2014**
Global Comments	
	Submit MS Word clean and tracked changes versions of all REMS documents.
	Please verify that all changes to the REMS and REMS materials are reflected in the REMS Supporting Document.
REMS Document	
(b) (4)	

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

/s/

AMARILYS VEGA
09/26/2014

CYNTHIA L LACIVITA
09/26/2014
Concur