

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-341**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

1/25/10



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 24, 2010

To: Mary Parks M.D., Director  
Division of Metabolism and Endocrinology Products (DMEP)

Through: Claudia Karwoski, Pharm.D., Director  
Division of Risk Management (DRISK)

From: **OSE Victoza REMS Review Team**  
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Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Victoza<sup>®</sup> (Liraglutide [rDNA origin]) Injection

Application Type/Number: NDA 22-341

Applicant/sponsor: Novo Nordisk, Inc.

OSE RCM #: 2009-1325

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## 1 INTRODUCTION

This review follows a request from the Division of Metabolic and Endocrine Products (DMEP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) amendment for Victoza<sup>®</sup>, which was submitted by Novo Nordisk, Inc. December 22, 2009.

Victoza (liraglutide) is an incretin mimetic with the proposed indication to improve glycemic control in patients with Type 2 Diabetes Mellitus as an adjunct to diet and exercise. It is available as 6 mg/mL solution to be administered subcutaneously via a 3 mL ~~injection~~ in 0.6 mg, 1.2 mg, or 1.8 mg doses.

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### 1.1 BACKGROUND

The sponsor's original submission (NDA 22-341) received May 23, 2008 contained a proposed Risk Management Plan that included routine pharmacovigilance, labeling and a patient leaflet to address the potential risk of medullary thyroid cancer (MTC) and the risk of pancreatitis.

A public Advisory Committee meeting was held on April 2, 2009 at which committee voted 6-yes and 6-no with one abstention with regard to the question "assuming the remainder of the risk:benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of liraglutide".

The risk benefit profile was also discussed at a regulatory briefing on June 26, 2009. Suggestions were made regarding the usefulness of monitoring serum calcitonin levels or limiting liraglutide to certain treatment settings. Dr. Joffe, Medical Officer in DMEP, in his review states that "routine screening with serum calcitonin will create frequent conundrums for the healthcare provider, lead to unnecessary further workup, and probably unnecessary surgeries (as occurred in the liraglutide development program). For this reason, serum calcitonin should not be routinely recommended for patients treated with liraglutide in clinical practice. Instead, my recommendation is that liraglutide-treated patients undergo a regular neck physical exam (which is standard medical practice) with further workup of detected abnormalities, as needed".

A Type-A meeting was held with the sponsor on June 1, 2009. At this time, DMEP proposed to Novo Nordisk that "if approved, a Medication Guide (MG) and Risk Evaluation and Mitigation Strategy (REMS) to assess the efficacy of the MG will likely be required. The MG should provide information for patients regarding both the MTC risk and the pancreatitis risk". DRISK completed a memo on June 19, 2009 to DMEP concurring with the decision to implement a REMS that included a Medication Guide (MG) and a timetable for submission of assessments. We also stated "should DMEP raise further concerns about risks outlined above or identify additional risks associated with Victoza warranting more extensive risk mitigation, including a communication plan and/or Elements to Assure Safe Use, please send a consult to OSE Division of Risk Management".

Novo Nordisk submitted a proposed REMS consisting only of a MG element on July 8, 2009. OSE was consulted on August 28, 2009 to review MG-only REMS. The DRISK REMS review was submitted September 8, 2009 with an amendment memo October 8, 2009 following a meeting with DMEP and DEPI to clarify REMS goals and assessments and delineate the REMS assessment plan from postmarketing requirements. The MG review was completed November 17, 2009.

While DRISK was not consulted regarding the need for or content of a REMS with a communication plan, a REMS Notification Letter requesting a revision to the proposed REMS was sent to the sponsor December 21, 2009. A REMS Amendment containing a proposed REMS

with a MG, communication plan, and REMS Supporting Document was submitted to the Agency December 22, 2009.

We reviewed the sponsor's REMS submission based on the REMS Notification letter.

## **2 MATERIAL REVIEWED**

- Novo Nordisk, Inc. Revised REMS (including proposed REMS, Communication Plan materials and REMS Supporting Document), dated January 12, January 20, and January 21, 2010 (response to comments in OSE Interim Reviews #1 and #2 of January 12 and January 15, 2010, respectively).
- Novo Nordisk, Inc. Proposed Prescribing Information (PI) for Victoza® (liraglutide [rDNA origin] injection), revised 1/2010.
- Novo Nordisk, Inc. Proposed REMS Amendment (including proposed REMS and REMS Supporting Document), NDA 22-341 Victoza®, dated December 22, 2009.
- FDA REMS Notification Letter to Novo Nordisk, dated December 21, 2009.
- Mills, Sharon, BSN, RN, CCRP. DRISK Review of Patient Labeling (Medication Guide and Instructions for Use), NDA 22-341 (Victoza®), dated November 17, 2009.
- Diaz, Jessica, RN, BSN, DRISK Medication Guide REMS review and amendment memo, dated September 8 and October 8, 2009 respectively.
- Novo Nordisk Cover Letter re: NDA Amendment- Proposed REMS and Medication Guide submission, dated July 8, 2009.
- Division Director's Memo, NDA 21-919 (Byetta®), Mary Parks, M.D., DMEP, dated June 18, 2009; signed November 1, 2009.
- FDA Approval Letter to Amylin Pharmaceuticals, NDA 021919 Byetta® (exenatide) Injection, dated October 30, 2009.
- Amylin Pharmaceuticals approved REMS and REMS Supporting Document for Byetta®, dated October 30, 2009.
- Cross-Discipline Team Leader Review, NDA 22-341 (Victoza®), Hylton Joffe, M.D., M.M.Sc. Signed October 15, 2009.
- Worthy, K, Pharm.D. DRISK Victoza REMS Memo, dated June 19, 2009.

## **3 RESULTS OF REVIEW**

### **3.1 PROPOSED REMS**

#### **3.1.1 GOAL**

The goal of the REMS for Victoza (liraglutide [rDNA origin] injection) is:

- To inform providers about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Victoza.
- To inform patients about the serious risks associated with Victoza.

Each element is described below and the final formatted REMS is presented in Appendix A.

#### **3.1.2 REMS ELEMENTS**

The REMS includes a MG, communication plan, and a timetable for assessment with the information needed for assessment. Each element is described below.

### **3.1.2.1 MEDICATION GUIDE**

A MG will be dispensed with each Victoza prescription in accordance with 21 CFR 208.24. Victoza is dispensed in cartons containing either two or three pre-filled disposable pens with cartridges that can deliver doses of 0.6 mg, 1.2 mg, or 1.8 mg. A copy of the MG will be packaged with each carton. Additional copies of the MG will be available via the product website ([www.victoza.com](http://www.victoza.com)), by request through the sponsor's toll-free information number, (1-877-484-2869), and through the sponsor's sales representatives and Medical Science Liaisons (MSLs).

The review of the proposed MG was completed November 17, 2009.

### **3.1.2.2 COMMUNICATION PLAN**

Novo Nordisk will implement a communication plan that includes a Dear Healthcare Professional Letter, Highlighted Information for Prescribers, and a Direct Mail Letter for healthcare providers likely to prescribe Victoza in the specialties of Internal Medicine, Family Practice, and all practitioners in the Endocrinology specialty. The communication plan will convey the potential risk of medullary thyroid tumors and the risk of acute pancreatitis (including necrotizing pancreatitis).

These healthcare providers will be identified through sources including the company call plan physician list, IMS data, the American Medical Association, and the American Association of Clinical Endocrinologists (AACE) to update Endocrinologist lists.

#### ***3.1.2.2.1 DEAR HEALTHCARE PROFESSIONAL LETTER***

Novo Nordisk will disseminate a Dear Healthcare Professional (DHCP) Letter within 60 days of the product being available in pharmacies. The target audience for the DHCP Letter includes those specialties listed above and also any newly identified prescribers of Victoza through 3 years of product approval.

The DHCP Letter is presented in Appendix B.

#### ***3.1.2.2.2 DIRECT MAIL LETTER***

A Direct Mail Letter containing the information included in the DHCP Letter will also be mailed once a year post launch for a total of 3 years to all prescribers who are likely to prescribe Victoza.

The Direct Mail Letter is presented in Appendix C.

#### ***3.1.2.2.3 HIGHLIGHTED INFORMATION FOR PRESCRIBERS***

The Highlighted Information for Prescribers will be distributed by Novo Nordisk representatives during the first discussion of Victoza with all Healthcare Professionals visited during the first 6 months after product launch. The Highlighted Information for Prescribers will also accompany the Direct Mail Letter.

The Highlighted Information for Prescribers is presented in Appendix D.

These materials will also be available via a REMS-specific linkage from the Victoza website. The Victoza REMS landing page screenshot is presented in Appendix E.

The Medication Guide, the Highlighted Information for Prescribers, and professional labeling will also be available via hardcopy from Novo Nordisk sales specialists, through Novo Nordisk's Call Center.

All components of the communication plan will be updated to reflect any changes in labeling for the risks outlined in the REMS.

### **3.1.2.3 ELEMENTS TO ASSURE SAFE USE**

The REMS does not include any Elements to Assure Safe Use.

### **3.1.2.4 IMPLEMENTATION SYSTEM**

An implementation system is not a required component of the proposed REMS if there are no elements to assure safe use.

## **3.2 ASSESSMENT OF THE REMS**

Novo Nordisk will submit REMS Assessments to FDA at 1 year, 2 years, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novo Nordisk will submit each assessment so that it will be received by the FDA on or before the due date.

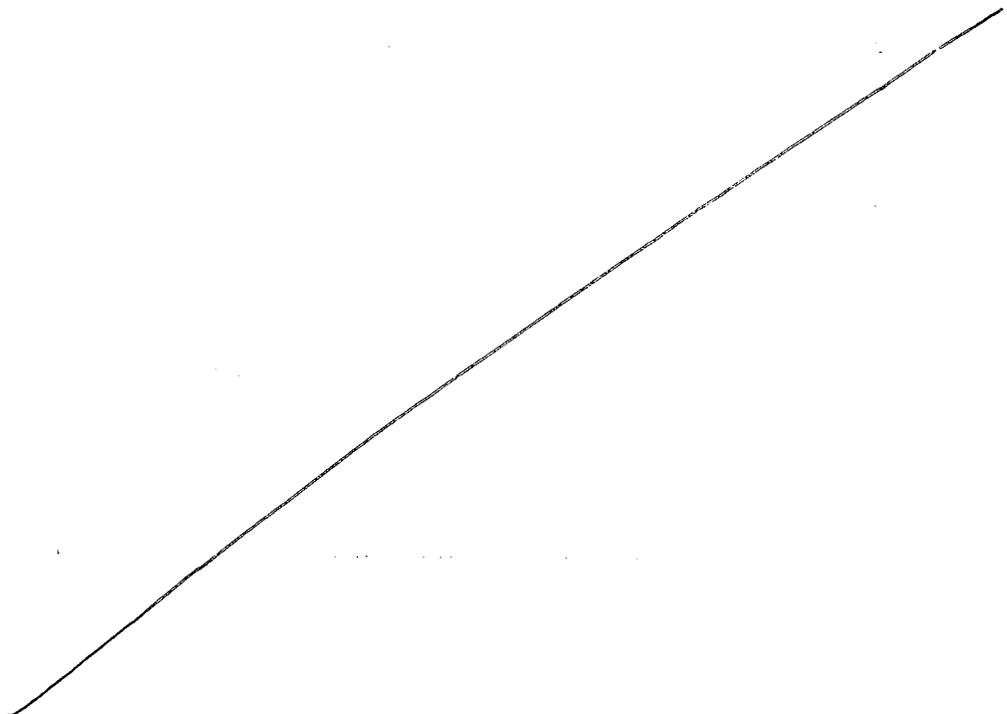
## **3.3 INFORMATION NEEDED FOR ASSESSMENT OF THE REMS**

Information needed for assessment is not a required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS supporting documents.

The REMS Information Notification letter specified that the following information will be needed for assessment of the REMS:

- 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.



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#### **4 DISCUSSION**

The sponsor's proposed REMS addresses the requirements stipulated by FDA in the REMS Notification Letter issued on December 21, 2009.

We note a registry to collect information on the risk of medullary thyroid carcinoma in humans will be a post-marketing requirement. The current REMS materials include a brief statement alerting prescribers that a registry will be established. The sponsor has agreed to send an additional voluntary communication (DHCP Letter) with information about the registry once the details of the registry are finalized.

We acknowledge that numerous factors must be considered when determining the risk management approach for a particular drug product. As part of the DRISK's risk evaluation process, we assess the risk approach from various aspects including consistency - by looking at the risk across various therapeutic areas and within the drug's own drug class. We noted that the REMS for Byetta (exenatide) to address the risks of pancreatitis and renal failure was approved on October 30, 2009 with a Medication Guide and Communication Plan consisting of a single dear healthcare provider letter. We note that the risk management approach for Victoza was generally similar but more involved for a risk both drugs share. \_\_\_\_\_

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## 5 CONCLUSION AND RECOMMENDATIONS

The Division of Risk Management and the OSE Victoza Review Team find the proposed REMS for Victoza, including the REMS document (Appendix A), the DHCP Letter (Appendix B), and Direct Mail Letter (Appendix C), the Highlighted Information for Prescribers (Appendix D), and the Victoza web landing page screenshot (Appendix E) acceptable.

We also note that DMEP has followed DRISK's recommendation to incorporate the information needed for assessment of the REMS into the approval letter.

OSE recommends approval of the Victoza REMS as submitted on January 21, 2010.

## **APPENDIX A: VICTOZA REMS**

### **NDA 22-341 VICTOZA (liraglutide [rDNA origin] injection)**

Novo Nordisk Inc.

100 College Road West, Princeton, NJ 08540

Contact: Mary Ann McElligott, PhD Phone: 609-987-5831

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL**

- To inform providers about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Victoza<sup>®</sup>.
- To inform patients about the serious risks associated with Victoza<sup>®</sup>.

#### **II. REMS ELEMENTS**

##### **A. Medication Guide**

A Medication Guide will be dispensed with each VICTOZA prescription. VICTOZA is dispensed in cartons containing either two or three pre-filled disposable pens with cartridges that can deliver doses of 0.6 mg, 1.2 mg, or 1.8 mg. A copy of the Medication Guide will be packaged in each carton. Therefore, Novo Nordisk will meet the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

Additional copies of the Medication Guide will be available via the product website ([www.victoza.com](http://www.victoza.com)), by request through the Sponsor's toll-free information number (1-877-484-2869), and through the sponsor's sales representatives and Medical Science Liaisons (MSLs).

Please see the appended Medication Guide.

**B. Communication Plan**

In accordance with FDCA 505-1(e)(3), Novo Nordisk will implement the following elements of a communication plan to healthcare providers (HCP) likely to prescribe VICTOZA:

**i. A Dear HCP (DHCP) Letter** addressing the potential risk of medullary thyroid tumors and the risk of acute pancreatitis and appropriate patient selection will be mailed to HCP. The timing of the mailing will be within 60 days after product approval. The DHCP Letter will contain the FDA-approved labeling. The intended audience for this DHCP letter will be healthcare professionals who are likely to prescribe VICTOZA and all endocrinology specialists and others identified through professional organizations (e.g. AMA, AACE). These include physicians, nurse practitioners, and physicians' assistants, predominantly in the specialties of Endocrinology, Internal Medicine, and Family Practice. Any newly identified (through 3 years after product approval) prescribers of Victoza will be fully detailed on the contents of the Communication Plan.

Please see the appended Dear Healthcare Professional Letter.

**ii. A Direct Mail Letter** containing the information included in the DHCP letter will also be mailed once per year post launch for a total of 3 years to all prescribers who are likely to prescribe VICTOZA.

Please see the appended Direct Mail Letter.

**iii. The Highlighted Information for Prescribers** will be distributed by Novo Nordisk representatives during the first discussion of VICTOZA with all HCPs visited during the first six months after product launch. The Highlighted Information for Prescribers will also be sent with the Direct Mail Letter.

Please see the appended Highlighted Information for Prescribers.

Novo Nordisk will make the REMS, the DHCP letter, the Medication Guide, the Highlighted Information for Prescribers, and professional labeling available via a REMS-specific linkage from the VICTOZA website. The Medication Guide, the Highlighted

Information for Prescribers and professional labeling will also be available via hardcopy from Novo Nordisk representatives and through Novo Nordisk's Call Center.

Please see the appended Victoza REMS landing page screenshot.

**C. Elements to Assure Safe Use**

The REMS for VICTOZA can be approved without Elements to Assure Safe Use.

**D. Implementation System**

Because the REMS for VICTOZA can be approved without Elements to Assure Safe Use, an implementation system is not required.

**E. Timetable for Submission of Assessments**

Novo Nordisk will submit REMS Assessments to FDA at 1 year, 2 years, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novo Nordisk will submit each assessment so that it will be received by the FDA on or before the due date.

## APPENDIX B: DEAR HEALTHCARE PROFESSIONAL LETTER

### IMPORTANT DRUG WARNING

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information about Victoza. The Food and Drug Administration (FDA) has approved VICTOZA (liraglutide [rDNA origin] injection), a once daily human GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus. VICTOZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of VICTOZA outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis. Novo Nordisk has established an informational program for healthcare professionals to help minimize these risks.

There is a Boxed Warning for VICTOZA:

#### **WARNING: RISK OF THYROID C-CELL TUMORS**

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 Victoza 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. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

#### **Potential Risk of Medullary Thyroid Carcinoma**

- 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 VICTOZA, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

#### **Risk of Acute Pancreatitis**

- In clinical trials studying VICTOZA, there were more cases of pancreatitis with VICTOZA than with comparators.
- After initiation of VICTOZA, 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, VICTOZA and other potentially suspect drugs should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated.
- If pancreatitis is confirmed, VICTOZA should not be restarted.
- Use with caution in patients with a history of pancreatitis.

#### **Appropriate Patient Selection**

- VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- VICTOZA is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- VICTOZA has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis.
- VICTOZA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- VICTOZA has not been studied in combination with insulin.

#### **Adverse Events**

Healthcare professionals should report any serious adverse events thought to be associated with VICTOZA use to:

- Novo Nordisk at 1-877-4-VICTOZA (1-877-484-2869)
- FDA's MedWatch reporting system:
  - By phone at 1-800-FDA-1088 (1-800-332-1088)
  - by facsimile at 1-800-FDA-0178 (1-800-332-0178)
  - by mail using FDA Form 3500
  - online (<http://www.fda.gov/medwatch/index.html>)

Sincerely,

Alan C. Moses, M.D.

Global Chief Medical Officer, Novo Nordisk  
Enclosure: VICTOZA Full Prescribing Information

**This letter has been reviewed and approved by the FDA as part of the Victoza REMS.**

## **APPENDIX C: DIRECT MAIL LETTER**

Dear Healthcare Professional:

VICTOZA (liraglutide [rDNA origin] injection) is a once daily human GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus. VICTOZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2).

Novo Nordisk would like to highlight the following information on appropriate patient selection:

- VICTOZA is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- VICTOZA has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using VICTOZA. Use with caution in patients with a history of pancreatitis.
- VICTOZA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- VICTOZA has not been studied in combination with insulin.

Novo Nordisk wishes to remind you of important information concerning VICTOZA related to:

- potential risk of medullary thyroid carcinoma
- risk of acute pancreatitis

Please take time to read the attached document. Please refer to the Full Prescribing Information for further product information.

We invite you to contact our Novo Nordisk Customer Care Center at 1-877-4-VICTOZA (1-877-484-2869) if you have any questions about the information contained in this letter or in the attached overview.

Sincerely,

Alan C. Moses, M.D., Global Chief Medical Officer, Novo Nordisk

Enclosures: VICTOZA Full Prescribing Information, "Potential Risk of Medullary Thyroid Carcinoma and Risk of Pancreatitis" document

**This letter has been reviewed and approved by the FDA as part of the Victoza REMS.**

## **APPENDIX D: HIGHLIGHTED INFORMATION FOR PRESCRIBERS**

### **VICTOZA (liraglutide [rDNA origin] injection)**

#### **Highlighted Information for Prescribers**

This information is being provided to prescribers of VICTOZA as part of the Risk Evaluation and Mitigation Strategy (REMS) plan for VICTOZA. REMS plans have been required by the U.S. Food and Drug Administration (FDA) since 2008 for certain drugs with serious risks to ensure that the benefits of the drug outweigh the risks of the drug.

The purpose of this information is to inform prescribers of VICTOZA about the following:

- potential risk of medullary thyroid carcinoma (MTC)
- risk of acute pancreatitis

#### **INDICATIONS AND USAGE**

VICTOZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

#### **APPOPRIATE PATIENT SELECTION**

- VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- VICTOZA is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- VICTOZA has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza. Use with caution in patients with a history of pancreatitis
- VICTOZA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- VICTOZA has not been studied in combination with insulin.

#### **POTENTIAL RISK OF MEDULLARY THYROID CARCINOMA**

There is a Boxed Warning for VICTOZA:

#### **WARNING: RISK OF THYROID C-CELL TUMORS**

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 Victoza 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. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2). Based on the finding in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

- 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 Victoza, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

**RISK OF ACUTE PANCREATITIS**

VICTOZA labeling contains a warning describing the risk of acute pancreatitis:

- There are no conclusive data establishing a risk of pancreatitis with VICTOZA treatment.
- After initiation of VICTOZA, 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, VICTOZA and other potentially suspect drugs should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated.
- If pancreatitis is confirmed, VICTOZA should not be restarted.
- Use with caution in patients with a history of pancreatitis.

*Refer to the Full Prescribing Information for further product information.*

If you have any questions about these materials, please call the Novo Nordisk Customer Care Center at 1-877-484-2869.

**This brochure has been reviewed and approved by the FDA as part of the Victoza REMS.**

## APPENDIX E: WEB LANDING PAGE SCREENSHOT

Medication Guide

### REMS Program

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

In order for Novo Nordisk to communicate certain risks to ensure that Victoza® is prescribed and taken safely, Novo Nordisk has worked with the FDA to develop materials to communicate the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma. The REMS program is designed to inform health care providers and patients about the potential risks with Victoza®. To learn more about serious risks, read the important safety information provided in the links below, including the Medication Guide, and discuss it with your patients.

The goals of the Victoza® REMS are:

- To inform providers about the risk of including acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Victoza®.
- To inform patients about the serious risks associated with Victoza®.

To learn more download these important documents:

- [Full Prescribing Information](#)
- [Patient Medication Guide](#)
- [Full Medication Guide](#)
- [Informational Video](#)
- [Medication Guide](#)

### Indications and Usage:

Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Victoza® should not be used to treat type 1 diabetes mellitus or diabetic ketoacidosis. It has not been studied in combination with insulin. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. It has not been studied sufficiently in patients with a history of pancreatitis.

### Important Safety Information:

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 Victoza® 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. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

In clinical trials, there were more cases of pancreatitis among Victoza®-treated patients than among comparator-treated patients. If pancreatitis is suspected, Victoza® should be discontinued. Victoza® should not be re-initiated if pancreatitis is confirmed. Use with caution in patients with a history of pancreatitis.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia. There have been no studies establishing conclusive evidence of myocardial infarction risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions reported in patients treated with Victoza® are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including anaphylaxis, were more common among Victoza®-treated patients than among comparator-treated patients in clinical trials.

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not indicated for use in pediatric patients.

Victoza® should be used with caution in patients with renal impairment and in patients with hepatic impairment.

Please see [CONTRAINDICATIONS AND IMPORTANT WARNINGS](#).

Victoza® is available by prescription.

Novo Nordisk provides patient assistance for those who qualify. Please call 866-310-7549 to learn more about Novo Nordisk assistance programs.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](#), or call 1-800-FDA-1088.



Usage: 0.9 mg Liraglutide Subcutaneous Injection  
Victoza® is a registered trademark of Novo Nordisk A/S.  
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
JDA-22341	GI-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

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KENDRA C WORTHY  
01/24/2010

CLAUDIA B KARWOSKI  
01/25/2010  
concur

## REMS Interim Review Comments

1/15/10

<b>Drug Name:</b> Victoza® (Liraglutide [rDNA origin]) Injection	<b>BLA/NDA:</b> NDA 022341	<b>Date:</b> January 15, 2010 <b>Comment Set # 2</b>
<b>DRISK Scientific Lead:</b>  LCDR Kendra Worthy, Pharm.D., Risk Management Analyst		<b>Reviewers:</b>  <ul style="list-style-type: none"> <li>• Kate Heinrich, MA, Health Education Reviewer (DRISK)</li> <li>• Suzanne Berkman Robottom, Pharm.D., Risk Management Analyst Team Leader (DRISK)</li> </ul>
<b>RCM #:</b> 2009-1325		

**Materials Reviewed:**

- Novo Nordisk, Inc. Revised REMS (including proposed REMS, Communication Plan materials and REMS Supporting Document), dated January 12, 2010.
- Novo Nordisk, Inc. Proposed REMS Amendment (including proposed REMS and REMS Supporting Document), NDA 22-341 Victoza®, dated December 22, 2009.
- Novo Nordisk, Inc. Proposed Prescribing Information (PI) for Victoza® (liraglutide [rDNA origin] injection), revised 1/2010.

**Introduction:**

The comments below are DRISK's review of the revised REMS, REMS Supporting Document, and appended Communication Plan materials (DHCP Letter, Direct Mail Letter, and Highlighted Information for Prescribers) included in the proposed REMS for Victoza® (Liraglutide [rDNA origin]) Injection submitted on January 12, 2010. Please request that the sponsor respond to these comments as soon as possible for final approval.

Attached to this review (in Appendices A-D) includes an edited (with track changes) proposed REMS, DHCP Letter, Direct Mail Letter, and Highlighted Information for Prescribers.

**Comments to DMEP:**

- We acknowledge your previous comments in response to our comments dated January 8, 2010. Please let us know if you have any questions regarding the comments included in this document.
- Please review the DHCP Letter, Direct Mail Letter, and Highlighted Information for Prescribers and make any revisions necessary to ensure it is consistent with the most up-to-date label. If there is additional information that should be included in these communications, please let us know (e.g., "there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients (2.2 vs 0.6 cases per 1000 patient years," other information to give further context to the risks).
- We note the inclusion of the word "potential" when referring to the risk of medullary thyroid tumors in the Communication Plan materials. Generally, we would recommend deleting this word, as it can be redundant and/or minimize the risk. Hence, we deleted the word "potential"

throughout the CP materials. However, we note the risk was referred to as a "potential risk" in the REMS Notification Letter on page 2 but not on page 1. Please advise.

- Novo Nordisk proposes to include information about a registry for medullary thyroid carcinoma in some of the CP materials. We assume this will be a PMR. However, if the registry will not be established at the time the CP materials are disseminated, we are not sure how helpful it will be to include as a way to promote the registry without more details or instructions. Please advise.

**Comments to the Sponsor:**

Please find attached an edited (with track changes) proposed REMS, DHCP Letter, Direct Mail Letter, and Highlighted Information for Prescribers. These edits have incorporated the comments you received January 11 pertaining to these materials as well as your revised REMS we received January 12, 2010.

If you concur with the edits and have no further revisions, accept all changes in these materials and resubmit the proposed REMS and REMS Supporting Document for final review and approval. Please state in the cover letter that the complete REMS submission is identical to the version included in this communication with any exceptions noted. Submit track changes as well as a clean Word copy.

**REMS Goals**

1. Please revise the patient-directed goal to state, "to inform patients about the risks associated with Victoza." We acknowledge our editing error.

**REMS Website**

1. Remove the Victoza product homepage from the REMS document. Include only the REMS landing page as part (and appended to) the REMS.
2. Remove the RESOLVE logo from the webpage and all REMS materials, as it is promotional and not part of the REMS educational materials.
3. We cannot review or comment on the entire webpage presentation because the Indications and Usage and Important Safety Information sections include placeholder text. Revise and resubmit the landing page.

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  √   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

Application  
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Submission  
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Submitter Name

Product Name

NDA-22341

GI-1

NOVO NORDISK  
INC

VICTOZA (LIRAGLUTIDE)

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/s/

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KENDRA C WORTHY  
01/15/2010

1/12/10

**REMS Interim Review Comments**

<b>Drug Name:</b> Victoza® (Liraglutide [rDNA origin]) Injection	<b>BLA/NDA:</b>  NDA 022341	<b>Date:</b> January 8, 2010
		<b>Comment Set # 1</b>
<b>DRISK Scientific Lead:</b>  LCDR Kendra Worthy, Pharm.D., Risk Management Analyst		<b>Reviewers:</b>  <ul style="list-style-type: none"> <li>• Kate Heinrich, MA, Health Education Reviewer (DRISK)</li> <li>• Suzanne Berkman Robottom, Pharm.D., Risk Management Analyst Team Leader (DRISK)</li> </ul>
<b>RCM #:</b> 2009-1325		

**Materials Reviewed:**

- Cross-Discipline Team Leader Review, NDA 22-341 (Victoza®), Hylton Joffe, M.D., M.M.Sc. Signed October 15, 2009.
- Amylin Pharmaceuticals approved REMS and REMS Supporting Document for Byetta®, dated October 30, 2009.
- FDA REMS Notification Letter to Novo Nordisk, signed December 21, 2009.
- Novo Nordisk, Inc. Proposed REMS Amendment (including proposed REMS and REMS Supporting Document), NDA 22-341 Victoza®, dated December 22, 2009.
- Novo Nordisk, Inc. Proposed REMS webpage screenshot, emailed January 7, 2010.
- Novo Nordisk, Inc. Proposed Prescribing Information (PI) for Victoza® (liraglutide [rDNA origin] injection), revised 1/2010.

**Introduction:**

The comments below are DRISK's preliminary review of the proposed REMS for Victoza® (Liraglutide [rDNA origin]) Injection.

Please request that the sponsor respond to these comments as soon as possible to facilitate further review.

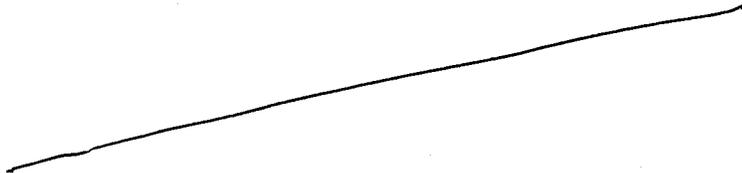
Attached to this review (in Appendix A) includes an edited (with track changes) Proposed REMS. We have included some high level comments on the DHCP Letter, Direct Mail Letter, and Highlighted Information for Prescribers and will provide track changes of these documents under separate cover after the sponsor has submitted the revised pieces.

**Comments to DMEP:**

1. These comments reflect the most current thinking in order to be efficient, anticipate and avoid known problems, and attempt consistency across REMS in various therapeutic areas, when applicable. The Victoza REMS should be revised to align with the current practices. For example, we recommend revising the goals of the REMS and stratify them by audience (professional vs. patient). We recommend the patient-related goal to be general, "to inform patients of the serious risks associated with Victoza." This approach allows for revisions to the Medication Guide and avoids the need to revise the patient-directed REMS goal each time new safety information is added to the Medication Guide.

If there are questions, concerns, or disagreement with our recommendations, please provide the opportunity for discussion.

2. Because we were not involved in developing the REMS with a Communication Plan for this REMS, please advise:
  - i. The REMS Notification Letter states that the CP must provide for dissemination of information about the risk of acute pancreatitis, including necrotizing pancreatitis, however we note "necrotizing pancreatitis" is not included in the labeling provided. Please advise, as the REMS should be consistent with labeling. If necessary, add a comment to the sponsor to address this.
  - ii.



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3. Consider requesting expedited reporting of the serious adverse events outlined in the REMS in the Action Letter.
4. We remind you to include the Information Needed for Assessment as outlined in the REMS Notification Letter in the Victoza Action Letter. We note that standard language for assessing distribution of the Medication Guide was not included the Notification Letter. This may have been removed as Victoza is considered unit of use. If this is not the case, the following should be included in the Action Letter and the sponsor should be alerted that these assessments are required and included in the REMS Supporting Document.
  - i. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
  - ii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

**Comments to the Sponsor:**

**REMS**

**1. REMS Goals:**

Revise REMS goal as follows:

- To inform providers about the risk of including acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Victoza®.
- To educate patients about the serious risks associated with Victoza®.

**2. Communication Plan:**

Revise the Communication Plan as follows. All revisions should be made to the REMS and the REMS Supporting Document.

- A. A definite time period, including initiation date and end date, is needed in the communication plan for all communication activities. Currently you propose the DHCP letter to be sent out within 60 days of product launch, with no parameters for a launch date. We recommend sending the letter within a set timeframe, for example, within 60 days of approval of Victoza®.
- B. Broaden the intended audience of the Communication Plan to include all endocrinologists. Provide more detail about how the intended audience will be derived (which databases, numbers of healthcare professionals by specialty, etc...) for the healthcare professionals that are likely to prescribe Victoza® as well as all endocrinologists.
- C. Any new prescribers of Victoza should also be targeted in the communication plan. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 3 years after product launch. These details should be included in the REMS and the REMS Supporting Document.
- D. The follow-up Direct Mailer and Highlighted Information should be updated if labeling changes for the risks outlined in the REMS are approved. Include this information in the Supporting Document.
- E. DHCP Letter
  - a. The language of the DHCP Letter should reflect language in the Prescribing Information (PI), including the Boxed Warning. The letter should also delineate appropriate patient selection as required in the REMS Notification Letter you received on December 21, 2009.

- b. The DCHP Letter fails to address appropriate patient selection as requested in the REMS notification letter.
- F. Direct Mail Letter
- a. The Direct Mail Letter fails to include information on appropriate patient selection but includes part of the indication. The Direct Mail Letter should include the limitations to use (under indications, contraindications, etc... in labeling) in conjunction with the indication for use. This information should be presented in bulleted format.
  - b. Please submit the revised Direct Mail Letter.
- G. Highlighted Information for Prescribers
- a. You have proposed that Novo Nordisk representatives will distribute the Highlighted Information for Prescribers during the first discussion of Victoza<sup>®</sup> with all HCPs visited during the first six months after product launch. This brochure minimizes the risks of the drug by not including the Prescribing Information (PI), including the Boxed Warning, to fully explain the risks outlined in the REMS. Revise the Highlighted Information for Prescribers so that the content reflects the DHCP letter and the PI.
  - b. The Highlighted Information fails to include information on appropriate patient selection but includes part of the indication. The Highlighted Information should include the limitations of use (under indications, contraindications, etc... in labeling) in conjunction with the indication for use. This information should be presented in bulleted format.
  - c. Please submit the revised Highlighted Information for Prescribers.
- H. REMS Website
- a. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a direct link off the main website that includes REMS-specific materials. This link will direct users to a separate website that describes the REMS program and lists only approved REMS materials. The website should not be a means to promote Victoza or any other Sponsor product. Only this separate website or link will be considered a component of the Communication Plan.
  - b. Regarding the website, we recommend a link off of the Victoza<sup>®</sup> homepage to a REMS landing page. For example, the link could state: "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."

The landing page of the separate REMS link should then contain background information on the REMS, safety information, and the REMS communication materials. We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

In order for Novo Nordisk to communicate certain risks to ensure that Victoza<sup>®</sup> is prescribed and taken safely, Novo Nordisk has worked with the FDA to develop materials to communicate the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma. The REMS program is designed to inform health care providers and patients about the potential risks with Victoza<sup>®</sup>. To learn more about serious risks, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.

The goals of the Victoza<sup>®</sup> REMS are:

- To inform providers about the risk of including acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Victoza<sup>®</sup>.
- To educate patients about the serious risks associated with Victoza<sup>®</sup>.

c. Please submit the revised web screenshot(s).

### 3. Timetable for Assessment of the REMS:

A. Proposed Timetable: We recommend the following language, which is from the draft guidance, *"Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"*.

Novo Nordisk will submit REMS Assessments to FDA at 1 year, 2 years, 3 years, and 7 years from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novo Nordisk will submit each assessment so that it will be received by the FDA on or before the due date.

*[Note to sponsor: Delete the table]*

**REMS Supporting Document**

1. Revise the Supporting Document to be consistent with the REMS.
2. **Information Needed For Assessment (REMS Assessment Plan):**
  - A. Add the following to the Information Needed for Assessment (REMS Assessment Plan) section of the Supporting Document as outlined in the REMS Notification Letter you received on December 21, 2009:
    - a. An assessment of healthcare providers' awareness of:
      - i. Appropriate patient population characteristics, and
      - ii. the potential risk for medullary thyroid carcinoma
      - iii. the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.
    - b. Evaluation of healthcare providers' identification and treatment of:
      - i. medullary thyroid carcinoma after initiation of Victoza®
      - ii. acute pancreatitis after initiation of Victoza®
    - c. An assessment of the number of Victoza® prescribers identified to receive the Dear Healthcare Provider Letter and the number of DHCP letters mailed.
    - d. An assessment of the percentage of targeted physicians who are presented with the Highlighted Information for Prescribers via Sales Specialists or medical information department.

**General Comments**

1. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.
2. Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

3.



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  √   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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Submitter Name

Product Name

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JDA-22341

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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KENDRA C WORTHY  
01/12/2010

**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

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**NDA/BLA #s:** 22341  
**Products:** VICTOZA® (liraglutide) injection, 1.2 and 1.8 mg  
**SPONSOR:** Novo Nordisk, Inc.  
**FROM:** Curtis Rosebraugh, M.D., M.P.H.  
**DATE:** 19 December 2009

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a 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).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for VICTOZA (liraglutide) to ensure that the benefits of the drug outweigh the potential serious risk of medullary thyroid carcinoma identified in non-clinical studies and a signal of a serious risk of acute pancreatitis, including necrotizing pancreatitis, identified in the clinical trial data and in post-marketing reports for the only other approved glucagon-like peptide (GLP)-1 receptor agonist. In reaching this determination, we considered the following:

- A. Approximately 24 million people in the United States have type 2 diabetes of whom more than one-third will require more than one anti-diabetic agent to maintain adequate glycemic control within several years of initiation of drug therapy. In 2008, approximately ~~10~~ 10 patients filled a prescription for the only other approved GLP-1 receptor agonist. b(4)
- B. Patients with type 2 diabetes who require anti-diabetic medication for glycemic control are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated.

- C. VICTOZA (liraglutide) has been shown to achieve a mean placebo-adjusted reduction in hemoglobin A1c over 26 weeks of approximately 0.9-1.4%. Some of the complications listed above can be prevented or delayed with good glycemic control. VICTOZA (liraglutide) is an option for those individuals who are inadequately treated with lifestyle modification and other anti-diabetic therapies.
- 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, including necrotizing pancreatitis, VICTOZA (liraglutide) is associated with the following other adverse effects, including gastrointestinal adverse events such as nausea and diarrhea, serious hypoglycemia when used with an insulin secretagogue (e.g., a sulfonylurea), anti-liraglutide antibody formation, and immunogenicity-related events such as urticaria.
- F. VICTOZA (liraglutide) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for VICTOZA (liraglutide). FDA has determined that VICTOZA (liraglutide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of VICTOZA (liraglutide). FDA has determined that VICTOZA (liraglutide) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use VICTOZA (liraglutide).

The elements of the REMS will be a Medication Guide, a Communication Plan, and a timetable for submission of assessments of the REMS.

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AMY G EGAN  
12/22/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 13, 2010

To: Mary Parks, MD, Director  
**Division of Metabolism and Endocrinology Products**

Through: Claudia Karwoski, Pharm D, Director  
**Division of Risk Management (DRISK)**

From: LaShawn Griffiths, MSHS-PH, BSN, RN  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**  
Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

Subject: DRISK Review #2 of Patient Labeling (Medication Guide)

Drug Name(s): Victoza (liraglutide [rDNA origin]) Injection

Application Type/Number: NDA 22-341

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2008-929

## **1 INTRODUCTION**

This review is written in follow-up to the proposed "final" labeling for Victoza (liraglutide [rDNA origin]) Injection Prescribing Information (PI) submitted on December 21, 2009 and Medication Guide (MG) submitted by Novo Nordisk on December 10, 2009. Please refer to DRISK's original review of the patient labeling (MG and Instructions for Use (IFU)) for Victoza (liraglutide [rDNA origin]) Injection completed on November 17, 2009. Follow-up comments regarding the Instructions for Use were provided to DMEP by email on December 17, 2009 and January 8, 2010.

Please let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2 MATERIAL REVIEWED**

- Draft Victoza (liraglutide [rDNA origin]) Injection Prescribing Information (PI) submitted December 21, 2009
- Draft Victoza (liraglutide [rDNA origin]) Injection Medication Guide (MG) submitted on December 10, 2009

## **3 RESULTS OF REVIEW**

In our follow-up review of the MG, we have:

- made minimal changes to simplify wording and clarify concepts where possible
- ensured that the MG is consistent with the PI
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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       Draft Labeling (b5)

       Deliberative Process (b5)

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

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SHARON R MILLS  
01/13/2010

CLAUDIA B KARWOSKI  
01/13/2010  
concur

11/17/09



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: November 17, 2009

To: Mary Parks, MD, Director  
**Division of Metabolism and Endocrinology Products**

Through: Mary Willy, PhD., Deputy Director  
**Division of Risk Management**  
LaShawn Griffiths, MSHS-PH, BSN, RN  
**Patient Labeling Reviewer, Acting Team Leader**

From: Sharon R. Mills, BSN, RN, CCRP  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)

Drug Name(s): Victoza (liraglutide [rDNA origin]) injection

Application Type/Number: NDA 22-341

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2009-1325

## **1 INTRODUCTION**

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and IFU for Victoza (liraglutide [rDNA origin]) injection. Please let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. DRISK's review of the proposed REMS was sent to DMEP under separate cover dated October 8, 2009.

## **2 MATERIAL REVIEWED**

- Draft VICTOZA (liraglutide [rDNA origin]) injection Prescribing Information (PI) submitted May 23, 2008 and revised by the Review Division throughout the current review cycle; the most recent version provided to DRISK on November 3, 2009.
- Draft VICTOZA (liraglutide [rDNA origin] injection) Medication Guide (MG) submitted on July 8, 2009 and revised by the review division throughout the review cycle; the most recent version provided to DRISK on September 28, 2009.
- Draft Victoza (liraglutide [rDNA origin] injection) Patient Instructions for Use (IFU) submitted on May 23, 2008 and revised throughout the review division; most recent version submitted on September 30, 2009.

## **3 RESULTS OF REVIEW**

In our review of the MG and IFU, we have

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- rearranged information due to PLR format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

We recommend that the Applicant revise the Patient Instructions for Use for Victoza using a format similar to that used in the Byetta Pen User Manual to improve patient comprehension. The current format is too fragmented. The use of actual photographs in the Byetta IFU is helpful.

Our annotated MG and IFU are appended to this memo. Any additional revisions to the PI should be reflected in the MG and IFU.

Please let us know if you have any questions.

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       Draft Labeling (b5)

       Deliberative Process (b5)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22341

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ORIG-1

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NOVO NORDISK  
INC

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VICTOZA (LIRAGLUTIDE)

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/s/  
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SHARON R MILLS  
11/17/2009

MARY E WILLY  
11/17/2009  
I concur



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 7, 2009

To: Mary Parks, M.D., Director  
**Division of Metabolic and Endocrine Products (DMEP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management**

From: Jessica M. Diaz, RN, BSN  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: Addendum to VICTOZA REMS Review dated September 4, 2009

Drug Name(s): VICTOZA (liraglutide injection)  
Application Type/Number: NDA 22-341  
Applicant/sponsor: Novo Nordisk

OSE RCM #: 2009-1325

This memorandum serves as an addendum to the VICTOZA (liraglutide) Risk Evaluation and Mitigation Strategy (REMS) review completed September 4, 2009 from the Division of Risk Management (DRISK). In addition, this is a status and agreement update resulting from a meeting held September 23, 2009 between DRISK, Division of Metabolic and Endocrine Products (DMEP), and Division of Epidemiology (DEPI).

Meeting discussion items included questions from DRISK regarding: 1) the goal of the REMS, 2) the timetable for submission of assessments and 3) REMS Assessment Plan submitted as part of the REMS Supporting Document.

The proposed goal for this REMS was: *"The goal of the REMS for VICTOZA is to inform patients of the potential risks associated with the product, including pancreatitis and the theoretical risk of medullary thyroid carcinoma."* Generally, for the Medication Guide only REMS, DRISK with the concurrence of the Reviewing Division keeps the goal broad not specifically naming the risks. During the meeting DRISK, DMEP, and DEPI were in agreement to keep the goal statement general. The new goal statement for this REMS is: *"The goal of this REMS is to inform patients about the serious risks associated with the use of Victoza."*

The proposed REMS Assessment Plan includes \_\_\_\_\_  
\_\_\_\_\_ I3 Database Study (i3 Aperio) and Case Series Registry to evaluate Medullary Thyroid Carcinoma (MTC). During the meeting DRISK, DMEP, and DEPI were in agreement the I3 Database Study and Case Series Registry to evaluate MTC would be reviewed under separate cover by Diane Wysowski in DEPI and would not be part of the REMS Assessment Plan but are rather being considered as postmarketing requirements (PMRs). \_\_\_\_\_

b(4)

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/s/

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JESSICA M DIAZ  
10/07/2009

CLAUDIA B KARWOSKI  
10/08/2009  
concur

9/8/09



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: September 4, 2009

To: Mary Parks, M.D., Director  
**Division of Metabolic and Endocrine Products (DMEP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

From: Jessica M. Diaz, R.N., BSN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): VICTOZA (liraglutide injection)

Application Type/Number: NDA 22-341

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2009-1325

## 1 INTRODUCTION

This memorandum is in response to a request by the Division of Metabolic and Endocrine Products for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for VICTOZA (liraglutide injection). Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. DRISK's review of the Medication Guide will be sent under separate cover.

## 2 MATERIAL REVIEWED

- VICTOZA (liraglutide injection) Risk Evaluation and Mitigation Strategy (REMS) requested July 1, 2009
- Proposed VICTOZA (liraglutide injection) Risk Evaluation and Mitigation Strategy (REMS) and Supporting Document, submitted on July 8, 2009

## 3 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

### Comments to Novo Nordisk:

See the appended VICTOZA (liraglutide injection) REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

#### a. GOAL(S)

Revise your goal as follows:

*The goal of this REMS is to inform patients about the serious risks associated with the use of Victoza, including pancreatitis and the theoretical risk of medullary thyroid carcinoma.*

#### b. We remind you of the requirement to comply with 21 CFR 208.24:

- A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

"Dispense the enclosed Medication Guide to each patient." or

“Dispense the accompanying Medication Guide to each patient.”

- c. You are required to submit REMS Assessments to FDA at \_\_\_\_\_  
\_\_\_\_\_ **b(4)**
- d. Please submit for review a detailed plan to evaluate patients’ understanding about the safe use of VICTOZA (liraglutide injection). Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded “REMS-Other.” If you plan to conduct this assessment using a survey, your submission should include:
- All methodology and instruments that will be used to evaluate the patients’ understanding about the safe use of VICTOZA (liraglutide injection). This should include, but not be limited to:
    - Sample size and confidence associated with that sample size
    - How the sample will be determined (selection criteria)
    - The expected number of patients to be surveyed
    - How the participants will be recruited
    - How and how often the surveys will be administered
    - Explain controls used to minimize bias
    - Explain controls used to compensate for the limitations associated with the methodology
  - The survey instruments (questionnaires and/or moderator’s guide).
  - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please let us know if you have any questions.

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       Deliberative Process (b5)

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JESSICA M DIAZ  
09/04/2009

CLAUDIA B KARWOSKI  
09/08/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 19, 2009

To: Mary Parks, MD, Director  
Division of Metabolism and Endocrinology Products (DMEP)

Through: Claudia Karwoski, Pharm.D., Director (Acting)  
Division of Risk Management (DRISK)

From: Kendra Worthy, Pharm.D., Drug Risk Management Analyst  
(DRISK)  
Mary Dempsey, Risk Management Program Coordinator  
(DRISK)

Subject: Review of Risk Management Plan

Drug Name(s): Victoza® (liraglutide)

Application  
Type/Number: NDA 22-341

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2008-928

## **1 INTRODUCTION**

This memo is in response to the recent Type A meeting held on June 1, 2009 with Novo Nordisk regarding NDA 22-341 for Victoza (liraglutide), an incretin mimetic with the proposed indication to improve glycemic control in patients with Type 2 Diabetes Mellitus as an adjunct to diet and exercise. Novo Nordisk's initial submission in May 2008 contained a proposed Risk Management Plan that included routine pharmacovigilance, labeling, and a patient leaflet to address the risks of medullary thyroid cancer (MTC) and pancreatitis.

## **2 MATERIAL REVIEWED**

- Novo Nordisk's Proposed Risk Management Plan submission received May 23, 2008.
- Novo Nordisk's Type A Information Package submission received May 18, 2009
- May 29, 2009 e-mail communication from John Bishai, Project Manager, Division of Metabolism and Endocrinology Products (DMEP) re: Questions for the upcoming June 1<sup>st</sup> Type A Meeting for Liraglutide.

## **3 DISCUSSION AND CONCLUSION**

In preparation for the meeting, DMEP decided not to address Novo Nordisk's questions presented in their information package and instead created a list of questions to address with the applicant. Regarding risk management, DMEP proposed: "if approved, a Medication Guide (MG) and Risk Evaluation and Mitigation Strategy (REMS) to assess the efficacy of the MG will likely be required. The MG should provide information for patients regarding both the MTC risk and the pancreatitis risk".

At this time, DRISK concurs with implementing a REMS that includes a MG and a timetable for submission of assessments. Should DMEP raise further concerns about risks outlined above or identify additional risks associated with Victoza warranting more extensive risk mitigation, including a communication plan and/or Elements to Assure Safe Use, please send a consult to OSE Division of Risk Management.

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/s/  
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Mary Dempsey  
6/19/2009 01:04:23 PM  
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski  
6/22/2009 09:46:48 AM  
DRUG SAFETY OFFICE REVIEWER