APPENDIX A: REMS

Initial REMS approval: 01/ 2010

Most recent modification: 05/ 2011

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

Novo Nordisk Inc.

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

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

II. REMS ELEMENTS

A. Communication Plan

Novo Nordisk will implement the following elements of a communication plan to healthcare providers (HCP) likely to prescribe VICTOZA® to support implementation of this REMS:

The communication plan will include:

i. ***A Reminder Dear HCP (DHCP) Letter for Primary Care Providers*** addressing the potential risk of medullary thyroid tumors and the risk of acute pancreatitis and appropriate patient selection will be mailed to HCPs. The timing of the mailing will be within 60 days after approval of this REMS modification. The Reminder DHCP Letter will contain the FDA-approved labeling. The intended audience for this Reminder DHCP letter will be primary healthcare providers who are likely to prescribe VICTOZA® and others identified through professional organizations (e.g. AMA). These include physicians, nurse practitioners, and physicians' assistants, predominantly in the specialties of Internal Medicine and Family Practice. Any newly identified (through 3 years after product

approval) primary care prescribers of VICTOZA® will be fully detailed on the contents of the Communication Plan.

In addition, the *Reminder Dear Healthcare Professional Letter for Primary Healthcare Providers* will be distributed by Novo Nordisk representatives during the first discussion of VICTOZA® with all primary care providers visited during the first six months after approval of this REMS modification. The Novo Nordisk representative will discuss the risk message contained in the DHCP letter with the primary care provider visited.

Please see the appended *Reminder Dear Healthcare Professional Letter for Primary Healthcare Providers*.

ii. A *Direct Mail Letter* containing the information included in the DHCP letter will also be mailed once per year, beginning 6 months following dissemination of the Reminder DHCP Letter for Primary Care Providers for a total of 3 years following approval of this REMS modification to all prescribers who are likely to prescribe VICTOZA®.

Please see the appended *Direct Mail Letter.*

In addition, Novo Nordisk will send the DHCP Letter and the Direct Mail Letter to MedWatch at the same time the letters are disseminated to the target audience.

Novo Nordisk will make the REMS, the Direct Mail letter, the Medication Guide, and professional labeling available via a REMS-specific linkage from the VICTOZA® website. The Medication Guide 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.

B. 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 initial REMS. The assessments should be submitted by March 24 of each year. 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: REMINDER DEAR HEALTHCARE PROFESSIONAL LETTER FOR PRIMARY CARE PROVIDERS

IMPORTANT DRUG WARNING REMINDER CONCERNING VICTOZA®

SUBJECT: POTENTIAL RISKS OF THYROID C-CELL TUMORS AND ACUTE PANCREATITIS ASSOCIATED WITH VICTOZA®

Dear Primary Care Provider:

This letter is to remind you of important safety information about VICTOZA® (liraglutide [rDNA origin]) injection. This letter is being sent to you because a recent assessment of healthcare providers' understanding of the serious risks of VICTOZA® showed that some primary care providers are not fully aware of the serious risks associated with the use of VICTOZA®.

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

The Food and Drug Administration (FDA) has required Novo Nordisk to communicate the following risk information to potential prescribers.

You should note the following potential serious risks of VICTOZA®:

- There is potential risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) associated with VICTOZA®
- VICTOZA® may increase the risk of acute pancreatitis

Because of these risks, VICTOZA® is <u>not</u> recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Additional information about these risks is provided in the remainder of this letter.

<u>Potential Risk of Thyroid C-Cell Tumors, including Medullary Thyroid Carcinoma</u>

- 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).
- 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.

<u>Risk of Acute Pancreatitis</u>

- In clinical trials studying VICTOZA®, there were more cases of pancreatitis in patients treated with VICTOZA® than in patients treated 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.

Medullary Thyroid Cancer Registry

To further assess risk, Novo Nordisk will be systematically monitoring cases of medullary thyroid cancer (MTC) via MTC case series registry to identify any increase in the incidence of MTC related to the introduction of VICTOZA® into the US marketplace. All cases of medullary thyroid cancer, regardless of potential association with any drug treatment, should be reported to your state cancer registry.

To find out information on how to report a case to your state cancer registry, go to http://www.naaccr.org/Membership/MembershipDirectory.aspx.

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

APPENDIX C: DIRECT MAIL LETTER

IMPORTANT DRUG WARNING CONCERNING VICTOZA®

SUBJECT: POTENTIAL RISKS OF THYROID C-CELL TUMORS AND ACUTE PANCREATITIS ASSOCIATED WITH VICTOZA®

Dear Healthcare Professional:

This letter is to remind you of important safety information about VICTOZA® (liraglutide [rDNA origin]) injection. VICTOZA® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The Food and Drug Administration (FDA) has required Novo Nordisk to communicate the following risk information to potential prescribers.

You should note the following potential serious risks of VICTOZA®:

- There is potential risk of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) associated with VICTOZA®
- VICTOZA® may increase the risk of acute pancreatitis

Because of these risks, VICTOZA® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Additional information about these risks is provided in the remainder of this letter.

Potential Risk of Thyroid C-Cell Tumors, including Medullary Thyroid Carcinoma

- 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).
- 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 in patients treated with VICTOZA® than in patients treated 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.

Medullary Thyroid Cancer Registry

To further assess risk, Novo Nordisk will be systematically monitoring cases of medullary thyroid cancer (MTC) via MTC case series registry to identify any increase in the incidence of MTC related to the introduction of VICTOZA® into the US marketplace. All cases of medullary thyroid cancer, regardless of potential association with any drug treatment, should be reported to your state cancer registry.

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    - 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

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® (liraglutide [rDNA origin] injection) is prescribed and taken safely, Novo Nordisk has worked with the FDA to develop materials to communicate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis). The REMS program is designed to inform health care providers 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 potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with Victoza®.

To learn more, download these important documents:

- REMS Program for Victoza®
- Dear Healthcare Professional
- Full Prescribing Information
- 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.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. 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® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of Victoza® and insulin has not been studied.

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.

If pancreatitis is suspected, Victoza® should be discontinued. Victoza® should not be re-initiated if pancreatitis is confirmed.

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.

Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

In a 52-week monotherapy study (n=745) with a 52-week extension, the adverse reactions reported in ≥5% of patients treated with Victoza® 1.8 mg, Victoza® 1.2 mg, or glimepiride were constipation (11.8%, 8.4%, and 4.8%), diarrhea (19.5%, 17.5%, and 9.3%), flatulence (5.3%, 1.6%, and 2.0%), nausea (30.5%, 28.7%, and 8.5%), vomiting (10.2%, 13.1%, and 4.0%), fatigue (5.3%, 3.2%, and 3.6%), bronchitis (3.7%, 6.0%, and 4.4%), influenza (11.0%, 9.2%, and 8.5%), nasopharyngitis (6.5%, 9.2%, and 7.3%), sinusitis (7.3%, 8.4%, and 7.3%), upper respiratory tract infection (13.4%, 14.3%, and 8.9%), urinary tract infection (6.1%, 10.4%, and 5.2%), arthralgia (2.4%, 4.4%, and 6.0%), back pain (7.3%, 7.2%, and 6.9%), pain in extremity (6.1%, 3.6%, and 3.2%), dizziness (7.7%, 5.2%, and 5.2%), headache (7.3%, 11.2%, and 9.3%), depression (5.7%, 3.2%, and 2.0%), cough (5.7%, 2.0%, and 4.4%), and hypertension (4.5%, 5.6%, and 6.9%).

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

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

Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, or persistent hoarseness).

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.

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).

In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in no comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea.

The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the 5 controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator).

Victoza® causes a delay in gastric emptying, and thereby has the potential to impact absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with Victoza®.

Victoza® slows gastric emptying. Victoza® has not been studied in patients with pre-existing gastroparesis.

Adverse reactions reported in ≥5% of patients and occurring more frequently with Victoza® compared to exenatide were diarrhea (12.3% vs 12.1%), dyspepsia (8.9% vs 4.7%), and constipation (5.1% vs 2.6%). Rates of gastrointestinal adverse events, including nausea, were similar.

Please click here for Prescribing Information.

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

/s/

MARY H PARKS
05/18/2011