

PRODUCT MONOGRAPH

 **VICTOZA®**

liraglutide

6 mg/ml

Solution for Injection in a pre-filled pen

Human Glucagon Like Peptide-1 (GLP-1)

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VICTOZA®
(liraglutide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
subcutaneous	Injectable, 6 mg/ml	Disodium phosphate dihydrate, propylene glycol, phenol and water for injections <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

VICTOZA® contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae*, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor.

VICTOZA® is a clear, colorless solution. Each 1 mL of VICTOZA® solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 mL solution of VICTOZA® equivalent to 18 mg liraglutide (free-base, anhydrous).

INDICATIONS AND CLINICAL USE

VICTOZA® is indicated for once-daily administration for the treatment of adults with type 2 diabetes to improve glycemic control in combination with:

- Metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.
- Metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.

VICTOZA® should not be used in Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM).

Geriatrics (> 65 years of age): No difference in effectiveness was observed in clinical trial subjects ≥65 years of age. Patients >70 years may experience more gastrointestinal side effects when treated with VICTOZA®. Therapeutic experience in patients ≥75 years of age is limited. (See: WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; ADVERSE

REACTIONS, Adverse Drug Reaction Overview, Clinical Trial Adverse Drug Reactions, Gastrointestinal adverse events; and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Geriatrics

Pediatrics (<18 years of age): The safety and efficacy of VICTOZA® have not been studied in pediatric populations. VICTOZA® is not indicated for use in pediatric patients (see WARNINGS AND PRECAUTIONS, Special Population, Pediatrics).

CONTRAINDICATIONS

1. In patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
2. VICTOZA® is contraindicated in patients who are hypersensitive to liraglutide or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
3. In pregnancy or breast-feeding women

WARNINGS AND PRECAUTIONS

Serious Warnings and Precaution

Risk of Thyroid C-cell Tumours

- Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice (See PART II, Toxicology Section). It is unknown whether VICTOZA® causes thyroid C-cell tumours, 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 tumours. Patients should be counselled regarding the risk and symptoms of thyroid tumours (see **Contraindications, Warnings and Precautions, Adverse Drug Reactions and Toxicology**).

Carcinogenesis and Mutagenesis

Risk of Thyroid C-Cell Tumors:

VICTOZA® causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice (see PART II, TOXICOLOGY). Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether VICTOZA® will cause

thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies.

In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among VICTOZA® treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 subject-years). Two additional cases of thyroid C-cell hyperplasia in VICTOZA® treated patients and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one nonliraglutide-treated patient developed elevated calcitonin concentrations while on treatment. (See ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

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). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. 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. (See ADVERSE REACTIONS, Adverse Drug Reaction Overview and Clinical Trial Adverse Drug Reactions).

Cardiovascular

Increase in Heart Rate: A 24 h time-averaged increase in mean heart rate of 7-8 bpm was reported with VICTOZA® treatment in a clinical trial in healthy volunteers undergoing serial ECG monitoring (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). In patients with diabetes, a 2-4 bpm increase in mean pulse rate was observed in long term clinical trials. Because of limited clinical experience in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as ischemic heart disease and tachyarrhythmia, caution should be observed in these patients (see DRUG INTERACTIONS). The incidence of a composite endpoint for all tachyarrhythmia in pooled clinical trials in diabetic patients was higher for VICTOZA® than for placebo (see ADVERSE REACTIONS, Cardiovascular).

PR Interval Prolongation: A prolongation of the mean PR interval of up to 10 ms was reported with VICTOZA® treatment in a clinical trial in healthy volunteers (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). In healthy volunteers and in patients with diabetes, the incidence of first degree atrioventricular (AV) block was higher with VICTOZA® than with placebo (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac

Electrophysiology; ADVERSE REACTIONS, Cardiovascular). The clinical significance of these changes is not fully known; however, because of limited clinical experience in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) and heart rhythm disturbances (e.g., tachyarrhythmia), caution should be observed in these patients (see DRUG INTERACTIONS).

General

VICTOZA® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. VICTOZA® should not be administered intravenously or intramuscularly.

Endocrine and Metabolism

Hypoglycemia

Patients receiving VICTOZA® in combination with a sulfonylurea may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, major hypoglycemia requiring the assistance of another person for treatment occurred in 8 VICTOZA® treated patients. In another clinical trial comparing VICTOZA®+metformin to sitagliptin+metformin (Trial NN2211-1860), one additional major episode of hypoglycemia was reported in a VICTOZA® treated patient. In total, 9 patients treated with VICTOZA® in these clinical trials experienced major hypoglycemia. Six of these patients treated with VICTOZA® were also taking a sulfonylurea (see ADVERSE REACTION, Hypoglycemia). The risk of hypoglycemia can be lowered by reducing the dose of sulfonylurea.

Pancreatitis

In clinical trials conducted in adult patients with type 2 diabetes, more cases of pancreatitis were reported in the VICTOZA® treated group than in the comparator treated group (2.2 vs. 0.6 cases per 1000 subject-years). In a clinical trial comparing VICTOZA®+metformin to sitagliptin+metformin (Trial NN2211-1860), one additional case of pancreatitis was reported in a VICTOZA® treated patient. In the VICTOZA® treated group one fatal case of necrotizing pancreatitis was observed (See ADVERSE REACTIONS, Pancreatitis). The causality relationship to VICTOZA® is unclear. After initiation of VICTOZA® and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent or intermittent 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 medications 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.

Special Populations

Pregnant Women: There have been no studies conducted in pregnant women with VICTOZA®. Studies in animals have shown reproductive and developmental toxicity, including teratogenicity, at or above 0.8 times the clinical exposure (see PART II: TOXICOLOGY).

VICTOZA® should not be used during pregnancy (see CONTRAINDICATIONS). If a patient wishes to become pregnant, or pregnancy occurs, treatment with liraglutide should be discontinued.

Nursing Women: It is not known whether VICTOZA® is excreted in human milk. In lactating animals VICTOZA® was excreted unchanged in milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, women who are nursing should discontinue VICTOZA® treatment (see PART II: TOXICOLOGY).

Pediatrics (< 18 years of age): The safety and efficacy of VICTOZA® in pediatric patients has not been studied. VICTOZA® is not indicated in pediatric type 2 diabetes patients.

Geriatrics (>65 years of age): In the VICTOZA® clinical trials, a total of 797 (20%) of the patients were 65 years of age and over, of which 113 (2.8%) were 75 years of age and over. No differences in effectiveness were observed between subjects 65 years and over and younger subjects in the clinical studies. Patients >70 years experienced more gastrointestinal side effects when treated with VICTOZA®. (See ADVERSE REACTIONS, Adverse Drug Reaction Overview, Gastrointestinal adverse events and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Geriatrics and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics (>65 years of age)).

Cardiovascular - Patients with recent MI, Unstable Angina and Congestive Heart Failure: In clinical trials of VICTOZA®, subjects with clinically significant heart disease, acute myocardial infarction within 6 months, unstable angina pectoris and congestive heart failure (NYHA, class III to IV) were not studied. Therefore, VICTOZA® should be used with caution in this population.

Hepatic Insufficiency: The safety and efficacy of VICTOZA® in patients with hepatic insufficiency has not been studied. The use of VICTOZA® in patients with hepatic insufficiency is not recommended.

Renal Insufficiency: There is limited clinical experience with VICTOZA® in patients with mild renal insufficiency. There is very limited or no clinical experience in patients with moderate and severe renal insufficiency, including end-stage renal disease; use of VICTOZA® in these patients is not recommended (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Patients treated with VICTOZA® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Gastrointestinal Disease: The use of VICTOZA® is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhea see ADVERSE REACTIONS, Adverse Drug Reaction Overview and Clinical Trial Adverse Drug Reactions, Gastrointestinal adverse events). The safety of VICTOZA® in subjects with inflammatory bowel disease and diabetic gastroparesis has not been studied. VICTOZA® should not be used in this population.

Monitoring and Laboratory Tests

Regular self-monitoring of blood glucose is not needed in order to adjust the dose of VICTOZA®. However, when initiating treatment with VICTOZA® in combination with a sulfonylurea blood glucose self-monitoring may become necessary to reduce the dose of the sulfonylurea in order to reduce the risk of hypoglycemia.

However, patients should be informed that response to all diabetic therapies should be monitored by periodic measurement of A1C levels, with a goal of decreasing these levels towards the normal range. A1C is especially useful for evaluating long-term glycemic control.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In long term clinical trials, the most common adverse drug reactions were gastrointestinal disorders, infections and nervous system disorders. Discontinuation of treatment due to adverse events was most common with VICTOZA® (7.8%) as compared to comparator treatments (3.4%). The difference was driven by withdrawals due to gastrointestinal disorders.

In another clinical trial, comparing VICTOZA®+metformin to sitagliptin+metformin (Trial NN2211-1860), 14 (6.2%), 15 (6.8%) and 4 (1.8%) of patients discontinued treatment due to adverse events in liraglutide 1.2 mg + metformin, liraglutide 1.8 mg + metformin, and sitagliptin + metformin groups, respectively. Most of these discontinuations occurred during the 1st month of treatment.

Serious adverse events occurred in a similar proportion of patients treated with VICTOZA® (5.7%) as compared to other study treatments (5.6%), most commonly cardiac disorders (19.6 vs. 18.9 events per 1000 patient years respectively). In trial 1860 serious adverse events occurred in 2.7%, 2.8% and 1.8% of patients treated with Victoza® 1.2 mg + metformin, Victoza® 1.8 mg + metformin and sitagliptin + metformin respectively.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 provides a listing of the treatment-emergent adverse events with frequency $\geq 1\%$ from two 26 week combination trials 1572 and 1697 regardless of investigator assessment of causality. The two 26-week controlled clinical studies of VICTOZA® were LEAD™ 2 - 1572 for add on combination therapy with metformin and LEAD™ 5 – 1697 for add on combination therapy with metformin + sulfonylurea (see PART II: CLINICAL TRIALS).

Table 1 - Treatment-emergent adverse events from two 26 week combination trials 1572 and 1697

	Trial 1572 (LEAD™ 2)					Trial 1697 (LEAD™ 5)		
	Victoza® 0.6 mg + metformin	Victoza® 1.2 mg + metformin	Victoza® 1.8 mg + metformin	Placebo + metformin	Active Comparator (metformin + glimepiride)	Victoza® 1.8 mg + metformin + glimepiride	Placebo + metformin + glimepiride	Active Comparator (insulin glargine+ +metformin +glimepiride)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Safety Analysis Set	242	240	242	121	242	230	114	232
Blood and Lymphatic System Disorders								
Anemia	4 (1.7)	1 (0.4)	1 (0.4)	0 (0.0)	2 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)
Ear and Labyrinth Disorders								
Vertigo	1 (0.4)	1 (0.4)	3 (1.2)	0 (0.0)	2 (0.8)	3 (1.3)	0 (0.0)	1 (0.4)
Motion Sickness	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.8)	0 (0.0)
Eye Disorders								
Diabetic retinopathy	5 (2.1)	4 (1.7)	5 (2.1)	1 (0.8)	8 (3.3)	2 (0.9)	3 (2.6)	4 (1.7)
Cataract	3 (1.2)	2 (0.8)	3 (1.2)	2 (1.7)	1 (0.4)	1 (0.4)	0 (0.0)	2 (0.9)
Conjunctivitis	0 (0.0)	3 (1.3)	2 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriosclerotic retinopathy	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.7)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, Poisoning and Procedural Complications								
Soft tissue injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Fall	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.8)	1 (0.4)
Gastrointestinal Disorders								
Nausea	26 (10.7)	39 (16.3)	45 (18.6)	5 (4.1)	8 (3.3)	32 (13.9)	4 (3.5)	3 (1.3)
Diarrhea	23 (9.5)	20 (8.3)	36 (14.9)	5 (4.1)	9 (3.7)	23 (10.0)	6 (5.3)	3 (1.3)
Vomiting	13 (5.4)	16 (6.7)	18 (7.4)	1 (0.8)	1 (0.4)	15 (6.5)	4 (3.5)	1 (0.4)
Dyspepsia	9 (3.7)	5 (2.1)	17 (7.0)	1 (0.8)	3 (1.2)	15 (6.5)	1 (0.9)	4 (1.7)
Gastritis	8 (3.3)	6 (2.5)	12 (5.0)	1 (0.8)	2 (0.8)	3 (1.3)	0 (0.0)	1 (0.4)
Abdominal pain upper	5 (2.1)	7 (2.9)	8 (3.3)	0 (0.0)	3 (1.2)	10 (4.3)	2 (1.8)	2 (0.9)
Toothache	2 (0.8)	6 (2.5)	3 (1.2)	5 (4.1)	2 (0.8)	5 (2.2)	0 (0.0)	3 (1.3)
Abdominal pain	2 (0.8)	4 (1.7)	6 (2.5)	2 (1.7)	1 (0.4)	2 (0.9)	1 (0.9)	1 (0.4)
Constipation	5 (2.1)	11 (4.6)	6 (2.5)	2 (1.7)	4 (1.7)	5 (2.2)	0 (0.0)	2 (0.9)
Abdominal discomfort	3 (1.2)	2 (0.8)	3 (1.2)	0 (0.0)	2 (0.8)	3 (1.3)	2 (1.8)	1 (0.4)
Abdominal distension	2 (0.8)	2 (0.8)	2 (0.8)	0 (0.0)	4 (1.7)	3 (1.3)	1 (0.9)	1 (0.4)
Epigastric discomfort	2 (0.8)	2 (0.8)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	2 (0.8)	2 (0.8)	3 (1.2)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Gastroesophageal reflux disease	4 (1.7)	2 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions								
Fatigue	3 (1.2)	5 (2.1)	6 (2.5)	2 (1.7)	3 (1.2)	1 (0.4)	0 (0.0)	0 (0.0)
Asthenia	2 (0.8)	2 (0.8)	3 (1.2)	0 (0.0)	3 (1.2)	1 (0.4)	1 (0.9)	0 (0.0)
Influenza like illness	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	3 (1.2)	1 (0.4)	1 (0.9)	0 (0.0)
Early satiety	1 (0.4)	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.9)	1 (0.4)
Pyrexia	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)	5 (2.2)	1 (0.9)	5 (2.2)
Hepatobiliary Disorders								
Hepatic steatosis	6 (2.5)	2 (0.8)	1 (0.4)	0 (0.0)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Immune System Disorders								
Seasonal allergy	2 (0.8)	3 (1.3)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and Infestations								
Nasopharyngitis	27 (11.2)	21 (8.8)	21 (8.7)	11 (9.1)	30 (12.4)	21 (9.1)	10 (8.8)	26 (11.2)
Influenza	5 (2.1)	1 (0.4)	8 (3.3)	2 (1.7)	8 (3.3)	2 (0.9)	5 (4.4)	8 (3.4)

	Trial 1572 (LEAD™ 2)					Trial 1697 (LEAD™ 5)		
	Victoza® 0.6 mg + metformin	Victoza® 1.2 mg + metformin	Victoza® 1.8 mg + metformin	Placebo + metformin	Active Comparator (metformin + glimepiride)	Victoza® 1.8 mg + metformin + glimepiride	Placebo + metformin + glimepiride	Active Comparator (insulin glargine+ +metformin +glimepiride)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Pharyngitis	2 (0.8)	2 (0.8)	2 (0.8)	0 (0.0)	1 (0.4)	2 (0.9)	5 (4.4)	2 (0.9)
Upper respiratory tract infection	4 (1.7)	8 (3.3)	5 (2.1)	3 (2.5)	3 (1.2)	2 (0.9)	0 (0.0)	2 (0.9)
Acute tonsillitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	3 (1.3)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.4)	1 (0.4)	1 (0.9)	3 (1.3)
Bronchitis	5 (2.1)	9 (3.8)	4 (1.7)	1 (0.8)	9 (3.7)	7 (3.0)	1 (0.9)	3 (1.3)
Respiratory tract infection	0 (0.0)	0 (0.0)	4 (1.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.9)	1 (0.4)
Gastroenteritis	6 (2.5)	4 (1.7)	3 (1.2)	2 (1.7)	4 (1.7)	3 (1.3)	1 (0.9)	3 (1.3)
Urinary tract infection	3 (1.2)	5 (2.1)	3 (1.2)	3 (2.5)	3 (1.2)	3 (1.3)	2 (1.8)	3 (1.3)
Tooth abscess	0 (0.0)	0 (0.0)	3 (1.2)	1 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Pneumonia	1 (0.4)	3 (1.3)	2 (0.8)	1 (0.8)	3 (1.2)	0 (0.0)	2 (1.8)	3 (1.3)
Onychomycosis	3 (1.2)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	4 (1.7)	4 (1.7)	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.8)	3 (1.3)
Viral infection	2 (0.8)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.4)	3 (1.3)	1 (0.9)	2 (0.9)
Investigations								
Weight decreased	0 (0.0)	2 (0.8)	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatine phosphokinase increased	2 (0.8)	3 (1.3)	2 (0.8)	1 (0.8)	4 (1.7)	2 (0.9)	0 (0.0)	0 (0.0)
Blood calcitonin increased	3 (1.2)	1 (0.4)	1 (0.4)	3 (2.5)	2 (0.8)	3 (1.3)	0 (0.0)	0 (0.0)
Urine albumin / creatinine ratio increased	2 (0.8)	1 (0.4)	0 (0.0)	2 (1.7)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders								
Anorexia	6 (2.5)	10 (4.2)	14 (5.8)	1 (0.8)	1 (0.4)	10 (4.3)	1 (0.9)	0 (0.0)
Decreased appetite	4 (1.7)	14 (5.8)	10 (4.1)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.9)	0 (0.0)
Dyslipidemia	2 (0.8)	2 (0.8)	2 (0.8)	2 (1.7)	2 (0.8)	3 (1.3)	3 (2.6)	1 (0.4)
Hyperlipidaemia	1 (0.4)	1 (0.4)	1 (0.4)	3 (2.5)	3 (1.2)	1 (0.4)	1 (0.9)	2 (0.9)
Hyperglycaemia	1 (0.4)	0 (0.0)	1 (0.4)	3 (2.5)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders								
Back pain	7 (2.9)	5 (2.1)	6 (2.5)	4 (3.3)	9 (3.7)	7 (3.0)	3 (2.6)	8 (3.4)
Arthralgia	6 (2.5)	0 (0.0)	3 (1.2)	3 (2.5)	7 (2.9)	4 (1.7)	3 (2.6)	6 (2.6)
Muscle spasms	5 (2.1)	0 (0.0)	2 (0.8)	3 (2.5)	3 (1.2)	2 (0.9)	3 (2.6)	3 (1.3)
Pain in extremity	0 (0.0)	2 (0.8)	7 (2.9)	1 (0.8)	2 (0.8)	1 (0.4)	1 (0.9)	0 (0.0)
Musculoskeletal pain	3 (1.2)	1 (0.4)	3 (1.2)	3 (2.5)	1 (0.4)	3 (1.3)	2 (1.8)	4 (1.7)
Osteoarthritis	3 (1.2)	1 (0.4)	1 (0.4)	2 (1.7)	2 (0.8)	0 (0.0)	1 (0.9)	2 (0.9)
Myalgia	1 (0.4)	3 (1.3)	4 (1.7)	2 (1.7)	4 (1.7)	0 (0.0)	1 (0.9)	3 (1.3)
Neck pain	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.8)	3 (1.2)	3 (1.3)	0 (0.0)	1 (0.4)
Nervous System Disorders								
Headache	13 (5.4)	22 (9.2)	30 (12.4)	8 (6.6)	23 (9.5)	22 (9.6)	9 (7.9)	13 (5.6)
Dizziness	5 (2.1)	7 (2.9)	5 (2.1)	1 (0.8)	2 (0.8)	3 (1.3)	2 (1.8)	1 (0.4)
Sciatica	3 (1.2)	2 (0.8)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Psychiatric Disorders								
Anxiety	0 (0.0)	1 (0.4)	4 (1.7)	0 (0.0)	0 (0.0)	1 (0.4)	3 (2.6)	0 (0.0)
Depression	0 (0.0)	4 (1.7)	3 (1.2)	0 (0.0)	3 (1.2)	2 (0.9)	3 (2.6)	0 (0.0)
Insomnia	0 (0.0)	2 (0.8)	3 (1.2)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders								

	Trial 1572 (LEAD™ 2)					Trial 1697 (LEAD™ 5)		
	Victoza® 0.6 mg + metformin	Victoza® 1.2 mg + metformin	Victoza® 1.8 mg + metformin	Placebo + metformin	Active Comparator (metformin + glimepiride)	Victoza® 1.8 mg + metformin + glimepiride	Placebo + metformin + glimepiride	Active Comparator (insulin glargine+ +metformin +glimepiride)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Pharyngolaryngeal pain	3 (1.2)	4 (1.7)	2 (0.8)	1 (0.8)	3 (1.2)	2 (0.9)	2 (1.8)	1 (0.4)
Cough	4 (1.7)	3 (1.3)	2 (0.8)	1 (0.8)	5 (2.1)	4 (1.7)	1 (0.9)	7 (3.0)
Skin and Subcutaneous Tissue Disorders								
Pruritus	2 (0.8)	3 (1.3)	1 (0.4)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	1 (0.4)
Rash	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.8)	3 (1.2)	3 (1.3)	0 (0.0)	2 (0.9)
Hyperhidrosis	1 (0.4)	0 (0.0)	1 (0.4)	2 (1.7)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Vascular Disorders								
Hypertension	5 (2.1)	7 (2.9)	5 (2.1)	2 (1.7)	6 (2.5)	7 (3.0)	3 (2.6)	5 (2.2)
Vascular calcification	2 (0.8)	2 (0.8)	1 (0.4)	1 (0.8)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic calcification	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriosclerosis	3 (1.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hematoma	3 (1.2)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2 provides a listing of the treatment-emergent adverse events with frequency $\geq 1\%$ from the 26 week trial NN2211-1860 regardless of investigator assessment of causality. The controlled clinical study of VICTOZA® was with add on metformin combination therapy. (see PART II: CLINICAL TRIALS).

Table 2 - Treatment-Emergent Adverse Events in trial 1860 (Adverse events with frequency $\geq 1\%$)

	Victoza® 1.2 mg + metformin N= 221	Victoza® 1.8 mg + metformin N= 218	Sitagliptin 100 mg + metformin N= 219
Preferred Term	N (%)	N (%)	N (%)
Gastrointestinal Disorders			
Nausea	46 (20.8)	59 (27.1)	10(4.6)
Diarrhea	16 (7.2)	25 (11.5)	10 (4.6)
Vomiting	17 (7.7)	21 (9.6)	9 (4.1)
Dyspepsia	7 (3.2)	14 (6.4)	5 (2.3)
Constipation	10 (4.5)	11 (5.0)	6 (2.7)
Flatulence	2 (0.9)	5 (2.3)	1 (0.5)
Gastroesophageal Reflux Disease	3 (1.4)	5 (2.3)	2 (0.9)
Abdominal Distension	2 (0.9)	4 (1.8)	1 (0.5)
Abdominal Pain upper	5 (2.3)	4 (1.8)	2 (0.9)
Abdominal Discomfort	5 (2.3)	3 (1.4)	3 (1.4)
Abdominal Pain	5 (2.3)	2 (0.9)	6 (2.7)
Infections and Infestations			
Nasopharyngitis	21 (9.5)	28 (12.8)	26 (11.9)
Rhinitis	1 (0.5)	8 (3.7)	2 (0.9)
Upper Respiratory Tract Infection	10 (4.5)	7 (3.2)	8 (3.7)
Bronchitis	3 (1.4)	3 (1.4)	5 (2.3)
Gastroenteritis	2 (0.9)	3 (1.4)	2 (0.9)
Sinusitis	4 (1.8)	3 (1.4)	4 (1.8)
Influenza	13 (5.9)	2 (0.9)	5 (2.3)
Pharyngitis	1 (0.5)	2 (0.9)	3 (1.4)
Urinary Tract Infection	4 (1.8)	1 (0.5)	2 (0.9)
Lower Respiratory Tract Infection	0.0	0.0	3 (1.4)
Nervous System Disorders			
Headache	20 (9.0)	25 (11.5)	22 (10.0)
Dizziness	8 (3.6)	9 (4.1)	6 (2.7)

	Victoza® 1.2 mg + metformin N= 221	Victoza® 1.8 mg + metformin N= 218	Sitagliptin 100 mg + metformin N= 219
Preferred Term	N (%)	N (%)	N (%)
Diabetic neuropathy	1 (0.5)	3 (1.4)	1 (0.5)
Hypoaesthesia	2 (0.9)	0.0	3 (1.4)
Musculoskeletal and connective tissue disorders			
Back pain	8 (3.6)	8 (3.7)	10 (4.6)
Muscle spasms	3 (1.4)	4 (1.8)	0.0
Myalgia	0.0	4 (1.8)	5 (2.3)
Pain in extremity	1 (0.5)	4 (1.8)	5 (2.3)
Arthralgia	5 (2.3)	3 (1.4)	6 (2.7)
Musculoskeletal pain	2 (0.9)	3 (1.4)	3 (1.4)
Tendonitis	4 (1.8)	1 (0.5)	0.0
General disorders and administration site conditions			
Fatigue	7 (3.2)	9 (4.1)	1 (0.5)
Injection site hematoma	5 (2.3)	6 (2.8)	0.0
Metabolism and Nutrition Disorders			
Decreased appetite	7 (3.2)	12 (5.5)	2 (0.9)
Anorexia	8 (3.6)	6 (2.8)	1 (0.5)
Dyslipidaemia	4 (1.8)	1 (0.5)	4 (1.8)
Hyperglycemia	0.0	1 (0.5)	3 (1.4)
Hyperlipidemia	0.0	1 (0.5)	3 (1.4)
Investigations			
Blood calcitonin increased	6 (2.7)	9 (4.1)	5 (2.3)
C-reactive protein increased	2 (0.9)	2 (0.9)	4 (1.8)
Weight decreased	4 (1.8)	2 (0.9)	0.0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1 (0.5)	5 (2.3)	3 (1.4)
Cough	4 (1.8)	2 (0.9)	3 (1.4)
Nasal Congestion	0.0	0.0	4 (1.8)
Injury, Poisoning and procedural complications			
Contusion	3 (1.4)	3 (1.4)	3 (1.4)
Skin and subcutaneous tissue disorders			
Rash	4 (1.8)	3 (1.4)	2 (0.9)
Hyperhidrosis	3 (1.4)	1 (0.5)	2 (0.9)
Vascular disorders			
Hypertension	5 (2.3)	10 (4.6)	5 (2.3)
Cardiac Disorders			
Palpitations	3 (1.4)	0.0	0.0
Eye Disorders			
Diabetic retinopathy	3 (1.4)	2 (0.9)	1 (0.5)
Psychiatric disorders			
Insomnia	3 (1.4)	2 (0.9)	1 (0.5)
Endocrine disorders			
Goitre	2 (0.9)	1 (0.5)	4 (1.8)

Medullary thyroid cancer: Calcitonin was measured throughout the clinical development program. The serum calcitonin assay used in the VICTOZA® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper normal limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in patients treated with VICTOZA® compared to patients treated with placebo but not compared to patients receiving active comparator. At these

timepoints, the adjusted mean serum calcitonin values (~1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with VICTOZA® 1.8 mg/day.

The proportion of subjects shifting from below the upper normal limit (UNR) of the reference range to above UNR for calcitonin were 2.5% in the liraglutide group, 1.7% in placebo group and 2.0% in the active comparator group.

In trials with on-treatment serum calcitonin measurements up to 5-6 months, 1.9% of patients treated with VICTOZA® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of VICTOZA®. In trials with on-treatment serum calcitonin measurements up to 12 months, 1.3% of patients treated with VICTOZA® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with VICTOZA® 1.2 mg, placebo and active control, respectively. VICTOZA® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin.

Patients with MTC usually have calcitonin values >50 ng/L. In VICTOZA® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one patient treated with VICTOZA® and no comparator-treated patients developed serum calcitonin >50 ng/L. The patient treated with VICTOZA® who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of VICTOZA®

The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104.

Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of patients treated with VICTOZA®, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of VICTOZA®. The clinical significance of these findings is unknown (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions and Carcinogenesis and Mutagenesis).

Papillary thyroid cancer: In the completed trials the rates of papillary thyroid carcinoma were 1.9 and 0.6 (liraglutide vs. non-liraglutide) events per 1000 subjects-years of exposure. Papillary (follicular) thyroid cancers occurred at a higher frequency in the liraglutide clinical development programme than in the general Canadian population. Subjects included in the liraglutide clinical trial program underwent thyroid related assessments, leading to a high number of

thyroidectomies. The majority of papillary carcinomas were incidental findings arising from thyroidectomies performed as a result of elevations in serum calcitonin; all but one of the papillary carcinomas were microcarcinomas of less than 1.0 cm. In subjects with pre-existing thyroid disease, the rates of thyroid neoplasms were comparable for liraglutide and placebo (28.8 per 1000 subject-years and 29.3 per 1000 subject-years; none in active comparator).

Neoplasms: In the intermediate and long-term trials, 115 treatment emergent neoplasm adverse events were reported and of these, 45 events were classified as malignant neoplasms. The proportion and rate (shown in brackets) of subjects with neoplasm adverse events (benign and malignant) was 1.8% (26.9 cases per 1000 subject-years), 1.2% (17.0 per cases 1000 subject-years) and 1.3% (25.3 cases per 1000 subject-years) for liraglutide, active comparator and placebo, respectively. The proportion and rate of subjects with malignant neoplasm adverse events was 0.8% (10.9 cases per 1000 subject-years), 0.5% (7.2 cases per 1000 subject-years) and 0.3% (6.3 cases per 1000 subject-years) for liraglutide, active comparator and placebo, respectively.

Thyroid neoplasms were the most common neoplasm adverse events. The proportion and rate of subjects with benign thyroid neoplasms were higher for subjects treated with liraglutide compared to subjects treated with active comparator and placebo [liraglutide: 1.1% (16.0 cases per 1000 subject-years); active comparator: 0.6% (9.8 cases per 1000 subject-years); placebo: 1.0% (19.0 cases per 1000 subject-years)]. With regard to malignant neoplasms which are of more clinical relevance, prostate cancer, breast cancer, thyroid cancer, basal cell carcinoma, rectal cancer, renal cell carcinoma and colon cancer were the most commonly reported across treatment groups. The proportion of subjects with malignant prostate cancer, breast cancer, renal cell carcinoma and colon cancer were similar for subjects treated with liraglutide and either one of the comparators. No cases of rectal cancer or basal cell carcinoma were reported with comparators. The remaining malignant neoplasms occurred at low rates with no apparent pattern in type of neoplasms.

In another clinical trial comparing VICTOZA[®]+metformin to sitagliptin+metformin (Trial NN2211-1860) over 52 weeks, considering all adverse events in the system organ class “neoplasms benign, malignant and unspecified (incl cysts)”, 2 subjects (0.9%) reported 2 events, 8 subjects (3.7%) reported 9 events and 2 subjects (0.9%) reported 2 events for liraglutide 1.2 mg + metformin, liraglutide 1.8 mg + metformin and sitagliptin + metformin, respectively. Of these, there was 1 malignant neoplasm (epiglottic carcinoma) reported in the liraglutide 1.2 mg + metformin group, 3 malignant neoplasms (breast cancer, colon cancer and pancreatic carcinoma) reported in the liraglutide 1.8 mg + metformin group and 1 malignant neoplasm (renal cancer) reported in the sitagliptin + metformin group. No thyroid cancers were observed.

Cardiovascular: Adverse events identified using a composite endpoint for all tachyarrhythmias in pooled intermediate and long term trials, including open label arms, occurred at rates of 16.5, 6.1, and 15.3 per 1000 subject-years in the liraglutide, placebo and active comparator groups respectively. The respective proportions were 0.7, 0.2 and 0.7 per cent. The most commonly reported episodes of tachyarrhythmia were extrasystoles. The rate of pooled events of atrial fibrillation, atrial flutter, supraventricular tachycardia and supraventricular arrhythmia was 6.4

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per 1000 subject-years in the liraglutide group and 5.6 per 1000 subject-years in the active comparator group; no events were reported in the placebo group. Rates of adverse events related to tachyarrhythmia reported as Serious Adverse Events were 2.7, 0 and 2.8 per 1000 subject-years in the VICTOZA®, placebo and active comparator groups respectively.

In pooled long term trials, the rate of first-degree AV block was reported to be 2.6, 0 and 1.4 per 1000 subject-years in the liraglutide, placebo and active comparator groups.

In the above trials patients were excluded in case of known clinically significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure, at the discretion of the Investigator, and uncontrolled treated/untreated hypertension (systolic blood pressure =180 mmHg and/or diastolic blood pressure =100 mmHg). (See also WARNINGS AND PRECAUTIONS, Special Populations, Cardiovascular – patients with recent MI, unstable angina and congestive heart failure; DRUG INTERACTIONS, Drug-Drug Interactions, Drugs that increase the Heart Rate and Drugs that cause PR interval prolongation; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology).

In trial 1860, by 26 weeks, the overall adverse event of cardiac disorders occurred at rates of 2.7%, 0.9% and 0.9% in patients receiving liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin and sitagliptin+metformin respectively. By 52 weeks, the overall adverse event of cardiac disorders occurred at rates of 4.1%, 1.8% and 1.4% in patients receiving liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin and sitagliptin+metformin group.

Pancreatitis: In clinical trials of VICTOZA® there were 8 cases of pancreatitis among VICTOZA® treated patients and 1 case among comparator-treated patients (2.7 vs. 0.82 cases per 1000 subject-years). Five cases with VICTOZA® were reported as acute pancreatitis and three cases with VICTOZA® were reported as chronic pancreatitis. All events were serious except for one case of chronic pancreatitis in a patient treated with VICTOZA®. One fatal case of pancreatitis with necrosis was observed, in a VICTOZA® treated patient.

Four additional cases of pancreatitis have subsequently been reported in clinical trials of VICTOZA®. One of these was a case of acute pancreatitis in a patient whose treatment remains blinded. The remaining 3 cases occurred in VICTOZA® treated patients; 2 cases were acute pancreatitis, and 1 case was chronic pancreatitis. (See WARNINGS AND PRECAUTIONS, Pancreatitis).

Hypoglycemia: Major hypoglycemic episodes in the long-term phase 3a trials were rare (9 episodes in 8 subjects). In a phase 3b clinical trial, comparing VICTOZA®+metformin to sitagliptin+ metformin (Trial NN2211-1860) one major episode of hypoglycemia was reported in a VICTOZA® treated patient.

Seven of these major episodes were reported when liraglutide was used in combination with glimepiride. When liraglutide was used in combination with a sulfonylurea, an increased rate of

hypoglycemia was observed (see also WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia and DOSAGE AND ADMINISTRATION, Dosing Considerations).

In trial 1572 (LEAD™ 2) the rate of minor hypoglycemic episodes was 0.14, 0.03, 0.09, 0.13 and 1.23 events/subject year in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, placebo + metformin and glimepiride+metformin groups respectively; the corresponding proportion of affected subjects was 3.3%, 0.8%, 2.5%, 2.5% and 16.9%, respectively. Rates of minor nocturnal hypoglycemia were 0.00, 0.02, 0.00, 0.02 and 0.05 events/subject year, respectively.

In trial 1697 (LEAD™ 5) the rate of minor hypoglycemic episodes was 1.16, 0.95 and 1.29 events/subject year in the liraglutide 1.8mg+metformin+glimepiride, placebo+ metformin+ glimepiride and insulin glargine+glimepiride+metformin groups respectively; the corresponding proportion of affected subjects was 27.4%, 16.7% and 28.9% respectively. Major hypoglycemic episodes were only reported in the liraglutide group where 6 events were reported in 5 subjects. Rates of major hypoglycemia were 0.06, 0.00, 0.00 events/subject year and rates of nocturnal hypoglycemia were 0.16, 0.19, 0.23 events/ subject year, in the liraglutide 1.8mg+metformin+ glimepiride, placebo+metformin+glimepiride and insulin glargine+ glimepiride+metformin groups respectively.

In trial 1860 the rate of minor hypoglycemia episodes was 0.18, 0.37 and 0.11 events/subject year in the liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin and sitagliptin+metformin groups respectively; the corresponding proportion of affected subjects was 5.4%, 5.0% and 4.6% respectively. The rates of all hypoglycemia episodes as well as minor episodes were significantly higher in the liraglutide 1.8 mg+metformin treatment group as compared to the sitagliptin+metformin group.

Gastrointestinal adverse events: In pooled long term clinical trials, gastrointestinal adverse events were reported in 41% of VICTOZA® treated patients and were dose related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among VICTOZA® treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. Approximately 13% of VICTOZA® treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. Most episodes of nausea were mild or moderate in severity and declined over time (see Figure 1).⁴ Withdrawals due to gastrointestinal adverse events occurred in 5.0% of VICTOZA® treated patients and 0.5% of comparator-treated patients, mainly during the first 2 – 3 months of the trials.

In trial NN2211-1860, 16.3%, 17.4%, 2.7% of patients reported nausea during the first 2 weeks of treatment in the liraglutide 1.2mg+metformin, liraglutide 1.8 mg+metformin and sitagliptin+metformin groups respectively.

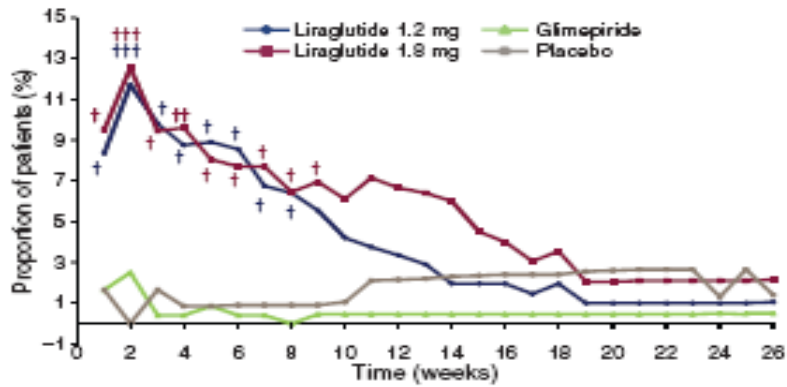
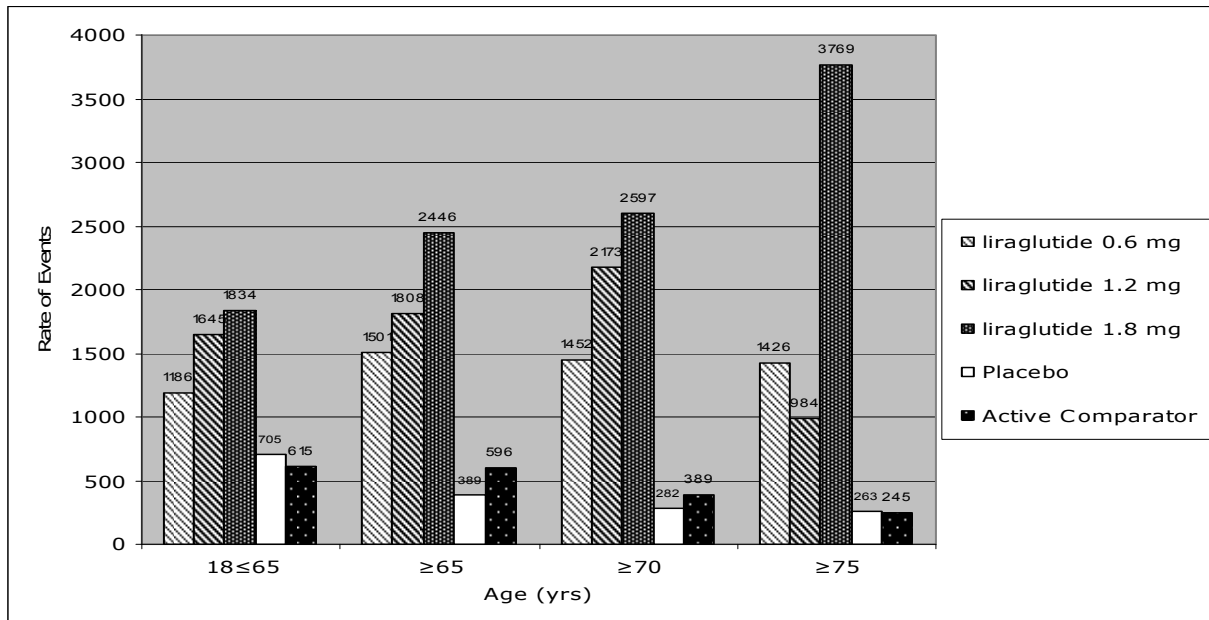


Figure 1 Observed proportion of patients experiencing nausea by treatment over time in LEAD™-2 †††p<0.0001, ††p<0.01, †p<0.5 vs. placebo.⁴

The rate of gastrointestinal disorders in VICTOZA® treated subjects increased with age, especially at the 1.8 mg dose of VICTOZA®. (See also INDICATIONS AND CLINICAL USE, Geriatrics (>65 years of age); WARNINGS AND PRECAUTIONS, Special Populations, Gastrointestinal disease; DOSAGE AND ADMINISTRATION, Dosing considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Gastric emptying).

Figure 2 Rate of Events with Gastrointestinal Disorders by Treatment and Age Group - All Long-term Trials - Safety Analysis Set



Immunogenicity: Approximately 50-70% of VICTOZA® treated patients in pooled clinical trials of 26 weeks or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Anti-liraglutide antibodies were detected in 8.6% of the VICTOZA® treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimated percentage of patients who developed antibodies. Cross

reacting antibodies to native GLP-1 occurred in 6.9% of VICTOZA® treated patients in a 52 week monotherapy trial and 4.8% of VICTOZA® treated patients in 26 week combination therapy trials. The antibodies cross-reacting with native GLP-1 were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of VICTOZA® treated patients in a 52 week monotherapy trial and 1.0% of VICTOZA® treated patients in 26 week combination therapy trials.

Antibody formation was not associated with reduced efficacy of VICTOZA® when comparing mean HbA1c of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with VICTOZA® treatment.

The most frequent adverse event categories for subjects without antibodies were gastrointestinal disorders (35.7%), infections and infestations (36.1%) and nervous system disorders (13.6%). The most frequent adverse event categories for subjects with antibodies were infections and infestations (40%), gastrointestinal disorders, (36.9%) and musculoskeletal and connective tissue disorders (20.6%). Two (2) subjects with liraglutide antibodies reported 4 events of hypersensitivity (rate: 33.6 events per 1000 subject-years of exposure), whereas 10 subjects without liraglutide antibodies reported 10 events (rate: 5.5 events per 1000 subject-years of exposure). Drug hypersensitivity was reported by 1 subjects with liraglutide antibodies (rate: 8.4 events per 1000 subject-years of exposure), whereas 4 subjects without antibodies reported 5 events (rate: 2.8 events per 1000 subject-years of exposure).

In clinical trials of VICTOZA®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of VICTOZA® treated patients (rate 12.2 events per 1000 subject-years of exposure with total liraglutide) and among 0.4% of total comparator-treated patients (rate 6.3 events per 1000 subject-years of exposure.) Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

Injection site reactions: Overall injection site reactions have been reported in approximately 2% of subjects receiving VICTOZA® in long-term controlled trials, most frequently bruising and pain. The rate of injection site disorders was 18.1, 27.6 and 37.6 events per 1000 subject-years of exposure for patients treated with liraglutide 0.6, 1.2 and 1.8mg as compared to 34.0 and 14.9 events per 1000 subject-years of exposure for patients treated with placebo and active comparator.

In a clinical trial comparing VICTOZA®+metformin to sitagliptin+metformin (Trial NN2211-1860), overall injection site reactions was reported in 3% of patients receiving VICTOZA®, most frequently injection site hematoma, bruising and pain. The rate of injection site disorders was 10 events reported in 8 patients out of 221 patients with liraglutide 1.2 mg and 13 events in 7 patients out of 218 patients with liraglutide 1.8 mg. There were no injection site reactions in the comparator group, as expected with oral administration only.

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Less than 0.2% of VICTOZA® treated patients discontinued due to injection site reactions. None of these patients were tested positive for liraglutide antibodies.

Less Common Clinical Trial Serious Adverse Drug Reactions (SAEs) and Rare Adverse Drug Reactions of interest ≥0.1% and <1% from long term clinical trials.

Cardiac Disorders: Angina Pectoris, Acute Myocardial Infarction, Myocardial Infarction Coronary Artery Disease, Atrial Fibrillation, Cardiac Failure Congestive, Supraventricular Tachycardia

Eye Disorders: Cataract

GI disorders: Appendicitis Perforated, Gastritis, Inguinal Hernia, Pancreatitis

Infections and Infestations: Upper Respiratory Tract Infection, Bronchitis, Gastroenteritis, Osteomyelitis.

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps): Papillary Thyroid Cancer, Prostate Cancer, Breast Cancer, **Musculoskeletal and Connective Tissue Disorders:** Intervertebral Disc Potrusion, Osteoarthritis

Nervous System Disorders: Cerebrovascular Accident, Syncope

Injury, Poisoning and Procedural Complications: Fall

General Disorders and Administration Site Conditions: Chest Pain

Metabolism and Nutrition Disorders: Hypoglycemia

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary Embolism

Post-Market Adverse Drug Reactions

VICTOZA® has been marketed since July 2009. As of 31 March 2010, Novo Nordisk has received 367 adverse drug reaction reports from market use of VICTOZA® comprising 767 adverse drug reactions of which 303 were non-serious reports and 64 were serious reports. Most adverse reactions were reported in the category of gastrointestinal disorders (235 non-serious, 62 serious of which 21 were serious unexpected events), general disorders and administrative site conditions (114 non-serious and 12 serious of which 9 were serious unexpected events), investigations (56 non-serious and 20 serious events of which 20 were serious unexpected events), nervous system disorders (57 non-serious and 10 serious of which 10 were serious unexpected events), skin and subcutaneous tissue disorder (31 non-serious and 5 serious of which 5 were serious unexpected events), metabolism and nutrition disorders (28 non-serious and 14 serious of which 14 were serious unexpected events), psychiatric disorders (14 non-serious and 9 serious of which 9 were serious unexpected events), musculoskeletal and connective tissue disorders (17 non-serious and 4 serious of which 4 were serious unexpected events), renal and urinary disorders (8 non-serious and 9 serious of which 9 were serious unexpected events), respiratory, thoracic and mediastinal disorders (8 non-serious and 4 serious of which 4 were serious unexpected events) and vascular disorders (4 non-serious and 6 serious of which 6 were serious unexpected adverse events). The adverse events reported do not change the safety profile for VICTOZA®.

DRUG INTERACTIONS

No clinically significant drug interaction has been demonstrated with VICTOZA®.

Drug-Drug Interactions

In vitro assessment of drug-drug interaction

VICTOZA® has shown very low potential to be involved in pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interaction

Drug-drug interaction has been investigated using acetaminophen, digoxin, lisinopril, griseofulvin and atorvastatin representing various degrees of solubility and permeability properties. In addition, the effect of liraglutide on the absorption of ethinylestradiol and levonorgestrel administered in an oral combination contraceptive drug has been investigated.

The delay of gastric emptying caused by liraglutide did not affect the absorption of orally administered medicinal products to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA®.

Acetaminophen

VICTOZA® did not change the overall exposure (AUC) of acetaminophen following a single dose of 1000 mg. Acetaminophen C_{max} was decreased by 31% and median t_{max} was delayed up to 15 min.

Atorvastatin

VICTOZA® did not change the overall exposure (AUC) of atorvastatin following single dose administration of atorvastatin 40 mg. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin

VICTOZA® did not change the overall exposure (AUC) of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin C_{max} increased by 37% while median t_{max} did not change.

Digoxin

A single dose administration digoxin 1mg with liraglutide showed a reduction of digoxin AUC by 16 %; C_{max} decreased by 31%, . Digoxin median time to maximum concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril

A single dose administration of lisinopril 20 mg with liraglutide resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with liraglutide.

Oral contraceptives

VICTOZA® lowered ethinylestradiol and levonorgestrel C_{max} by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. T_{max} was 1.5 h later with liraglutide for both compounds. There was no clinically relevant effect on the overall

exposure (AUC) of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Warfarin and other coumarin derivatives

No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR (International Normalized Ratio) is recommended.

Insulin

Combination of liraglutide with insulin has not been evaluated and is therefore not recommended.

Drugs that Increase Heart Rate

VICTOZA® causes an increase in heart rate (see ACTIONS AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). The impact on the heart rate of co-administration of VICTOZA® with other drugs that increase heart rate, (e.g., sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of VICTOZA® with these drugs should be undertaken with caution.

Drugs that Cause PR Interval Prolongation

VICTOZA® causes an increase in the PR interval (see ACTIONS AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). The impact on the PR interval of co-administration of VICTOZA with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digitalis glycosides, and HIV protease inhibitors) has not been evaluated in drug-drug interaction studies. As a result, co-administration of VICTOZA with these drugs should be undertaken with caution.

Drug-Food Interactions

There are no known interactions with food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For all patients VICTOZA® is administered once daily at any time, independent of meals. VICTOZA® should be initiated with a dose of 0.6 mg once daily for at least one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg once daily. Based on clinical response and after at least one week the dose can be increased to 1.8 mg once daily to achieve maximum efficacy for glycemic control.

VICTOZA® can be added to existing metformin therapy. The current dose of metformin can be continued unchanged at the discretion of the physician.

VICTOZA® can be added to combined metformin and sulfonylurea therapy. During clinical trials physicians were advised, at their discretion, to lower the dose of sulfonylurea to minimize the risk of unacceptable hypoglycemia.

Recommended Dose and Dosage Adjustment

Renal Insufficiency: No dose adjustment is required for patients with mild renal insufficiency. There is limited clinical experience with VICTOZA® in patients with mild renal insufficiency. There is very limited or no clinical experience with VICTOZA® in patients with moderate and severe renal insufficiency, including end-stage renal disease; use of VICTOZA® in these patients is not recommended. (See WARNINGS AND PRECAUTIONS, Special Population; and ACTION AND CLINICAL PHARMACOLOGY, Special Population and Conditions).

Hepatic Insufficiency: The safety and efficacy of VICTOZA® in patients with hepatic insufficiency have not been studied. The use of VICTOZA® in patients with hepatic insufficiency is not recommended. (See WARNINGS AND PRECAUTIONS, Special Population; and ACTION AND CLINICAL PHARMACOLOGY, Special Population and Conditions).

Geriatrics (>65 years of age): In the VICTOZA® clinical trials, a total of 797 (20%) of the patients were 65 years of age and over and 113 (2.8%) were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. (See WARNINGS AND PRECAUTIONS, Special Population; ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Gastrointestinal adverse events; and ACTION AND CLINICAL PHARMACOLOGY, Special Population and Conditions).

Pediatrics (<18 years of age): The safety and efficacy of VICTOZA® have not been studied in pediatric populations. VICTOZA® is not indicated for use in pediatric patients.

Missed Dose

If a dose of VICTOZA® is missed take your dose on the next day as usual. Do not take an extra dose or increase the dose on the following day to make up for the missed dose.

Administration

VICTOZA® is administered once daily at anytime, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed if needed without dose adjustment.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In a clinical study of VICTOZA®, one patient with type 2 diabetes experienced a single overdose of 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting. No hypoglycemia was reported. The patient recovered without complication. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

VICTOZA® (liraglutide) is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, G_s, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

Pharmacodynamics

VICTOZA® has 24-hour duration of action and improves long-term glycemetic control by lowering fasting and postprandial blood glucose in patients with type 2 diabetes mellitus. Inadequately controlled hyperglycemia is associated with an increased risk of diabetic complications, including cardiovascular disorders and diabetic nephropathy, retinopathy and neuropathy.¹

VICTOZA® 1.8 mg and 1.2 mg reduced the mean fasting glucose by 3.90 mmol/L and 3.33 mmol/L, respectively, when compared to placebo (Figure 3). Following a standard meal, the difference versus placebo in mean 2-hour postprandial glucose concentration was 6.02 mmol/L and 5.63 mmol/L. In addition, VICTOZA® 1.8 mg and 1.2 mg decreased the incremental postprandial glucose (defined as the difference between blood glucose values 90 minutes post and immediately before the meal across all three meals) on average by 1.1 mmol/L and 1.08 mmol/L, respectively.

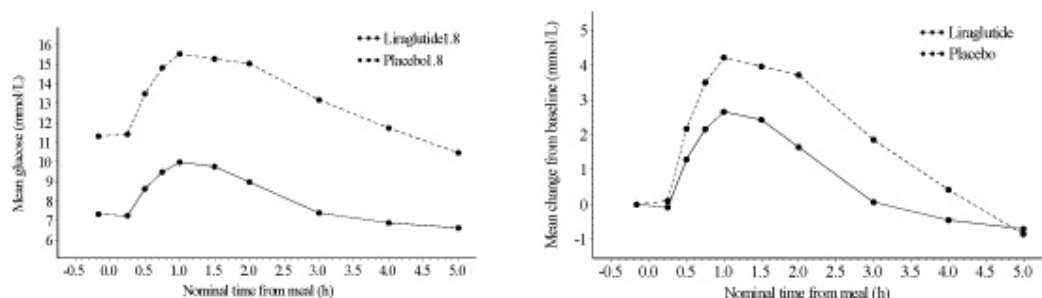


Figure 3 Mean absolute (left) and incremental (right) postprandial plasma glucose concentrations in patients with type 2 diabetes treated with liraglutide 1.8 mg or placebo in a cross-over design (N=18) (Trial 1698)

Glucose dependent insulin secretion: VICTOZA® increased insulin secretion in relation to increasing glucose concentrations. Using a stepwise graded glucose infusion, the insulin secretion rate was increased following a single dose of liraglutide in patients with type 2 diabetes to a level comparable to that observed in healthy subjects (Fig 4).

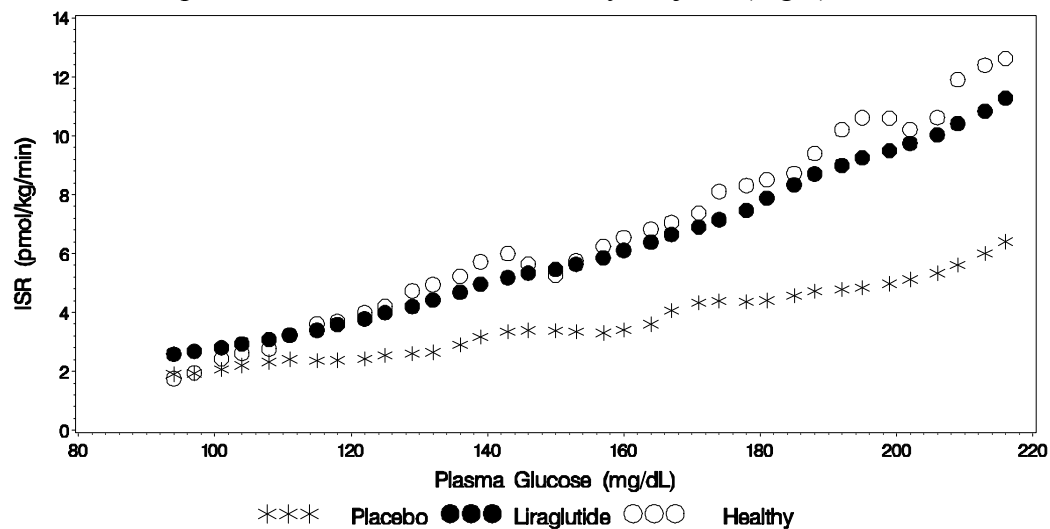


Figure 4 Mean Insulin Secretion Rate (ISR) versus glucose concentration following single dose 7.5 µg/kg (~0.66 mg) or placebo in subjects with type 2 diabetes (N=10) and untreated healthy subjects (N=10) during graded glucose infusion (Trial 2063).

Glucagon secretion: VICTOZA® lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of VICTOZA® of ~0.7 mg did not impair glucagon response to low glucose concentrations. Furthermore, due to increased insulin and lower glucagon secretion, a lower endogenous glucose release has been observed with VICTOZA®.

Gastric emptying: VICTOZA® caused a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appeared in the circulation.

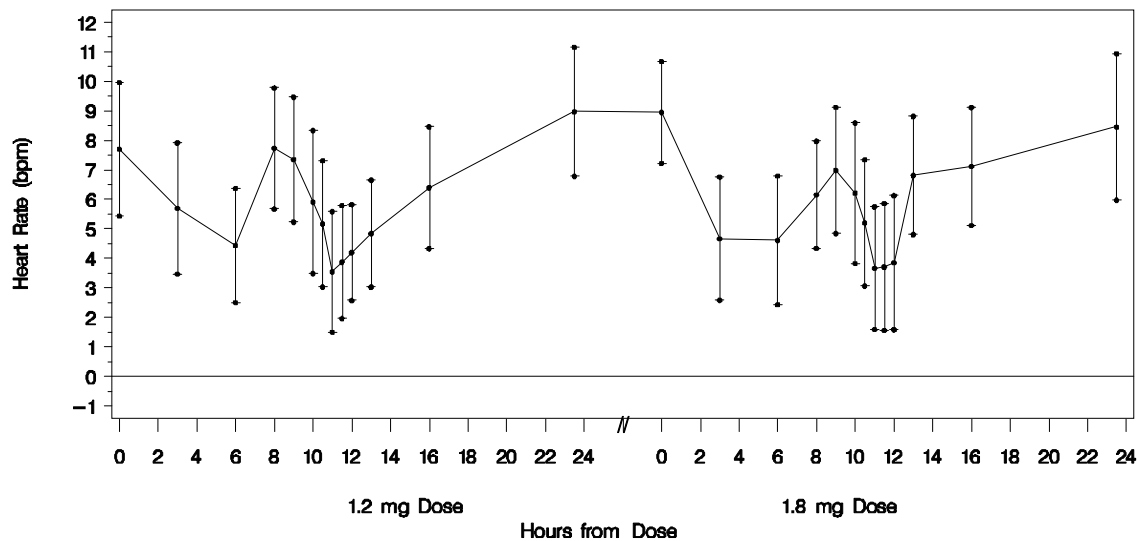
Cardiac Electrophysiology: A randomised, double-blind, 2-period crossover, placebo-controlled trial was performed in 51 healthy volunteers (25 M/26 F, 18-44 years). Following randomisation, subjects in the liraglutide treatment arm received 0.6 mg s.c. liraglutide daily for the first week of treatment, 1.2 mg s.c. daily for the second week of treatment, and 1.8 mg s.c.

daily for the third week of treatment according to an upward titration design. At the end of the second and third weeks, immediately following the seventh and final doses of 1.2 and 1.8 mg liraglutide, respectively, subjects had 24 hours of serial ECG monitoring. Subjects randomised to the placebo arm had an identical schedule of treatment and assessments with a placebo s.c. injection.

Heart Rate: Liraglutide was associated with statistically significant increases in heart rate at all time points during treatment with the 1.2 mg dose on day 14 and the 1.8 mg dose on day 21. The incidence of subjects with heart rate values greater than 90 bpm was 20.0% for liraglutide 1.2 mg versus 8.0% for placebo and 23.5% for liraglutide 1.8 mg versus 3.9% for placebo.

Figure 5

Time-matched Difference between Baseline Subtracted (Delta) Liraglutide and Placebo HR (bpm)

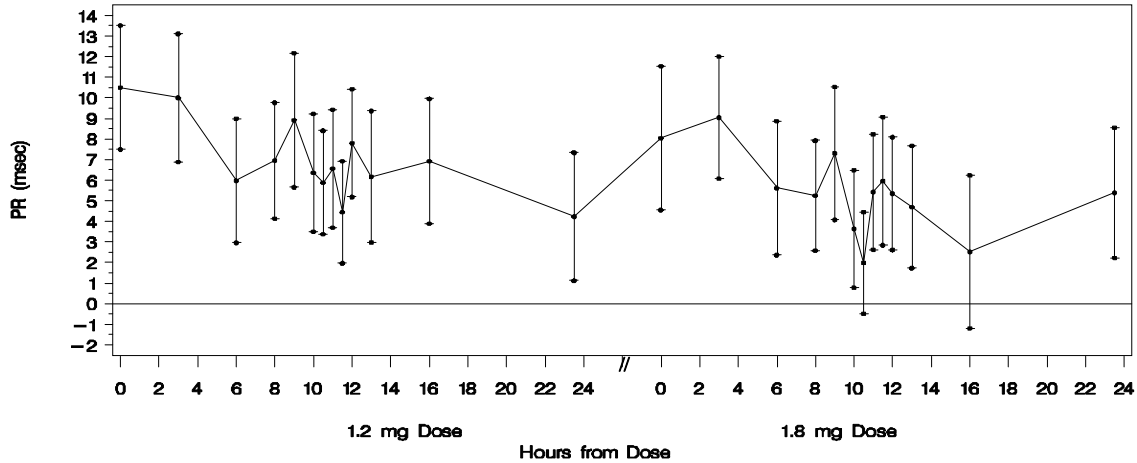


Delta: The difference between HR at current time and HR at baseline for each patient
 LCL: Lower Confidence Limit UCL: Upper Confidence Limit

PR Interval: Liraglutide at a dose of 1.2 mg caused statistically significant increases in the PR interval at all time points on day 14. The 1.8 mg dose of liraglutide resulted in statistically significant PR interval prolongation at 10 of 12 post-dose time points on day 21. The maximum placebo- and baseline-adjusted mean PR interval prolongation was 10.0 ms (90% CI: 6.9, 13.1) for the 1.2 mg dose and 9.0 ms (90% CI: 6.1, 12.0) for the 1.8 mg dose. Treatment-emergent PR values >200 ms were reported for 4% of subjects in the liraglutide arm and 2% of subjects in the placebo arm. The incidence of subjects who had PR values >200 ms at baseline that increased in magnitude and/or frequency during treatment was 6% for the liraglutide arm and 2% for the placebo arm.

Figure 6

Time-matched Difference between Baseline Subtracted (Delta) Liraglutide and Placebo PR (msec)

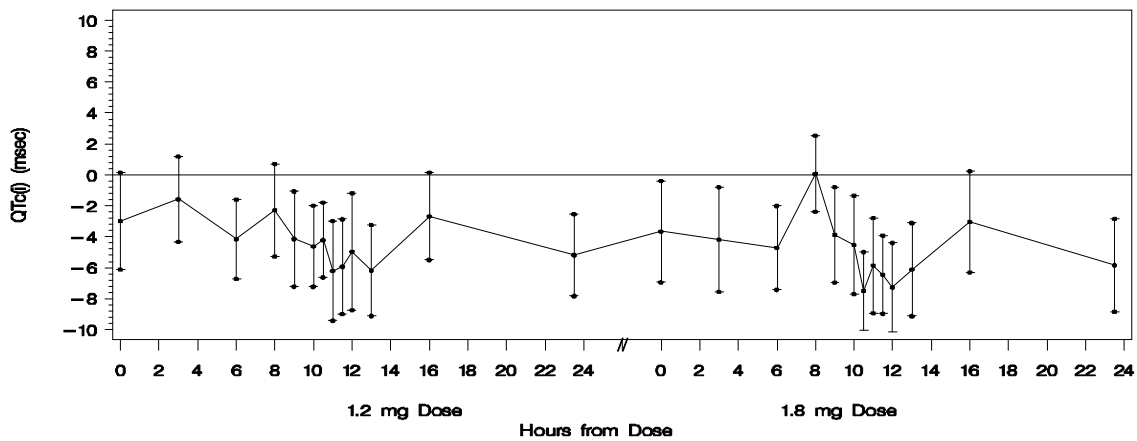


Delta: The difference between PR at current time and PR at baseline for each patient
LCL: Lower Confidence Limit UCL: Upper Confidence Limit

QT Interval: Liraglutide at 1.2 mg and 1.8 mg doses was associated with statistically significant shortening of the QTc interval at most post-dose time points. The clinical significance of an acquired, drug-induced QTc shortening of this magnitude is not known.

Figure 7

Time-matched Difference between Baseline Subtracted (Delta) Liraglutide and Placebo QTc (msec)



Delta: The difference between QTc at current time and QTc at baseline for each patient
LCL: Lower Confidence Limit UCL: Upper Confidence Limit

Pharmacokinetics

Absorption: The absorption of VICTOZA® following subcutaneous administration is slow, reaching maximum concentration 8-12 hours post dosing. Estimated maximum liraglutide concentration was 9.4 nmol/L for a subcutaneous single dose of liraglutide 0.6 mg. At 1.8 mg liraglutide, the average steady state concentration of liraglutide (AUC_{τ/24}) reached approximately 34 nmol/L. VICTOZA® exposure (AUC) increased approximately linearly with the dose (μg/kg) with increasing slope due to accumulation between days 1 and 11. The inter-subject coefficient of variation for liraglutide AUC was 11% following single dose administration. VICTOZA® can be administered subcutaneously in the abdomen, thigh, or upper arm.

The absolute bioavailability of VICTOZA® following subcutaneous administration is approximately 55%.

Distribution: The apparent volume of distribution after subcutaneous administration is 11-17 L. The mean volume of distribution after intravenous administration of VICTOZA® is 0.07 L/kg. VICTOZA® is extensively bound to plasma protein (>98%).

Metabolism: During 24 h following administration of a single [³H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤ 9 % and ≤ 5% of total plasma radioactivity exposure). VICTOZA® is endogenously metabolized in a similar manner to large proteins without a specific organ as major route of elimination.

Excretion: Following a [¹H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The urine and feces radioactivity was mainly excreted during the first 6-8 days, and corresponded to three minor metabolites, respectively.

The mean clearance following s.c. administration of a single dose of VICTOZA® is approximately 1.2 L/h with an elimination half-life of approximately 13 hours.

Special Populations and Conditions

Pediatrics (<18 years of age): VICTOZA® has not been studied in pediatric patients.

Geriatrics (>65 years of age): Exposure (AUC) to VICTOZA® is independent of age (See DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY.)

Gender: After adjusting for body weight, AUC(0-t), C_{max}, t_{max}, AUC(0-∞), CL/F, V_z/F, and t_{1/2} appeared to be comparable between male and female subjects after administration of a single dose of liraglutide. A pharmacokinetic study in healthy subjects indicated that gender has no clinically meaningful effect on the pharmacokinetics of VICTOZA®.

Race: There seems to be no clinically relevant effect on the pharmacokinetics of VICTOZA®

based on the results of a population pharmacokinetic analysis which included subjects of White, Black, Asian and Hispanic groups

Hepatic Insufficiency: Subjects with varying degrees of hepatic insufficiency displayed a reduced exposure to VICTOZA®. After a single-dose, the AUC in mild (Child Pugh score 5-6), moderate, and severe (Child Pugh score > 9) compared to healthy subjects was lower on average by 23%, 13% and 44% respectively.

Renal Insufficiency: Subjects with varying degrees of renal insufficiency displayed a reduced exposure to VICTOZA®. After a single-dose, the AUC in mild (CrCL 50-80 mL/min), moderate (CrCL 30-50 mL/min), severe (CrCL < 30 mL/min) and end-stage renal disease requiring dialysis compared to healthy subjects was lower on average by 33%, 14%, 27% and 26%, respectively.

Obesity: Body weight significantly affects the pharmacokinetics of VICTOZA® based on results of ANCOVA analyses. The exposure of VICTOZA® decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of VICTOZA® provided adequate systemic exposures over the body weight range of 40 – 160 kg evaluated in the clinical trials. VICTOZA® was not studied in patients with body weight >160 kg.

STORAGE AND STABILITY

VICTOZA® should be stored in a refrigerator (2°C-8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA® and do not use VICTOZA® if it has been frozen.

After initial use of the VICTOZA® pen, the product can be stored for 30 days at room temperature (not above 30°C) or in a refrigerator (2 - 8°C).

SPECIAL HANDLING INSTRUCTIONS

VICTOZA® should be kept with the pen cap on when pen is not in use in order to protect from light. VICTOZA® should be protected from excessive heat and sunlight. Always remove the injection needle after each injection and store the VICTOZA® pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VICTOZA® comes in a pre-filled disposable pen, comprising of a pen injector assembled with a cartridge (3 mL).

VICTOZA® contains the following non-medicinal ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injections.

The cartridge is made of glass (type 1), containing a bromobutyl rubber closure shaped as a plunger and closed with a bromobutyl/polyisoprene rubber closure. The pen injector is made of polyolefin and polyacetal. When incinerated these materials only result in non-toxic waste products (carbondioxide and water).

VICTOZA® multidose pen can deliver 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.

Pack sizes available:

VICTOZA® Pen multidose (0.6, 1.2 or 1.8 mg): 1 pen (total supply 10 days), 2 pens (total supply 20 days) or 3 pens (total supply 30 days).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: VICTOZA®

Chemical name: Liraglutide

Molecular formula and molecular mass:

$C_{172}H_{265}N_{43}O_{51}$
3751.20 dalton

Structural formula:



Physicochemical properties: 1 ml contains 6 mg of liraglutide (produced by recombinant DNA technology in *Saccharomyces cerevisiae*). Each pre-filled pen contains 3 mL equivalent to 18 mg salt-free anhydrous liraglutide, a human GLP-1 analogue.

Product Characteristics

VICTOZA® (liraglutide) is a clear colorless solution

CLINICAL TRIALS

Study demographics and trial design

The efficacy and safety of Victoza® were evaluated in three randomized double-blind, controlled clinical trials 1572 (LEAD™ 2), 1697 (LEAD™ 5), and 1860.

Table 3: Summary of baseline demographics and study design for trials 1572, 1697 and 1860

Study #	Trial Design	Dosage, Route of Administration, and Duration	Study subjects (n=number) [‡]	Gender N(%)		Age
				Male	Female	
1572	Multicentre, randomised, double-blind, double-dummy, placebo-controlled trial with an active control arm	VICTOZA® 0.6 mg once daily + metformin 1500 - 2000 mg/day Or VICTOZA® 1.2 mg once daily + metformin 1500 - 2000 mg/day Or VICTOZA® 1.8 mg once daily + metformin 1500 - 2000 mg/day Or Placebo+metformin 1500 - 2000 mg/day Or glimepiride 4 mg+ metformin 1500 - 2000 mg/day VICTOZA® was administered subcutaneously and metformin and glimepiride were administered orally, once daily for 26 weeks	1087*	633 (58.2)	454 (41.8)	Mean (SD) 56.7 (9.5) Range 25-79
1697	Multicentre, randomised, double-blind, placebo-controlled trial with an open-label treat-to-target insulin glargine control arm	VICTOZA® 1.8 mg once daily+metformin 2000 mg/day +glimepiride 2 - 4 mg/day Or Placebo+metformin 2000 mg/day +glimepiride 2 - 4 mg/day Or insulin glargine+metformin 2000 mg/day+glimepiride 2 - 4 mg/day VICTOZA® and glargine were administered subcutaneously and metformin and glimepiride were administered orally, once daily for 26 weeks	576*	325 (56.4)	251 (43.6)	Mean (SD) 57.6 (9.9) Range 24-80
1860	Multicentre, 26-week, randomised, open-label, active comparator, three-armed, parallel-group, with a 52-week extension.	VICTOZA® 1.2 mg once daily+ metformin ≥1500 mg/day Or VICTOZA® 1.8 mg once daily+ metformin ≥1500 mg/day Or sitagliptin + metformin ≥1500 mg/day VICTOZA® was administered subcutaneously and sitagliptin and metformin were administered orally, once daily for 26 weeks	665*	352 (53.9)	313 (37.1)	Mean (SD) 55.3 (9.2) Range 23-79

SD = Standard Deviation

* Randomized and exposed patients

In LEAD™ 2, most (87%) subjects were white and 9% were categorized as Asian or Pacific Islanders. Subjects had a mean duration of diabetes of 7.4 yrs (range 4 months to 41 years).

Before entering the trial, 36% of subjects were treated with a single oral antidiabetic agent and 64% of subjects were treated with two or more oral antidiabetic agents.

In LEAD™ 5, most subjects were white (75%) and 16% were categorized as Asian or Pacific Islanders. Subjects had a mean duration of diabetes of 9 years (range 5 months to 44 years). Before entering the trial, 6% of subjects were treated with a single oral antidiabetic agent and 84% of subjects were treated with two or more oral antidiabetic agents.

In 1860, subjects had a mean weight of 93.8 kg, a mean BMI of 32.8 kg/m², a mean duration of diabetes of 6.2 years and a mean baseline HbA_{1c} of 8.5 %. The majority of subjects (86.6%) were white with 7.2% of subjects being Black or African American. Approximately 16% were of Hispanic or Latino ethnicity.⁵

Combination Therapy with Metformin (LEAD™ 2)

In a 26-week study, 1091 patients with type 2 diabetes and at least 3 months of treatment with various oral antidiabetic agents were randomized in a 2:2:2:1:2 manner to VICTOZA® 1.8 mg, VICTOZA® 1.2 mg, VICTOZA® 0.6 mg, placebo or glimepiride, all as add-on to metformin. At the time of randomisation, subjects were stratified with respect to their previous OAD therapy (monotherapy or combination therapy). Randomisation took place after a 3-week forced metformin titration period followed by a metformin maintenance period of another 3 weeks. During the titration period, the dose of metformin was increased to 2000 mg. After randomisation, a 2-week titration period commenced followed by a 24-week maintenance treatment period with fixed doses of VICTOZA® and glimepiride (4 mg). The glimepiride dose used in the study was less than the maximum approved dose of glimepiride in Canada (8mg), but equal to the maximal dose approved in some of the other participating countries. During the trial, the VICTOZA® and glimepiride doses were fixed, while the dose of metformin was to be maintained throughout the study if possible. However, the dose level could be decreased to a minimum of 1500 mg and increased again to 2000 mg at the discretion of the investigator.² The percentage of patients who discontinued due to ineffective therapy was 5.4% in the VICTOZA® 1.8mg *plus* metformin group and 3.7% in the glimepiride *plus* metformin group. Treatment with VICTOZA® 1.8 mg and 1.2 mg (but not 0.6 mg) in combination with metformin resulted in mean reductions in HbA_{1c} that were non-inferior to treatment with glimepiride in combination with metformin (Table 4).²

Table 4 Results of a 26 week trial of VICTOZA® (liraglutide) in combination with metformin^a

	Victoza® 1.8 mg+ Metformin	Victoza® 1.2 mg+ Metformin	Placebo+ Metformin	Glimepiride 4 mg+ Metformin
Intent-to-Treat Population (N)	242	240	121	242
HbA_{1c} (%) (Mean)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline (adjusted mean) ^b	-1.0	-1.0	+0.1	-1.0
Difference from glimepiride + metformin arm (adjusted mean) ^b	0.0	0.0		
95% Confidence Interval	(-0.2, 0.2)	(-0.2, 0.2)		
Patients (%) achieving A _{1c} <7%	42	35	11	36
Fasting Plasma Glucose (mmol/L) (Mean)				

	Victoza® 1.8 mg+ Metformin	Victoza® 1.2 mg+ Metformin	Placebo+ Metformin	Glimepiride 4 mg+ Metformin
Baseline	10.05	9.94	10.11	10
Change from baseline (adjusted mean) ^b	-1.68	-1.63	+0.40	-1.31
Difference from glimepiride + metformin arm (adjusted mean) ^b	-0.38	-0.33		
Body Weight (kg) (Mean)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline (adjusted mean) ^b	-2.8	-2.6	-1.5	+1.0
Difference from glimepiride + metformin arm (adjusted mean) ^b	-3.8**	-3.5**		
95% Confidence Interval	(-4.5, -3.0)	(-4.3, -2.8)		

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

** p-value <0.0001

Combination Therapy with metformin Trial 1860

In a 26 week study, 665 patients with type 2 diabetes and inadequately controlled with metformin monotherapy were randomised in a (1:1:1) manner to receive a once-daily dose of 1.2 mg liraglutide, 1.8 mg of liraglutide, or 100 mg of sitagliptin as an add-on to their stable pre-trial metformin dose (≥ 1500 mg). Twenty-six weeks after randomization, all subjects completing the trial were offered continued participation in the trial extension. Of these, 89.7 % of patients entered the additional 52 weeks of treatment.

After randomization, patients assigned to VICTOZA® 1.2 mg or 1.8 mg underwent a titration scheme with weekly 0.6 mg increments to reach a final dose of 1.2 mg or 1.8 mg per day. VICTOZA® and metformin doses were fixed during the trial.

The percentage of patients who discontinued due to ineffective therapy after 52 weeks of treatment was 2.7% in the VICTOZA® 1.2mg + Metformin group, 1.4% in the VICTOZA® 1.8mg + Metformin group and 5.0% in the Sitagliptin + Metformin group. Treatment with VICTOZA® 1.2 mg and 1.8 mg, both in combination with metformin, resulted in a statistically significant mean reduction in HbA_{1c} compared to Sitagliptin + Metformin (See table 5) at Weeks 26.⁵

Table 5 Results of a 26 Week Trial 1860 of Victoza® versus sitagliptin (both in combination with metformin)

	Victoza® 1.2 mg + metformin	Victoza® 1.8 mg + metformin	Sitagliptin + metformin
Full Analysis Set Population (N)	221	218	219
HbA_{1c} (%) (Mean)			
N	211	214	210
Baseline	8.4	8.4	8.5
Change from baseline (adjusted mean) ^b	-1.24	-1.50	-0.9
Difference from sitagliptin + metformin arm (adjusted mean) ^b	-0.34**	-0.60	
95% Confidence Interval	-0.51;-0.16	-0.77;-0.43	
Patients (%) achieving A _{1c} <7%	43.4	54.6	22.4

	Victoza® 1.2 mg + metformin	Victoza® 1.8 mg + metformin	Sitagliptin + metformin
FPG (mmol/L) (Mean)			
N	210	212	210
Baseline	10.1	10.0	10.0
Change from baseline (adjusted mean) ^b	-1.87	-2.14	-0.83
Body Weight (kg) (Mean)			
N	215	214	215
Baseline	93.9	94.9	93.1
Change from baseline (adjusted mean) ^b	-2.86	-3.38	-0.96

^aIntent-to-treat population using last observation carried forward

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

Testing for statistical superiority was performed only after VICTOZA® 1.2 mg and 1.8 mg in combination with metformin was demonstrated to be non-inferior to sitagliptin treatment in combination with metformin.

After 12 months of treatment, the reductions in HbA_{1c} observed after the first 6 months with both liraglutide doses in combination with metformin were sustained. The estimated mean changes in HbA_{1c} after 52 weeks of treatment were -1.29% and -1.51% in the liraglutide+ metformin groups (1.2 and 1.8 mg) and -0.88% in the sitagliptin+metformin group. The estimated proportion of subjects who achieved the ADA target of HbA_{1c} < 7%, at Week 52, were 50.3 % in the 1.2 mg liraglutide + metformin group, 63.3 % in the 1.8 mg liraglutide + metformin group and 27.1 % in the sitagliptin + metformin group.⁵

Combination Therapy with Metformin and Sulfonylurea (LEAD™ 5)

In a 26 week study, 581 patients with type 2 diabetes and at least 3 months of treatment with various oral antidiabetic regimens were randomized to VICTOZA® 1.8mg, placebo or insulin, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, the doses of metformin and glimepiride were increased to 2000 mg and 4 mg respectively. The glimepiride dose used in the study was less than the maximum approved dose of glimepiride in Canada (8mg) but equal to the maximal dose approved in some of the other participating countries and within the usual maintenance dose of 1-4 mg. After randomization, patients randomized to VICTOZA® 1.8 mg underwent a 2 week period of titration with VICTOZA®. During the trial, the VICTOZA® and metformin doses were fixed, while the dose of glimepiride could be reduced to 3 or 2 mg/day. Patients titrated the glargine dose twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18.³

Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤5.5 mmol/L; therefore, optimal titration of the insulin glargine dose was not achieved in most patients. Insulin titration used the in the AT.LANTUS study.

The percentage of patients who discontinued due to ineffective therapy was 0.9% in the VICTOZA® 1.8mg *plus* glimepiride *plus* metformin group, 11.3% in the placebo *plus*

glimepiride *plus* metformin group and 0.4% in the insulin glargine *plus* glimepiride *plus* metformin group. Treatment with VICTOZA® 1.8 mg in combination with glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo in combination with glimepiride and metformin, (See table 6).³

Table 6 - Results of a 26 week trial of VICTOZA® (liraglutide) in combination with metformin and sulfonylurea^a

	Victoza® 1.8 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Insulin glargine + Metformin + Glimepiride
Intent-to-Treat Population (N)	230	114	232
HbA1c (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean) ^b	-1.3	-0.2	-1.1
Difference from placebo + metformin +glimepiride arm (adjusted mean) ^b	-1.1**		
95% Confidence Interval	(-1.3, -0.9)		
Patients (%) achieving A1c <7%	53	15	46
Fasting Plasma Glucose (mmol/l) (Mean)			
Baseline	9.17	9.44	9.11
Change from baseline (adjusted mean) ^b	-1.55	+0.55	-1.77
Body Weight (kg) (Mean)			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean) ^b	-1.8	-0.4	1.6

^a Intent-to-treat population using last observation on study

^b Least squares mean adjusted for baseline value

**p-value <0.0001

DETAILED PHARMACOLOGY

Pharmacodynamic studies showed that liraglutide is a potent, selective and full agonist on the cloned human GLP-1 receptor and on the cloned monkey, pig, rabbit, rat and mouse receptors. The main molecular mechanisms of the protracted action profile of liraglutide is self-association, which results in slow absorption, binding to albumin, and higher enzymatic stability against the dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidase (NEP) enzymes. The apparent reduced potency in the presence of albumin indicates that only the free fraction of liraglutide is responsible for its pharmacological effect *in vitro* as well as *in vivo*.

The hypoglycaemic effect of liraglutide was investigated in mice, rats and pigs, and was shown to be due to glucose-dependent insulin secretion; glucose-dependent lowering of glucagon; slowing of gastric emptying; and increased beta-cell mass (only during the diabetic stage).

TOXICOLOGY

Single dose toxicity

Single dose studies were performed in mice and rats in standard design studies and in monkeys in a maximum tolerated dose (MTD) study. A single dose of 10 mg/kg was generally well tolerated by mice and rats without mortality. In monkeys, a single SC administration of 5 mg/kg

was well tolerated without mortality. The observed reductions in body weight and food consumption can be regarded as pharmacologically mediated.

Repeat dose toxicity

Pivotal repeat dose studies were performed in mice, rats and Cynomolgus monkeys. An overview of the toxicological programme can be found in the tables below:

Table 7

Study ID	NN203261	NN204082
Species/strain	CD-1 mice	CD-1 mice
Drug	Liraglutide	Liraglutide
Dose Route	SC	SC
Animals/sex/group	Main study: 5 groups:10 males, 10 females/group Satellite study: 5 groups:16 males, 16 females/group	Main study: 4 groups:10 males, 10 females/group Satellite study: 4 groups:28 males, 28 females/group Antibody study: 4 groups 5-15 males, 5-15 females/group
Dose groups (mg/kg/day)	0, 0.1, 0.5, 1.0, 5.0	0, 0.2, 1.0, 5.0
Duration	4 weeks	13 weeks
NOEL/ NOAEL (mg/kg/day)	NOEL <0.1mg/kg NOAEL 5 mg/kg	NOEL < 0.2 mg/kg NOAEL <0.2 mg/kg

Study ID	NN980183	NN980189	NN200239
Species Strain	Rats/Sprague Dawley	Rats/Sprague Dawley	Rats/Sprague Dawley
Drug	Liraglutide	Liraglutide	Liraglutide
Dose Route	SC	SC	SC
Animals/Sex/Group	Main study: 4 groups: 10 males, 10 females/group Satellite study: 3 groups: 10 males, 10 females/group.	Main study: 4 groups: 10 males, 10 females/group Satellite study: 4 groups: 10 males, 10 females/group. Recovery study: 2 groups: 5 males, 5 females/group	4 groups: 15 males, 15 females/group
Dose Groups (mg/kg/day)	0, 0.1 , 0.25, 1.0	0, 0.1 , 0.25, 1.0	0, 0.1 , 0.25, 1.0
Duration	4 weeks	13 weeks treatment + 4 weeks recovery	26 weeks
NOEL/ NOAEL (mg/kg/day)	NOEL <0.1 mg/kg. NOAEL 1.0 mg/kg	NOEL <0.1 mg/kg NOAEL 1.0 mg/kg	NOEL <0.1 mg/kg NOAEL 1.0 mg/kg

Study ID	NN980184	NN990191	NN200241
Species/strain	Cynomolgus Monkeys	Cynomolgus Monkeys	Cynomolgus Monkeys
Drug	Liraglutide	Liraglutide	Liraglutide
Dose Route	SC	SC	SC

Study ID	NN980184	NN990191	NN200241
Animals/sex/group	4 groups: 3 males, 3 females/group	Main study: 4 groups: 4 males, 4 females/group. Recovery study: 2 groups: 2 males, 2 females/group	Main study: 4 groups: 4 males, 4 females/group. Recovery study: 2 groups: 2 males, 2 females/group
Dose groups (mg/kg/day)	0, 0.05, 0.5, 5.0	0, 0.05, 0.5, 5.0	0, 0.05, 0.5, 5.0
Duration	4 weeks	13 weeks treatment + 2 weeks recovery	52 weeks treatment + 4 weeks recovery
NOEL/ NOAEL (mg/kg/day)	NOEL < 0.05mg/kg NOAEL 5mg/kg	NOEL < 0.05mg/kg NOAEL 5mg/kg	NOEL 0.05mg/kg NOAEL 5mg/kg

In mice, rats and monkeys, decreased body weight gain and food consumption were seen during the first weeks of dosing which was attributed to the pharmacological action of liraglutide. Subsequently, body weight gain and food consumption were generally comparable to that of the control group. For all species, there were no toxicologically significant effects noted on hematology, clinical chemistry and urinary parameters. However, for mice only, histopathological examination of the thyroid gland revealed C-hyperplasia at all dose levels, first event after 9 weeks on treatment. Effects on C-cells (focal accumulations of C-cells) were already seen in the 4-week mouse study but these findings were not considered to be treatment-related. No effects on C-cells were seen in the rat and monkey studies up to 26 and 52 weeks.

An increase in pancreatic weight was observed at all dose levels, in male cynomolgus monkeys in the 28 day study and following 52 weeks treatment in both sexes. Further investigations of the pancreatic tissues collected in the 52-week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group. However, normal histological morphology of the pancreas was seen in all studies and no clinical or biochemical changes were seen in any of the four non-human primate studies. In addition, no effect on pancreatic weight was observed in an 87-week mechanistic study conducted in cynomolgus monkeys

Carcinogenicity

A 104-week carcinogenicity study was conducted in male and female mice at doses of 0.03, 0.2, 1.0, 3.0 mg/kg/day administered by subcutaneous bolus injection. The human exposure multiple (based on plasma AUC₀₋₂₄ comparison) values for the 0.03, 0.2, 1 and 3mg/kg/day doses were 0.2, 1.8, 10.0 and 45.0. Treatment resulted in an increased incidence of focal C-cell hyperplasia for males and females dosed at 1.0 and 3.0 mg/kg/day, and for females dosed at 0.2mg/kg/day, incidence rates for the 0, 0.03, 0.2, 1.0 and 3.0 mg/kg/day groups respectively, were 0%, 0%, 1.5%, 16.4% and 38.0% for males, and 0%, 0%, 10.4%, 10.5% and 33.3% for females. There was also a dose-related increase in benign thyroid C-cell adenomas in the 1.0 and the 3.0mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively, C-cell adenomas did not occur in control groups or in the 0.03 and 0.2mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. In addition, there was a treatment-related increase in fibrosarcomas on the dorsal skin and

subcutis, the body surface used for drug injection, in males in the 3mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6mg/mL) is 10-times higher than the concentration in the formulation used to administer 3mg/kg/day liraglutide to mice in the carcinogenicity study (0.6mg/mL). The NOAEL for this study is 0.03 mg/kg/day.

A 104-week carcinogenicity study was conducted in male and female rats at doses of 0.075, 0.25 and 0.75 mg/kg/day administered by bolus subcutaneous injection with exposures 0.5, 2.2 and 7.6 times the human exposure level, respectively, based on plasma AUC₀₋₂₄ comparison. There was a treatment-related increase in the incidence and severity of focal C-cell hyperplasia in the 0.25 and 0.75 mg/kg/day groups, incidence rates for the 0, 0.075, 0.25 and 0.75 mg/kg/day, respectively, were 22%, 29%, 40% and 48% for males, and 28%, 29%, 55% and 48% for females. In addition, there was a treatment-related increase in benign thyroid C-cell adenomas noted for males in the 0.25 and 0.75 mg/kg/day groups with incidences of 12%, 16%, 42% and 46% for females in all treated groups with incidences of 10%, 27%, 33% and 56% in the 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6% and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25 and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. The NOAEL for this study is <0.075 mg/kg/day.

The human relevance of thyroid C-cell tumours observed in rats and mice is unknown and could not be determined based on the results of the nonclinical studies (refer to Boxed Warnings and Precautions).

Mutagenesis

Liraglutide was not mutagenic or clastogenic with or without metabolic activation in the following tests: Ames test, human peripheral blood lymphocyte chromosome aberration test, and in vivo micronucleus test in the rat.

Reproduction

In rat fertility and embryo-fetal developmental study, rats were administered liraglutide subcutaneously at doses of 0.1, 0.25 and 1.0 mg/kg/day. Males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility, were observed up to the highest dose levels tested which represented, a systemic exposure 11 times the human exposure based on plasma AUC. Body weight gain and food intake were transiently reduced at all dose levels. At 1.0 mg/kg/day there was an increased incidence of early embryonic death, and an increase in the number of fetuses and litters with minimally kinked ribs. The fetal NOAEL/NOEL was therefore considered to be 0.25 mg/kg/day.

In a rabbit developmental study, pregnant females were administered liraglutide subcutaneously at doses of 0.01, 0.025 and 0.05 mg/kg/day from gestation day 6 through day 18 inclusive. The estimated systemic exposures were less than the human exposure at all doses, based on plasma

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AUC. Fetal weight was decreased and the incidence of total major fetal abnormalities was increased at all dose levels tested. Single cases of microphthalmia were noted at all dose levels. Since microphthalmia is a very rare malformation, and was not observed in the control group, nor in any of the historical control groups, this finding is considered to be related to treatment. In addition, there was an increase in the fetal incidence of connected parietals in the high dose group, and a single case of split sternum in the 0.025 and 0.05 mg/kg/day groups which could not be ruled out as unrelated to treatment. Minor abnormalities considered to be treatment related were an increase in the incidence of jugal(s) connected/fused to maxilla at all dose levels, and an increase in the incidence of bilobed/bifurcated gallbladder at 0.025 and 0.50 mg/kg/day. The noted findings exceeded the incidence noted in the concurrent and historical controls. Based on these data, a NOEL/NOAEL for embryo/fetal toxicity could not be determined. Liraglutide is considered to be a possible teratogen in rabbits due to the increased incidence of major abnormalities noted at all dose levels tested.

In a pre- and post-natal study, pregnant female rats were administered subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24. Estimated systemic exposures were 0.8-, 3-, and 11-times human exposure, based on plasma AUC. Reduced body weight gain/weight loss, and decreased food consumption were observed in all treated groups, evident primarily during the first 3 days of dosing. At 1.0 mg/kg/day, following the initial weight loss, the difference in absolute weight when compared to controls, was not recovered by the end of gestation. Lesser effects were noted at the lower dose levels. In addition, decreased weight gain was evident in F₀ females that had been treated with 1.0 mg/kg/day, between Days 1 and 14 of lactation. Litter size and survival were similar in all groups, but decreased weight gain was evident in the F₁ pups prior to weaning, at all dose levels.

The reduced body weight of F₁ pups persisted in the post-weaning period, but only at 1.0 mg/kg/day was there also a reduction in weight gain, which was noted for females during lactation and for males.

There were no apparent treatment-related effects on the development, behaviour, physiology or reproductive function of the F₁ animals, except for a slight reduction in body weights of F₂ pups at 1.0 mg/kg/day.

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PART III: CONSUMER INFORMATION

 **VICTOZA®**
(liraglutide)

This leaflet is part III of a three-part "Product Monograph" published when VICTOZA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VICTOZA®. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information may have changed.

Remember that your physician has prescribed this medicine only for you. Never give it to anyone else

ABOUT THIS MEDICATION

What the medication is used for:

VICTOZA® is used in combination metformin or with metformin and a sulfonylurea to improve blood sugar levels in adult patients with type 2 diabetes.

VICTOZA® should not be used in type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM).

What it does:

VICTOZA® belongs to a class of medicines called GLP-1 analog. VICTOZA® (liraglutide) helps your body to make more insulin when your blood sugar is high.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and/or does not use the insulin that your body produces as well as it should. When this happens, sugar (glucose) builds up in the blood. This can lead to serious problems.

When it should not be used:

Do not use VICTOZA® if:

- you or a member of your family have ever had medullary thyroid cancer
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- you are allergic to any of the ingredients in VICTOZA®
- you are pregnant or breastfeeding

What the medicinal ingredient is:

liraglutide

What the important nonmedicinal ingredients are:

Disodium phosphate dihydrate, propylene glycol, phenol and

water for injections.

What dosage forms it comes in:

Prefilled multidose pen that can deliver 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Possible Risk of thyroid tumours, including cancer

As part of drug testing, liraglutide, the active ingredient in VICTOZA® was given to rats and mice in long term studies. In these studies, liraglutide caused both rats and mice to develop medullary thyroid tumours, some of which were cancer. It is not known if VICTOZA® will cause thyroid tumours or a type of thyroid cancer called medullary thyroid cancer in people. Medullary thyroid cancer in humans is rare, however it is serious and potentially fatal.

If you develop tumours of the thyroid, it may have to be surgically removed. You should discuss any safety concerns you have about the use of VICTOZA® with your doctor.

BEFORE you use VICTOZA® talk to your doctor or pharmacist if:

- You or a member of your family has or has had medullary thyroid carcinoma, or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- You have type 1 diabetes
- You have ever had diabetic ketoacidosis (increased ketones in the blood or urine)
- You have ever had an allergic reaction to VICTOZA®
- You have a high heart rate (fast pulse)
- You have a condition called heart block
- You have any heart disease, such as angina, heart rhythm disturbances or congestive heart failure; or if you have ever had a myocardial infarction (heart attack)
- You have kidney problems
- You have liver problems
- You have gastrointestinal (digestive) problems
- You have ever had pancreatitis
- You are breast-feeding or plan to breast-feed.
- You are pregnant or plan to become pregnant

When initiating treatment with Victoza®, you may in some cases experience loss of fluids/ dehydration, e.g. in case of vomiting, nausea and diarrhea. It is important to avoid dehydration by drinking plenty of fluids. Contact your doctor if you have any questions or concerns.

VICTOZA® may increase heart rate and could cause changes

known as PR prolongation, which are detected by electrocardiogram (ECG) tracings. Increased heart rate is the same as a faster pulse. Rarely, drugs with these effects can cause changes in heart rhythm that could result in dizziness, palpitations (a feeling of rapid, pounding, or irregular heart beat), fainting or death. These heart rhythm changes are more likely if you have heart disease, or if you are taking certain other drugs. It is important to follow your doctor's advice about the dose of VICTOZA® or about any special tests that you may need. See **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM.**

VICTOZA® is not recommended for use in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Tell your physician, diabetes nurse or pharmacist if you are taking or have recently taken any other medicines. This includes prescription and non-prescription medicines and herbal supplements.

In particular, tell your physician, diabetes nurse or pharmacist if you are using any of the following medicines for diabetes:

- Insulin – using VICTOZA® is not recommended if you are using insulin.
- A sulfonylurea medicine (such as glibenclamide or glimepiride). This is because using VICTOZA® at the same time may cause your blood sugar to get too low (hypoglycemia).
- When you first start using these medicines together, your doctor may tell you to lower the dose of the sulfonylurea medicine.
- If you are not sure if the medicines you are taking contain a sulfonylurea, ask your doctor, diabetes nurse or pharmacist.

The following list includes some, but not all, of the drugs that may increase the risk of heart rhythm problems while receiving VICTOZA®. You should check with your doctor or pharmacist before taking any other medication with VICTOZA®:

- drugs to treat hypertension
- drugs to treat heart failure
- drugs to treat HIV infection
- drugs to treat attention deficit-hyperactivity disorder
- drugs to suppress appetite/cause weight loss
- decongestants
- drugs to treat asthma

PROPER USE OF THIS MEDICATION

Take VICTOZA® exactly as your physician has prescribed.

Usual dose:

VICTOZA® can be taken at any time of day. It does not matter when you take it in relation to meals.

The usual starting dose is 0.6 mg once a day. Your doctor will tell you how long to keep taking this dose. It will be for at least one week. Your dose will then be increased to 1.2 mg once a day. If your blood glucose is not controlled with a dose of 1.2 mg, your

doctor may tell you to increase the dose to 1.8 mg once a day. Do not change your dose unless your doctor has told you to.

You will not need to test your blood sugar levels each day in order to adjust your dose of VICTOZA®. However, if you are taking a sulfonylurea medicine as well as VICTOZA®, your doctor may advise you to test your blood sugar levels. This will help your doctor to decide if the dose of the sulfonylurea needs to be changed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you use more VICTOZA® than you should, talk to your doctor straight away. You may need medical treatment. If you use too much VICTOZA® you may feel sick (have nausea) or become sick (vomit).

Missed Dose:

If a dose of VICTOZA® is missed take your dose on the next day as usual. Do not take an extra dose or increase the dose on the following day to make up for the missed dose

Do not stop using VICTOZA® without talking to your doctor. If you stop using it, your blood sugar levels may increase.

Administering VICTOZA®:

VICTOZA® is an injection which is given under the skin (subcutaneously). Do not inject it into a vein or muscle. Before you use the pen for the first time, your doctor or diabetes nurse will show you how to use it. The best places to give yourself the injection are the front of your thighs, the front of your waist (abdomen) or your upper arm. You can give yourself the injection at any time of the day. **See Instructions for Use.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, VICTOZA® can cause side effects. The following side effects may happen with this medicine.

Very common (affect more than 1 in 10 people)

- Feeling sick (nausea). This usually goes away over time.
- Diarrhea.

Common (affects less than 1 in 10 people)

- Low blood sugar (hypoglycemia). This is usually mild. It is more likely if you are also taking a medicine for diabetes called a sulfonylurea. The warning signs of low blood sugar may come on suddenly. They can include: cold sweat, cool pale skin, headache, fast heart beat, feeling sick, feeling very hungry, changes in vision, feeling sleepy, feeling weak, nervous, anxious, or confused, difficulty concentrating, shaking (tremor). Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs. If you are already taking a sulfonylurea medicine when you start using VICTOZA®, your doctor may tell you to reduce the dose of the sulfonylurea.
- Headache.
- Being sick (vomiting)
- Burping.
- Indigestion

- Inflamed stomach (gastritis). The signs include stomach pain, feeling sick (nausea) and being sick (vomiting).
- Gastro-esophageal reflux disease (GERD). The signs include heartburn.
- Painful or swollen tummy (abdomen).
- Constipation.
- Wind (flatulence).
- Infection of the upper airways.

If any of the side effects do not go away or get worse, or if you notice any side effects not listed in the leaflet, please tell your physician, diabetes nurse or pharmacist.

- **When VICTOZA® is being used, you can keep it for 1 month either at room temperature (not above 30°C) or in a refrigerator (2°C to 8°C).**
- Do not use VICTOZA® if it has been frozen.
- Do not use VICTOZA® if it is not clear and colourless.
- Always remove the injection needle after each injection and store your VICTOZA® pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate.
- When you are not using the pen, keep the cap on. This will protect the medicine from light.
- Protect VICTOZA® from high temperatures and sunlight.
- Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Chest pain or symptoms of a possible heart rhythm disturbance / dizziness, palpitations, fainting or seizures, you should seek immediate medical attention		T	T
Rare	Pancreatitis / persistent, severe abdominal pain with or without vomiting		T	
Rare	Severe hypoglycemia / disorientation, loss of consciousness, and seizures		T	
Very Rare	Thyroid tumour / lump in the neck, difficulty in swallowing difficulty in breathing or persistent hoarseness		T	

This is not a complete list of side effects. For any unexpected effects while taking VICTOZA®, contact your doctor or pharmacist-

HOW TO STORE IT

Keep out of reach and sight of children.

Do not use VICTOZA® after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

- **Before you start to use VICTOZA®, store it in a refrigerator (2°C to 8°C) away from the freezer compartment. Do not freeze it.**

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program

Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.novonordisk.ca> or by contacting the sponsor, Novo Nordisk Canada Inc., at 1-800-465-4334.

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