

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>Pr</sup>**Victoza**<sup>®</sup>

liraglutide injection

6 mg/mL

Solution for Injection in a pre-filled pen

Human Glucagon Like Peptide-1 (GLP-1)

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## RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	[03/2024]
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### TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

<b>TABLE OF CONTENTS</b>	<b>2</b>
<b>PART I: HEALTH PROFESSIONAL INFORMATION</b>	<b>4</b>
<b>1 INDICATIONS</b>	<b>4</b>
1.1 Pediatrics	4
1.2 Geriatrics	4
<b>2 CONTRAINDICATIONS</b>	<b>5</b>
<b>3 SERIOUS WARNINGS AND PRECAUTIONS BOX</b>	<b>5</b>
<b>4 DOSAGE AND ADMINISTRATION</b>	<b>5</b>
4.1 Dosing Considerations	5
4.2 Recommended Dose and Dosage Adjustment	6
4.4 Administration	7
4.5 Missed Dose	7
<b>5 OVERDOSAGE</b>	<b>7</b>
<b>6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING</b>	<b>7</b>
<b>7 WARNINGS AND PRECAUTIONS</b>	<b>8</b>
7.1 Special Populations	11
7.1.1 Pregnant Women	11
7.1.2 Breast-feeding	11
7.1.3 Pediatrics	11
7.1.4 Geriatrics	12
<b>8 ADVERSE REACTIONS</b>	<b>12</b>
8.1 Adverse Reaction Overview	12
8.2 Clinical Trial Adverse Reactions	12
8.2.1 Clinical Trial Adverse Reactions (Pediatrics)	27
8.3 Less Common Clinical Trial Adverse Reactions	28
8.5 Post-Market Adverse Reactions	28
<b>9 DRUG INTERACTIONS</b>	<b>29</b>
9.2 Drug Interactions Overview	29
9.4 Drug-Drug Interactions	29
9.5 Drug-Food Interactions	33
9.6 Drug-Herb Interactions	33
<b>10 CLINICAL PHARMACOLOGY</b>	<b>33</b>
10.1 Mechanism of Action	33

10.2 Pharmacodynamics .....	33
10.3 Pharmacokinetics .....	37
<b>11 STORAGE, STABILITY AND DISPOSAL.....</b>	<b>38</b>
<b>12 SPECIAL HANDLING INSTRUCTIONS.....</b>	<b>38</b>
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>40</b>
<b>13 PHARMACEUTICAL INFORMATION .....</b>	<b>40</b>
<b>14 CLINICAL TRIALS .....</b>	<b>40</b>
14.1 Trial Design and Study Demographics .....	40
14.2 Study Results .....	43
<b>16 NON-CLINICAL TOXICOLOGY .....</b>	<b>54</b>
<b>PATIENT MEDICATION INFORMATION.....</b>	<b>58</b>

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

Victoza<sup>®</sup> is indicated for once-daily administration for the treatment of adults, with type 2 diabetes to improve glycemic control in combination with:

- diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance.
- 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.
- metformin and a sodium glucose cotransporter 2 inhibitor (SGLT2i), when diet and exercise plus dual therapy with metformin and a SGLT2i do not achieve adequate glycemic control.
- metformin and basal insulin, when diet and exercise plus dual therapy with Victoza<sup>®</sup> and metformin do not achieve adequate glycemic control (see [14 CLINICAL TRIALS](#)).

**Add-on combination in patients with established cardiovascular disease:** Victoza<sup>®</sup> is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease (see [14 CLINICAL TRIALS](#)).

There is limited clinical experience with the combination of Victoza<sup>®</sup> and prandial (short-acting) insulin.

Victoza<sup>®</sup> is not a substitute for insulin. Victoza<sup>®</sup> should not be used in type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM).

#### 1.1 Pediatrics

**Pediatrics (≥ 10 years of age):** In adolescents and children aged 10 years and above with type 2 diabetes, Victoza<sup>®</sup> is indicated as an adjunct to metformin with or without basal insulin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.

#### 1.2 Geriatrics

**Geriatrics (≥ 65 years of age):** No overall difference in safety or efficacy was observed in clinical trial subjects' ≥ 65 years of age compared to younger patients, but greater sensitivity of older individuals cannot be ruled out (see [7 WARNINGS AND PRECAUTIONS](#), Special Populations, Geriatrics; [8 ADVERSE REACTIONS](#), Adverse Reaction Overview, Clinical Trial Adverse Drug Reactions, Gastrointestinal adverse events; and [4 DOSAGE AND ADMINISTRATION](#) DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Geriatrics).

## 2 CONTRAINDICATIONS

- Liraglutide is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- In patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- In pregnant or breastfeeding women.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

### Serious Warnings and Precautions

#### 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 [16 NON-CLINICAL TOXICOLOGY](#)). It is unknown whether Victoza<sup>®</sup> 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<sup>®</sup> 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 [2 CONTRAINDICATIONS](#), [7 WARNINGS AND PRECAUTIONS](#), [8 ADVERSE REACTIONS](#) and [16 NON-CLINICAL TOXICOLOGY](#))

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

For all patients Victoza<sup>®</sup> is administered once daily at any time, independent of meals. Victoza<sup>®</sup> 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<sup>®</sup> can be added to existing metformin therapy. The current dose of metformin can be continued unchanged at the discretion of the doctor.

Victoza<sup>®</sup> can be added to combined metformin and sulfonylurea therapy. During clinical trials doctors were advised, at their discretion, to lower the dose of sulfonylurea to minimize the risk of unacceptable hypoglycemia.

Victoza® can be added to combined metformin and SGLT2i therapy. The current dose of metformin and the SGLT2i can be continued unchanged at the discretion of the doctor.

When using Victoza® with insulin, administer as separate injections. Never mix. It is acceptable to inject Victoza® and insulin in the same body region but the injections should not be adjacent to each other.

#### In children and adolescents aged 10 years and above

Victoza® can be added to existing metformin therapy with or without basal insulin. The current dose of metformin can be continued unchanged at the discretion of the doctor. The current dose of basal insulin should be decreased at the discretion of the doctor. (See [7 WARNINGS AND PRECAUTIONS](#), Monitoring and Laboratory Tests)

## 4.2 Recommended Dose and Dosage Adjustment

**Renal Insufficiency:** No dose adjustment is required for patients with mild, moderate or severe renal insufficiency (creatinine clearance 60-90 mL/min, 30-59 mL/min and < 30 mL/min respectively). There is very limited or no clinical experience with Victoza® in patients with end-stage renal disease; use of Victoza® in these patients is not recommended (see [7 WARNINGS AND PRECAUTIONS](#), Special Populations; and [10 CLINICAL PHARMACOLOGY](#), Special Populations and Conditions).

In the LEADER trial (see [14 CLINICAL TRIALS](#)), 3907 (41.8%) patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m<sup>2</sup>), 1934 (20.7%) patients had moderate renal impairment (eGFR 30 to 60 mL/min/1.73 m<sup>2</sup>) and 224 (2.4%) patients had severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup>) at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.

**Hepatic Insufficiency:** There is limited clinical experience in patients with mild, moderate or severe hepatic insufficiency. No dose adjustment is required for patients with hepatic impairment. (See [10 CLINICAL PHARMACOLOGY](#), Special Populations 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 difference in safety or efficacy were observed between these patients compared to younger patients, but greater sensitivity of older individuals cannot be ruled out.

In the LEADER trial, a total of 3493 (37.4%) of the patients were 65 to 74 years of age, 794 (8.5%) were 75 to 84 years of age, and 42 (0.4%) were 85 years of age or older at baseline. No overall difference in safety or efficacy was observed between these patients compared to younger patients (see [7 WARNINGS AND PRECAUTIONS](#), Special Populations; [8 ADVERSE REACTIONS](#), Clinical Trial Adverse Drug Reactions, Gastrointestinal adverse events; and [10 CLINICAL PHARMACOLOGY](#), Special Populations and Conditions).

**Pediatrics (≥ 10 years of age):** 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 may be increased to 1.2 mg once daily if additional glycemic control is required. Based on clinical response and after at least one week the dose may be increased to 1.8 mg once daily if additional glycemic

control is required. (See [7 WARNINGS AND PRECAUTIONS](#), Monitoring and Laboratory Tests)

No data are available for children below 10 years of age.

#### 4.4 Administration

Victoza<sup>®</sup> is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Injection sites should always be rotated within the same region in order to reduce the risk of cutaneous amyloidosis (See [8.5 Post-Market Adverse Reactions](#)). The injection site and timing can be changed if needed without dose adjustment.

#### 4.5 Missed Dose

If a dose of Victoza<sup>®</sup> 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.

### 5 OVERDOSAGE

From clinical trials and marketed use overdoses have been reported up to 40 times the recommended maintenance dose (72 mg). One case of a 10-fold overdose (18 mg daily) given for 7 months has been reported. All patients recovered without complications. The patients reported severe nausea, vomiting and diarrhea. Severe hypoglycemia has been observed.

In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored.

For management of a suspected drug overdose, contact your regional poison control centre.

### 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table – Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
subcutaneous	Injectable, 6 mg/mL	Disodium phosphate dihydrate, propylene glycol, phenol and water for injections.

Victoza<sup>®</sup> comes in a pre-filled disposable pen, comprising of a pen injector assembled with a cartridge (3 mL).

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 (carbon dioxide 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.

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).

**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).

## 7 WARNINGS AND PRECAUTIONS

### General

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® should not be administered intravenously or intramuscularly.

In children and adolescent with type 2 diabetes mellitus, concurrent use of Victoza® and prandial insulin has not been studied.

The Victoza® pen should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

### Carcinogenesis and Mutagenesis

#### *Risk of Thyroid C-Cell Tumours*

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice (see [16 NON-CLINICAL TOXICOLOGY](#)). Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether Victoza® will cause thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumours could not be confirmed by clinical or nonclinical studies.

Cases of thyroid C-cell hyperplasia have been reported in clinical trials (see [8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions](#)). The data are insufficient to establish or exclude a causal relationship between thyroid C-cell tumours and Victoza® in humans.

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

Victoza® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. The clinical value of routine monitoring of serum calcitonin has not been established.

### Cardiovascular

#### *Patients with recent MI or stroke, or severe congestive heart failure:*

In clinical trials of Victoza®, patients with acute myocardial infarction or stroke within 2 weeks of trial inclusion, and severe congestive heart failure (NYHA class IV) were not studied. Therefore, Victoza® should be used with caution in this population.



### *Increase in Heart Rate*

A 24 h time-averaged increase in mean heart rate of 7 to 8 bpm was reported with Victoza<sup>®</sup> treatment in a clinical trial in healthy volunteers undergoing serial ECG monitoring (see [10 CLINICAL PHARMACOLOGY](#), Cardiac Electrophysiology). In patients with diabetes, including patients with established and high risk for CV disease in the LEADER trial, a mean increase in heart rate from baseline of 2 to 4 beats per minute was observed with Victoza<sup>®</sup> in long-term clinical trials. The incidence of a composite endpoint for all tachyarrhythmia in pooled Phase 3a clinical trials in diabetic patients was higher for Victoza<sup>®</sup> than for placebo (see [8 ADVERSE REACTIONS](#), Clinical Trial Adverse Drug Reactions, Cardiovascular).

### *PR Interval Prolongation*

A prolongation of the mean PR interval of up to 10 ms was reported with Victoza<sup>®</sup> treatment in a clinical trial in healthy volunteers (see [10 CLINICAL PHARMACOLOGY](#), Cardiac Electrophysiology). In healthy volunteers and in patients with diabetes, the incidence of first degree atrioventricular (AV) block was higher with Victoza<sup>®</sup> than with placebo (see [10 CLINICAL PHARMACOLOGY](#), Cardiac Electrophysiology; [8 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 [9 DRUG INTERACTIONS](#)).

### **Driving and Operating Machinery**

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines in particular when Victoza<sup>®</sup> is used in combination with a sulphonylurea or insulin. Avoid driving or operating machinery if you feel dizzy.

### **Endocrine and Metabolism**

#### **Hypoglycemia**

Patients receiving Victoza<sup>®</sup> in combination with a sulphonylurea or insulin may have an increased risk of hypoglycemia (see [8 ADVERSE REACTIONS](#), Clinical Trial Adverse Reactions, Hypoglycemia). The risk of hypoglycemia can be lowered by reducing the dose of sulphonylurea or insulin (see [8 ADVERSE REACTIONS](#), Clinical Trial Adverse Reactions Hypoglycemia; [4 DOSAGE AND ADMINISTRATION](#), Dosing Considerations). Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when Victoza<sup>®</sup> is used in combination with a sulphonylurea or insulin.

In pediatric patients aged 10 years and above, the risk of hypoglycemia was higher with Victoza<sup>®</sup> in combination with metformin with or without basal insulin.

### **Gastrointestinal Disease**

The use of Victoza<sup>®</sup> is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhea (see [8 ADVERSE REACTIONS](#), Adverse Reaction Overview and Clinical Trial Adverse Drug Reactions, Gastrointestinal adverse events). The safety of Victoza<sup>®</sup> in subjects with inflammatory bowel disease and diabetic gastroparesis has not been studied. Victoza<sup>®</sup> should not be used in this population.

Events of delayed gastric emptying have been reported in the post-marketing database (see [8.5 Post-Market Adverse Reactions](#)).

## **Hepatic/Biliary/Pancreatic**

### *Hepatic Insufficiency*

There is limited clinical experience in patients with mild, moderate or severe hepatic insufficiency. (See [4 DOSAGE AND ADMINISTRATION](#), Recommended Dose and Dosage Adjustment, Hepatic insufficiency and [10 CLINICAL PHARMACOLOGY](#), Special Population and Conditions, Hepatic insufficiency).

### *Pancreatitis*

Based on spontaneous post-marketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza<sup>®</sup> (see [8 ADVERSE REACTIONS](#), Clinical Trial Adverse reactions, Pancreatitis). After initiation of Victoza<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> should not be restarted.

Victoza<sup>®</sup> has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on Victoza<sup>®</sup>.

### *Acute Gallbladder Disease*

In the LEADER trial, 3.1% of Victoza<sup>®</sup>-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

## **Immune**

### *Hypersensitivity Reactions*

There have been post-marketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza<sup>®</sup>. If a hypersensitivity reaction occurs, discontinue Victoza<sup>®</sup> and other suspect medications; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to Victoza<sup>®</sup> (see [2 CONTRAINDICATIONS](#)).

Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza<sup>®</sup>.

## **Monitoring and Laboratory Tests**

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

In adolescents and children aged 10 years and above, due to the higher risks of hypoglycemia in pediatric patients with type 2 diabetes, additional blood glucose monitoring is recommended to reduce the risk of hypoglycemia especially asymptomatic hypoglycemia when Victoza<sup>®</sup> is added to metformin with or without basal insulin initially.

Patients should be informed that a 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.

### **Renal Insufficiency**

There have been post-marketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza<sup>®</sup> treated patients (see [8.5 Post-Market Adverse Reactions](#)). Some of these events were reported in patients without known underlying renal disease.

Patients treated with Victoza<sup>®</sup> should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. Renal insufficiency has been reported, usually in association with nausea, vomiting, diarrhea or dehydration which may sometimes require hemodialysis. Use caution in patients who experience dehydration (see [8 ADVERSE REACTIONS](#)).

### **Thyroid Disease**

Thyroid adverse events, such as goitre, have been reported in clinical trials, in particular in patients with pre-existing thyroid disease. Victoza<sup>®</sup> should therefore be used with caution in these patients.

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

There have been no studies conducted in pregnant women with Victoza<sup>®</sup>. Studies in animals have shown reproductive and developmental toxicity, including teratogenicity, at or above 0.8 times the clinical exposure (see [16 NON-CLINICAL TOXICOLOGY](#)).

Victoza<sup>®</sup> should not be used during pregnancy (see [2 CONTRAINDICATIONS](#)). If a patient wishes to become pregnant, or pregnancy occurs, treatment with liraglutide should be discontinued.

### **7.1.2 Breast-feeding**

It is not known whether Victoza<sup>®</sup> is excreted in human milk. In lactating animals Victoza<sup>®</sup> was excreted unchanged in milk. Because many drugs are excreted in human milk and because of the potential for tumourigenicity shown for liraglutide in animal studies, women who are nursing should discontinue Victoza<sup>®</sup> treatment (see [16 NON-CLINICAL TOXICOLOGY](#)).

### **7.1.3 Pediatrics**

**Pediatrics (≥ 10 years of age):** Victoza<sup>®</sup> can be used as an add-on to metformin with or without basal insulin in adolescents and children aged 10 years and above. The risk of hypoglycemia is higher in pediatric patients 10 years and above in combination with metformin with or without basal insulin. The safety and efficacy of Victoza<sup>®</sup> have not been established in children under 10 years of age.

#### 7.1.4 Geriatrics

**Geriatrics (>65 years of age):** In the Victoza® treatment arm of the glycemic control 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 safety and efficacy were observed between these patients and younger patients, but greater sensitivity of older individuals cannot be ruled out (see [8 ADVERSE REACTIONS](#), Clinical Trial Adverse Reactions, Gastrointestinal adverse events and [4 DOSAGE AND ADMINISTRATION](#), Recommended Dose and Dosage Adjustment, Geriatrics and [10 CLINICAL PHARMACOLOGY](#), Special Populations and Conditions, Geriatrics (>65 years of age)).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

A total of 12516 patients with type 2 diabetes have been treated with Victoza®, alone or in combination with other antidiabetic agents, including basal insulin and pre-mix insulin, in glycemic control and cardiovascular outcome trials.

In glycemic control trials that were 26 weeks or longer in duration, the most common adverse drug reactions were nausea and diarrhea. 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 (see [8 ADVERSE REACTIONS](#), Clinical Trial Adverse Reactions, Cardiovascular). Discontinuation of treatment due to adverse events was more common with Victoza® (7.8%) as compared to comparator treatments (3.4%). The difference was driven by withdrawals due to gastrointestinal disorders with 2.8% and 1.5% of Victoza® treated patients discontinuing due to nausea and vomiting, respectively.

### 8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse 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 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 [14 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)
System Organ Class Preferred Term	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<b>Safety Analysis Set</b>	242	240	242	121	242	230	114	232
<b>Blood and Lymphatic System Disorders</b>								
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)
<b>Ear and Labyrinth Disorders</b>								
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)
<b>Eye Disorders</b>								
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)
<b>Injury, Poisoning and Procedural Complications</b>								
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)
<b>Gastrointestinal Disorders</b>								
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)
<b>General Disorders and Administration Site Conditions</b>								

	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)
System Organ Class Preferred Term	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
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)
<b>Hepatobiliary Disorders</b>								
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)
<b>Immune System Disorders</b>								
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)
<b>Infections and Infestations</b>								
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)
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)
<b>Investigations</b>								
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)
<b>Metabolism and Nutrition Disorders</b>								
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)

	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)
System Organ Class Preferred Term	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
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)
<b>Musculoskeletal and Connective Tissue Disorders</b>								
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)
<b>Nervous System Disorders</b>								
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)
<b>Psychiatric Disorders</b>								
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)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>								
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)
<b>Skin and Subcutaneous Tissue Disorders</b>								
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)
<b>Vascular Disorders</b>								
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<sup>®</sup> was with add on metformin combination therapy (see [14 CLINICAL TRIALS](#)).

**Table 2 Treatment-Emergent Adverse Events in trial 1860**

	<b>Victoza<sup>®</sup> 1.2 mg + metformin N= 221</b>	<b>Victoza<sup>®</sup> 1.8 mg + metformin N= 218</b>	<b>Sitagliptin 100 mg + metformin N= 219</b>
<b>System Organ Class Preferred Term</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
<b>Gastrointestinal Disorders</b>			
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)
<b>Infections and Infestations</b>			
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 (0.0)	3 (1.4)
<b>Nervous System Disorders</b>			
Headache	20 (9.0)	25 (11.5)	22 (10.0)
Dizziness	8 (3.6)	9 (4.1)	6 (2.7)
Diabetic neuropathy	1 (0.5)	3 (1.4)	1 (0.5)
Hypoaesthesia	2 (0.9)	0 (0.0)	3 (1.4)
<b>Musculoskeletal and connective tissue disorders</b>			
Back pain	8 (3.6)	8 (3.7)	10 (4.6)
Muscle spasms	3 (1.4)	4 (1.8)	0 (0.0)
Myalgia	0 (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 (0.0)
<b>General disorders and administration site conditions</b>			
Fatigue	7 (3.2)	9 (4.1)	1 (0.5)
Injection site hematoma	5 (2.3)	6 (2.8)	0 (0.0)
<b>Metabolism and Nutrition Disorders</b>			
Decreased appetite	7 (3.2)	12 (5.5)	2 (0.9)



	<b>Victoza® 1.2 mg + metformin N= 221</b>	<b>Victoza® 1.8 mg + metformin N= 218</b>	<b>Sitagliptin 100 mg + metformin N= 219</b>
<b>System Organ Class</b> Preferred Term	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Anorexia	8 (3.6)	6 (2.8)	1 (0.5)
Dyslipidaemia	4 (1.8)	1 (0.5)	4 (1.8)
Hyperglycemia	0 (0.0)	1 (0.5)	3 (1.4)
Hyperlipidemia	0 (0.0)	1 (0.5)	3 (1.4)
<b>Investigations</b>			
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 (0.0)
<b>Respiratory, thoracic and mediastinal disorders</b>			
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 (0.0)	4 (1.8)
<b>Injury, Poisoning and procedural complications</b>			
Contusion	3 (1.4)	3 (1.4)	3 (1.4)
<b>Skin and subcutaneous tissue disorders</b>			
Rash	4 (1.8)	3 (1.4)	2 (0.9)
Hyperhidrosis	3 (1.4)	1 (0.5)	2 (0.9)
<b>Vascular disorders</b>			
Hypertension	5 (2.3)	10 (4.6)	5 (2.3)
<b>Cardiac Disorders</b>			
Palpitations	3 (1.4)	0 (0.0)	0 (0.0)
<b>Eye Disorders</b>			
Diabetic retinopathy	3 (1.4)	2 (0.9)	1 (0.5)
<b>Psychiatric disorders</b>			
Insomnia	3 (1.4)	2 (0.9)	1 (0.5)
<b>Endocrine disorders</b>			
Goitre	2 (0.9)	1 (0.5)	4 (1.8)

**Table 3** provides a listing of the treatment-emergent adverse events with frequency  $\geq 1\%$  from the 52-week trial NN2211-1842 (main and extension) regardless of investigator assessment of causality. NN2211-1842 is the controlled clinical study of Victoza® 1.8 mg and intensification with insulin detemir (see [14 CLINICAL TRIALS](#)).

**Table 3 Treatment-Emergent Adverse Events in trial 1842 (main and extension)  
(Adverse events with frequency  $\geq 1\%$ )**

	<b>Victoza® 1.8 mg + metformin N= 159</b>	<b>Levemir® (insulin detemir) + Victoza® 1.8 mg N= 163</b>	<b>Non-randomized N= 499</b>
<b>System Organ Class</b> Preferred Term	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
<b>Infections and infestations</b>			
Nasopharyngitis	32 (20.1)	23 (14.1)	48 (9.6)
Upper Respiratory Tract Infection	6 (3.8)	8 (4.9)	20 (4.0)
Influenza	6 (3.8)	5 (3.1)	11 (2.2)
Bronchitis	1 (0.6)	6 (3.7)	6 (1.2)
Gastroenteritis Viral	2 (1.3)	5 (3.1)	5 (1.0)
Urinary Tract Infection	2 (1.3)	4 (2.5)	11 (2.2)

	<b>Victoza® 1.8 mg + metformin N= 159</b>	<b>Levemir® (insulin detemir) + Victoza® 1.8 mg N= 163</b>	<b>Non-randomized N= 499</b>
<b>System Organ Class Preferred Term</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Lower Respiratory Tract Infection	0 (0.0)	3 (1.8)	0 (0.0)
Tooth Infection	1 (0.6)	3 (1.8)	3 (0.6)
Sinusitis	1 (0.6)	1 (0.6)	8 (1.6)
Gastroenteritis	2 (1.3)	2 (1.2)	5 (1.0)
Viral Upper Respiratory Tract Infection	2 (1.3)	1 (0.6)	0 (0.0)
Sialoadentis	0 (0.0)	2 (1.2)	0 (0.0)
Tooth Abscess	0 (0.0)	2 (1.2)	3 (0.6)
Viral Infection	1 (0.6)	2 (1.2)	3 (0.6)
Cystitis	1 (0.6)	0 (0.0)	5 (1.0)
<b>Gastrointestinal disorders</b>			
Diarrhoea	12 (7.5)	19 (11.7)	21 (4.2)
Nausea	10 (6.3)	6 (3.7)	17 (3.4)
Vomiting	5 (3.1)	8 (4.9)	15 (3.0)
Abdominal Pain Upper	3 (1.9)	6 (3.7)	4 (0.8)
Constipation	4 (2.5)	5 (3.1)	8 (1.6)
Dyspepsia	3 (1.9)	5 (3.1)	9 (1.8)
Haemorrhoids	0 (0.0)	4 (2.5)	0 (0.0)
Toothache	1 (0.6)	4 (2.5)	8 (1.6)
Abdominal Pain	3 (1.9)	2 (1.2)	5 (1.0)
Abdominal Distension	0 (0.0)	3 (1.8)	3 (0.6)
Abdominal Discomfort	2 (1.3)	1 (0.6)	2 (0.4)
Gastroesophageal Reflux Disease	2 (1.3)	1 (0.6)	2 (0.4)
Abdominal Hernia	1 (0.6)	2 (1.2)	0 (0.0)
<b>Investigations</b>			
Lipase increased	5 (3.1)	18 (11.0)	20 (4.0)
Blood Amylase Increased	2 (1.3)	4 (2.5)	7 (1.4)
Blood Creatine Phosphokinase Increased	3 (1.9)	2 (1.2)	4 (0.8)
White Blood Cell Count Increased	0 (0.0)	3 (1.8)	1 (0.2)
Blood Urea Increased	2 (1.3)	0 (0.0)	0 (0.0)
Alanine Aminotransferase Increased	0 (0.0)	2 (1.2)	1 (0.2)
Blood Calcitonin Increased	0 (0.0)	0 (0.0)	6 (1.2)
<b>General disorders and administration site conditions</b>			
Fatigue	3 (1.9)	6 (3.7)	2 (0.4)
Injection site hematoma	3 (1.9)	4 (2.5)	5 (1.0)
Injection site reaction	0 (0.0)	4 (2.5)	0 (0.0)
Pyrexia	2 (1.3)	3 (1.8)	0 (0.0)
Influenza like illness	1 (0.6)	2 (1.2)	5 (1.0)
Malaise	1 (0.6)	2 (1.2)	1 (0.2)
<b>Injury, poisoning and procedural complications</b>			
Incorrect Dose Administered	1 (0.6)	4 (2.5)	1 (0.2)
Fall	2 (1.3)	2 (1.2)	5 (1.0)
Skin Laceration	2 (1.3)	0 (0.0)	1 (0.2)
<b>Nervous system disorders</b>			
Headache	13 (8.2)	10 (6.1)	28 (5.6)
Dizziness	2 (1.3)	3 (1.8)	4 (0.8)
Lethargy	1 (0.6)	3 (1.8)	
<b>Skin and subcutaneous tissue disorders</b>			

	<b>Victoza® 1.8 mg + metformin</b> N= 159	<b>Levemir® (insulin detemir) + Victoza® 1.8 mg</b> N= 163	<b>Non-randomized</b> N= 499
<b>System Organ Class</b> Preferred Term	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Pruritus	4 (2.5)	3 (1.8)	2 (0.4)
Rash	3 (1.9)	3 (1.8)	4 (0.8)
Alopecia	2 (1.3)	3 (1.8)	1 (0.2)
Hyperhidrosis	0 (0.0)	3 (1.8)	2 (0.4)
Eczema	0 (0.0)	0 (0.0)	5 (1.0)
<b>Respiratory, thoracic and mediastinal disorders</b>			
Oropharyngeal Pain	7 (4.4)	4 (2.5)	7 (1.4)
Cough	3 (1.9)	5 (3.1)	4 (0.8)
Dyspnoea	2 (1.3)	0 (0.0)	6 (1.2)
Epistaxis	2 (1.3)	0 (0.0)	3 (0.6)
Asthma	0 (0.0)	2 (1.2)	0 (0.0)
Dysphonia	0 (0.0)	2 (1.2)	0 (0.0)
Nasal Congestion	1 (0.6)	2 (1.2)	0 (0.0)
<b>Musculoskeletal and connective tissue disorders</b>			
Back Pain	5 (3.1)	3 (1.8)	6 (1.2)
Arthralgia	3 (1.9)	3 (1.8)	7 (1.4)
Pain in Extremity	2 (1.3)	2 (1.2)	3 (0.6)
Myalgia	2 (1.3)	2 (1.2)	1 (0.2)
<b>Psychiatric disorders</b>			
Depression	2 (1.3)	3 (1.8)	6 (1.2)
Insomnia	2 (1.3)	3 (1.8)	7 (1.4)
Anxiety	1 (0.6)	2 (1.2)	3 (0.6)
Stress	0 (0.0)	2 (1.2)	1 (0.2)
<b>Eye disorders</b>			
Diabetic Retinopathy	1 (0.6)	2 (1.2)	4 (0.8)
<b>Vascular disorders</b>			
Hypertension	3 (1.9)	2 (1.2)	13 (2.6)
<b>Metabolism and nutrition disorders</b>			
Decreased Appetite	1 (0.6)	2 (1.2)	4 (0.8)
<b>Reproductive system and breast disorders</b>			
Erectile dysfunction	1 (0.6)	2 (1.2)	3 (0.6)
<b>Cardiac disorders</b>			
Atrioventricular Block First Degree	0 (0.0)	2 (1.2)	2 (0.4)
<b>Ear and labyrinth disorders</b>			
Ear Pain	3 (1.9)	1 (0.6)	1 (0.2)
Tinnitus	2 (1.3)	0 (0.0)	1 (0.2)
<b>Hepatobiliary disorders</b>			
Hepatic Steatosis	0 (0.0)	2 (1.2)	5 (1.0)
<b>Blood and lymphatic system disorders</b>			
Anaemia	1 (0.6)	2 (1.2)	2 (0.4)

**Table 4** provides a listing of the treatment-emergent adverse events, regardless of investigator assessment of causality, with a frequency > 5% from a 52-week active-controlled monotherapy trial (Trial 1573; LEAD™ 3) with a mean duration of exposure of 289, 280, and 274 days, in the Victoza® 1.8 mg, Victoza® 1.2 mg and glimepiride 8 mg treatment groups, respectively (see [14 CLINICAL TRIALS](#)).

**Table 4 Treatment Emergent Adverse Events (> 5%) by System Organ Class and Preferred Term Safety Population (1573)**

	Liraglutide 1.8 mg N=246	Liraglutide 1.2 mg N=251	Glimepiride N=248
System Organ Class Preferred Term	N (%)	N (%)	N (%)
<b>Gastrointestinal Disorders</b>	126 (51.2)	122 (48.6)	64 (25.8)
Constipation	28 (11.4)	21 (8.4)	12 (4.8)
Diarrhea	46 (18.7)	39 (15.5)	22 (8.9)
Flatulence	13 (5.3)	4 (1.6)	4 (1.6)
Nausea	72 (29.3)	69 (27.5)	21 (8.5)
Vomiting	23 (9.3)	31 (12.4)	9 (3.6)
<b>General Disorders and Administration Site Conditions</b>	41 (16.7)	33 (13.1)	37 (14.9)
<b>Infections and Infestations</b>	102 (41.5)	119 (47.4)	90 (36.3)
Influenza	20 (8.1)	17 (6.8)	9 (3.6)
Nasopharyngitis	9 (3.7)	17 (6.8)	13 (5.2)
Sinusitis	13 (5.3)	15 (6.0)	15 (6.0)
Upper Respiratory Tract Infection	24 (9.8)	23 (9.2)	14 (5.6)
Urinary Tract Infection	10 (4.1)	20 (8.0)	10 (4.0)
<b>Injury, Poisoning and Procedural Complications</b>	24 (9.8)	22 (8.8)	29 (11.7)
<b>Investigations</b>	23 (9.3)	16 (6.4)	18 (7.3)
<b>Metabolism and Nutrition Disorders</b>	35 (14.2)	38 (15.1)	28 (11.3)
<b>Musculoskeletal and Connective Tissue Disorders</b>	46 (18.7)	48 (19.1)	38 (15.3)
Back Pain	11 (4.5)	14 (5.6)	11 (4.4)
<b>Nervous System Disorders</b>	49 (19.9)	56 (22.3)	55 (22.2)
Dizziness	16 (6.5)	13 (5.2)	13 (5.2)
Headache	18 (7.3)	27 (10.8)	23 (9.3)
<b>Psychiatric Disorders</b>	21 (8.5)	21 (8.4)	14 (5.6)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	28 (11.4)	21 (8.4)	28 (11.3)
<b>Skin and Subcutaneous Tissue Disorders</b>	24 (9.8)	23 (9.2)	17 (6.9)
<b>Vascular Disorders</b>	15 (6.1)	11 (4.4)	17 (6.9)
Hypertension	8 (3.3)	7 (2.8)	15 (6.0)

**Table 5 Adverse Events (≥1%) by System Organ Class and Preferred Term (LEADER EX2211-3748)**

	Liraglutide N=4668 (%)	Placebo N=4672 (%)
System Organ Class Preferred Term	N (%)	N (%)
<b>Gastrointestinal Disorders</b>		
Diarrhea	89 (1.9)	31 (0.7)
Nausea	175 (3.7)	44 (0.9)
Vomiting	97 (2.1)	24 (0.5)
<b>Investigations</b>		
Lipase increased	47 (1.0)	21 (0.4)
<b>Hepatobiliary disorders</b>		
Cholecystitis acute*	50 (1.1)	32 (0.7)
Cholelithiasis	68 (1.5)	50 (1.1)

\* Combination of the two PTs cholecystitis and cholecystitis acute

\*\* Table is limited to those adverse events for which a meaningful difference in rate was observed.

**Medullary thyroid cancer:** see ([7 WARNINGS AND PRECAUTIONS](#), **Serious Warnings and Precautions**) Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the glycemic control trials, adjusted mean serum calcitonin concentrations were higher in Victoza<sup>®</sup>-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza<sup>®</sup>-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown.

**Papillary thyroid cancer:** In the completed trials the rates of papillary thyroid carcinoma were 1.5 and 0.5 (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).

**Thyroid disease:** Thyroid adverse events, such as goitre, have been reported in clinical trials, in particular in patients with pre-existing thyroid disease. Victoza<sup>®</sup> should therefore be used with caution in these patients.

**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<sup>®</sup> + metformin to sitagliptin + metformin (Trial NN2211-1860) over 52 weeks, considering all adverse events in the system organ class “neoplasms benign, malignant and unspecified (including 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.

In the LEADER trial, neoplasms were evaluated based on events confirmed by adjudication. The incidences of EAC confirmed overall neoplasms (liraglutide: 10.1%, 3.3 events per 100 patient years of observation; placebo: 9.0%, 3.0 events per 100 patient years of observation), benign neoplasms (liraglutide: 3.6%, 1.0 events per 100 patient years of observation; placebo: 3.1%, 1.0 events per 100 patient years of observation), and malignant neoplasms (liraglutide: 6.3%, 2.0 events per 100 patient years of observation; placebo: 6.0%, 1.8 events per 100 patient years of observation) were comparable between the treatment groups.

**Cardiovascular:** Adverse events identified using a composite endpoint for all tachyarrhythmias in pooled intermediate and long-term trials (Phase 3a LEAD™), 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 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 (Phase 3a LEAD™), 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 [7 WARNINGS AND PRECAUTIONS](#), Special Populations, Cardiovascular – patients with recent MI, unstable angina and congestive heart failure; [9.4 Drug-Drug Interactions](#), Drugs that increase the Heart Rate and Drugs that cause PR interval prolongation; [10 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.

**Increase in Heart Rate:** In patients with diabetes, a mean increase in heart rate from baseline of 2 to 3 beats per minute was observed with Victoza® in long-term clinical trials including LEADER. In the LEADER trial, no long-term adverse clinical impact of increased heart rate on the risk of cardiovascular events was observed and the proportion of patients with adverse events related to arrhythmias, was similar between Victoza® and placebo.

**Blood Pressure:** In the LEADER trial, systolic blood pressure was reduced with Victoza<sup>®</sup> vs placebo (-1.4 mmHg vs -0.2 mmHg; ETD: -1.20 mmHg [-1.92; -0.48]), whereas diastolic blood pressure decreased less with liraglutide vs placebo (-0.8 mmHg vs -1.4 mmHg, respectively, ETD: 0.59 [0.19; 0.99]) after 36 months.

**Pancreatitis:** In clinical trials of Victoza<sup>®</sup> there were 13 cases of pancreatitis among Victoza<sup>®</sup>-treated patients and 1 case among comparator-treated patients (2.4 vs. 0.5 cases per 1000 subject-years). Nine cases with Victoza<sup>®</sup> were reported as acute pancreatitis and 4 cases with Victoza<sup>®</sup> were reported as chronic pancreatitis. All events were serious except for one case of chronic pancreatitis in a patient treated with Victoza<sup>®</sup>. One fatal case of pancreatitis with necrosis was observed, in a Victoza<sup>®</sup>-treated patient. (see [7 WARNINGS AND PRECAUTIONS](#), Pancreatitis).

In the LEADER trial, acute pancreatitis was confirmed by adjudication in 18 Victoza<sup>®</sup>-treated patients (1.1 cases per 1000 patient years of observation) and 23 placebo-treated patients (1.7 cases per 1000 patient years of observation), both on a background of standard of care. In addition, there were no cases of chronic pancreatitis confirmed by adjudication in Victoza<sup>®</sup>-treated patients and 2 cases in placebo-treated patients. The LEADER trial enrolled 267 patients with a medical history of acute or chronic pancreatitis; of these 2 out of 147 (1.4%) in the Victoza<sup>®</sup> group and 6 out of 120 (5.0%) in the placebo group had a new event of acute pancreatitis confirmed by adjudication (see [7 WARNINGS AND PRECAUTIONS](#), Pancreatitis).

**Pancreatic enzymes:** Victoza<sup>®</sup> is associated with mean increases from baseline in pancreatic enzymes, lipase and amylase, of up to 38% and 21%, respectively (see [7 WARNINGS AND PRECAUTIONS](#), Pancreatitis). In the clinical trial program elevations of serum lipase and amylase were not predictive of pancreatitis. The clinical significance of elevated lipase and amylase values is unknown.

**Hypoglycemia:** Severe hypoglycemic episodes in the long-term phase 3a trials were rare (9 episodes in 8 subjects). In a phase 3b clinical trial, comparing Victoza<sup>®</sup> + metformin to sitagliptin + metformin (Trial NN2211-1860) one major episode of hypoglycemia was reported in a Victoza<sup>®</sup>-treated patient. When insulin detemir was added to Victoza<sup>®</sup> 1.8 mg and metformin, no severe hypoglycemic event (patient not able to self-treat) was observed.

Six of these severe episodes were reported when liraglutide was used in combination with glimepiride, thus when liraglutide was used in combination with a sulfonylurea or insulin, an increased rate of hypoglycemia was observed (see [7 WARNINGS AND PRECAUTIONS](#), Endocrine and Metabolism, Hypoglycemia and [4 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 1.8 mg + 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.

Severe hypoglycemic episodes were only reported in the liraglutide group where 6 events were reported in 5 subjects. Rates of severe 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 1.8 mg + 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.

In trial 1842 when insulin was added to Victoza® 1.8 mg and metformin no severe hypoglycemic event was observed. The rate of minor hypoglycemic episodes (patient able to self-treat) during the 26-week main trial and 26-week extension period was low across all treatment groups, at 0.23, 0.03 and 0.12 events per subject years for insulin detemir + liraglutide 1.8 mg + metformin, liraglutide 1.8 mg + metformin and non-randomized liraglutide 1.8 mg + metformin, respectively. The incidence of minor hypoglycemic episodes was statistically significantly higher in the detemir + liraglutide 1.8 mg + metformin treatment group than in the liraglutide 1.8 mg + metformin group ( $p=0.0011$ ), when excluding an outlier in the liraglutide 1.8 mg + metformin group with a medical history of frequent hypoglycemia.

In the LEADER trial, severe and confirmed hypoglycemia episodes were primarily seen in subjects treated with insulin, sulfonylurea (SU)/glinides or a combination of these at baseline (i.e., 90% of subjects with severe hypoglycemia in either treatment group were on insulin and/or SU/glinides at baseline). Severe episodes of hypoglycemia are characterized in **Table 6** below. The majority of hypoglycemia events were considered “symptomatic episodes”.

**Table 6 Characteristics of severe hypoglycemic episodes – summary – full analysis set**

	Liraglutide			Placebo		
	N (%)	E	R	N	E	R
Number of Subjects	4668			4672		
PYO	17341			17282		
Severe hypoglycemia episodes	114 (2.44)	17	1.0	153 (3.27)	25	1.4
Episodes with seizure or coma	21 (0.4)	26	0.1	18 (0.4)	18	0.1
Symptomatic episodes	111 (2.4)	17	0.9	145 (3.1)	24	1.3
Episodes related to exercise	9 (0.2)	9	0.0	11 (0.2)	13	0.0
Registered as an SAE	55 (1.2)	70	0.4	88 (1.9)	11	0.6

N: Number of subjects, %: Proportion of subjects, PYO: Patient years of observation, E: Number of events, R: Event rate per 100 patient years of observation, Severe: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, SAE: Serious adverse event, SU: Sulfonylureas

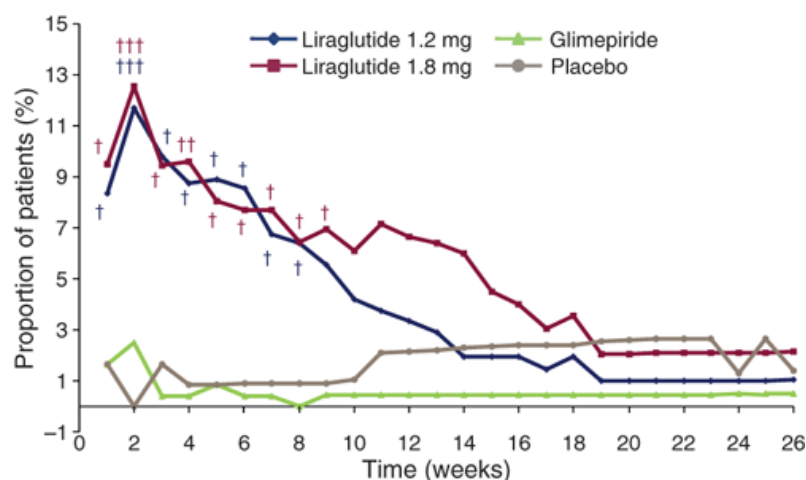


Serious adverse event as listed by the investigator in relation to the hypoglycemic episode.

**Gastrointestinal adverse events:** In pooled long term clinical trials, gastrointestinal adverse events were reported in 41% of Victoza<sup>®</sup> treated patients and were dose related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza<sup>®</sup> treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. Approximately 13% of Victoza<sup>®</sup> 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**). Withdrawals due to gastrointestinal adverse events occurred in 5.0% of Victoza<sup>®</sup> 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 1.2 mg + metformin, liraglutide 1.8 mg + metformin and sitagliptin + metformin groups respectively.

In trial NN2211-1842, 14.1%, 18.9% and 24.2% of patients reported nausea during the first 12 weeks of treatment in the insulin detemir + liraglutide 1.8 mg + metformin, liraglutide 1.8 mg + metformin and the non-randomized liraglutide 1.8 mg + metformin groups, respectively. During the subsequent 52 weeks of treatment, 2.5%, 1.9% and 3.6% of patients reported nausea in the insulin detemir + liraglutide 1.8 mg + metformin, liraglutide 1.8 mg + metformin and non-randomized liraglutide 1.8 mg + metformin groups, respectively. In total, 8.6% (N=85) of patients withdrew from the trial due to gastrointestinal adverse events.

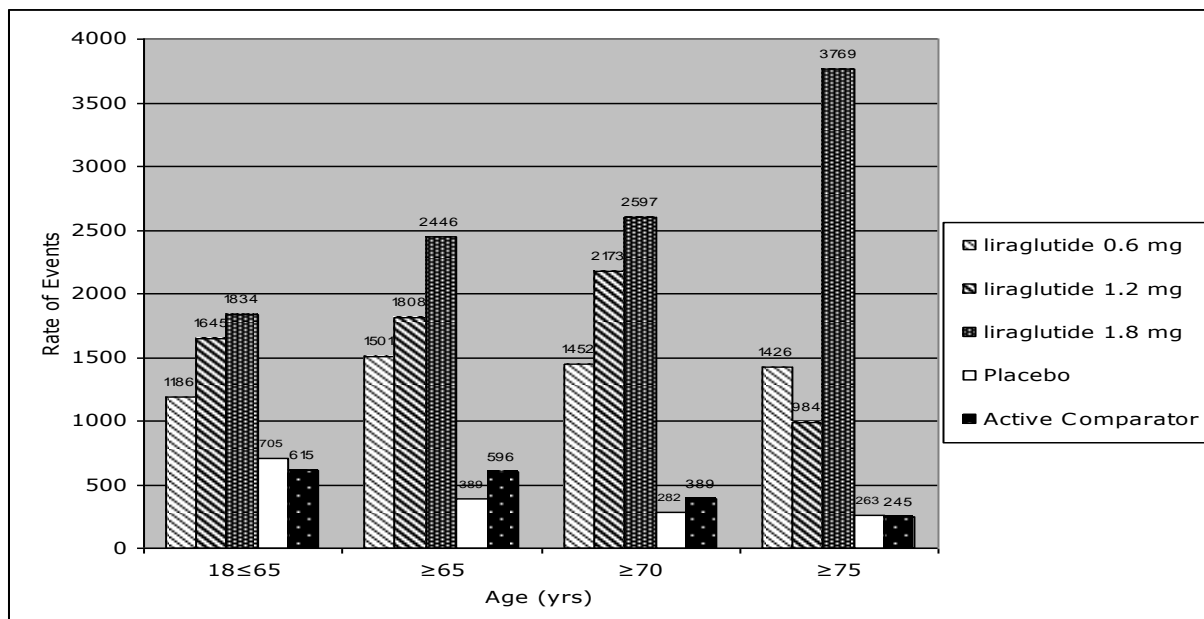


**Figure 1 Observed proportion of patients experiencing nausea by treatment over time in LEAD<sup>™</sup>-2 †††p<0.0001, ††p<0.01, † p<0.5 vs. placebo.**

The rate of gastrointestinal disorders in Victoza<sup>®</sup> treated subjects increased with age, especially at the 1.8 mg dose of Victoza<sup>®</sup> (see also [1 INDICATIONS](#), Geriatrics (>65 years of age). [7 WARNINGS AND PRECAUTIONS](#), Special Populations, Gastrointestinal disease; [4 DOSAGE AND ADMINISTRATION](#), Dosing considerations; [10 CLINICAL PHARMACOLOGY](#), Pharmacodynamics, Gastric emptying)

Patients with mild, moderate and severe renal insufficiency (creatinine clearance 60-90 mL/min, 30–59 mL/min and < 30 mL/min respectively) may experience more gastrointestinal effects

when treated with liraglutide.



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

**Cholelithiasis and cholecystitis:** In glycemic control trials of Victoza<sup>®</sup>, the incidence of cholelithiasis was 0.3% in both Victoza<sup>®</sup>-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both Victoza<sup>®</sup>-treated and placebo-treated patients.

In the LEADER trial, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in Victoza<sup>®</sup>-treated and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in Victoza<sup>®</sup>-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients.

**Immunogenicity:** Consistent with the potentially immunogenic properties and peptide pharmaceuticals, patients treated with Victoza<sup>®</sup> may develop anti-liraglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to liraglutide cannot be directly compared with the incidence of antibodies of other products.

Approximately 50 – 70% of Victoza<sup>®</sup>-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza<sup>®</sup>-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza<sup>®</sup>-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the

Victoza<sup>®</sup>-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies 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 the Victoza<sup>®</sup>-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the Victoza<sup>®</sup>-treated patients in the double-blind 26-week add-on combination therapy trials.

Antibody formation was not associated with reduced efficacy of Victoza<sup>®</sup> when comparing mean HbA<sub>1c</sub> 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 HbA<sub>1c</sub> with Victoza<sup>®</sup> treatment.

In five double-blind glycemic control trials of Victoza<sup>®</sup>, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza<sup>®</sup>-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza<sup>®</sup>-treated patients. 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.

In the LEADER trial, anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) Victoza<sup>®</sup>-treated patients with antibody measurement.

In a clinical trial with Victoza<sup>®</sup>-treated pediatric patients aged 10-17 years (See [14 CLINICAL TRIALS](#), ELLIPSE<sup>™</sup>), anti-liraglutide antibodies were detected in 1 (1.5%) subject at week 26 and 5 (8.5%) subjects at week 53. None of the 5 subjects had antibodies cross-reactive to native GLP-1 or had neutralizing antibodies.

**Injection site reactions:** Overall injection site reactions have been reported in approximately 2% of subjects receiving Victoza<sup>®</sup> 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<sup>®</sup> + metformin to sitagliptin + metformin (Trial NN2211-1860), overall injection site reactions were reported in 3% of patients receiving Victoza<sup>®</sup>, 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.

Less than 0.2% of Victoza<sup>®</sup>-treated patients discontinued due to injection site reactions. None of these patients were tested positive for liraglutide antibodies.

### 8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

In adolescents and children aged 10 years and above the frequency, type and severity of adverse reactions, other than minor hypoglycaemic episodes, were comparable to that observed in the adult population.

Rate of minor hypoglycemic episodes was higher with liraglutide compared to placebo. No severe hypoglycemic episodes occurred in the liraglutide treatment group.

**Table 7 Minor hypoglycemic episodes in pediatric subjects in trial 3659 and adult subjects in trial 1842 during the 52-week treatment period**

Trial	Treatment Arm	Minor Hypoglycemic Episodes	
		%	Rate
Trial 3659 A 26-week, double-blind, randomized, parallel group, placebo controlled multi-center trial followed by a 26-week open-label extension in pediatric patients with type 2 diabetes aged 10 years and above.	Liraglutide + Metformin + Insulin	40.0	1.24
	Placebo + Metformin + Insulin	13.3	0.52
	Liraglutide + Metformin	14.8	0.17
	Placebo + Metformin	5.1	0.09
Trial 1842 Multicentre, 26-week, randomized, open-label, parallel-group, multinational trial with a 26-week extension in adult patients with type 2 diabetes	Insulin detemir + Liraglutide 1.8 mg + metformin	-	0.23
	Liraglutide 1.8 mg + metformin	-	0.03
	Non-randomized Liraglutide 1.8 mg + Metformin (for 26-week extension)	-	0.12

### 8.3 Less Common Clinical Trial Adverse Reactions

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

**Eye Disorders:** Cataract

**Gastrointestinal Disorders:** Appendicitis Perforated, Gastritis, Inguinal Hernia, Pancreatitis,

**Immune System Disorders:** Anaphylactic reactions

**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 Protrusion,

**Nervous System Disorders:** Cerebrovascular Accident, Syncope

**Metabolism and Nutrition Disorders:** Dehydration, Hypoglycemia

**Renal and Urinary Disorders:** Renal impairment, Acute Renal failure

**Skin and Subcutaneous Tissue Disorder:** Pruritus

**Respiratory, Thoracic and Mediastinal Disorders:** Pulmonary Embolism

### 8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been reported during post-approval use of

Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Dehydration resulting from nausea, vomiting and diarrhea.
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis.
- Angioedema and anaphylactic reactions.
- Allergic reactions: rash and pruritus.
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death
- Medullary thyroid carcinoma.
- Hepatobiliary disorders: elevation of liver enzymes, hyperbilirubinemia, cholestasis, hepatitis
- Skin and subcutaneous tissue disorders: Cutaneous amyloidosis.
- Nervous system disorders: dysgeusia, dizziness.
- Gastrointestinal: delayed gastric emptying, ileus.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

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

### 9.4 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. Few patients treated with liraglutide reported at least 1 episode of severe diarrhea. Diarrhea may affect the absorption of concomitant oral medicinal products. Caution should be exercised when oral medications are concomitantly administered with Victoza®.

No drug-drug interaction studies have been performed in pediatric patients.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

### **Table 8 Established or Potential Drug-Drug Interactions**

Liraglutide	Source of Evidence	Effect	Clinical comment
Acetaminophen	CT	liraglutide did not change the overall exposure of acetaminophen following a single dose of 1 000 mg. Acetaminophen C <sub>max</sub> was decreased by 31% and median t <sub>max</sub> was delayed up to 15 min.	No dose adjustment for concomitant use of acetaminophen is required
Atorvastatin	CT	liraglutide did not change the overall exposure of atorvastatin to a clinical relevant degree following single dose administration of atorvastatin 40 mg. Atorvastatin C <sub>max</sub> was decreased by 38% and median t <sub>max</sub> was delayed from 1 h to 3 h with liraglutide.	no dose adjustment of atorvastatin is required when given with liraglutide
Griseofulvin	CT	Liraglutide did not change the overall exposure of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin C <sub>max</sub> increased by 37% while median t <sub>max</sub> did not change.	Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

Digoxin	CT	A single dose administration of digoxin 1 mg with liraglutide resulted in a reduction of digoxin AUC by 16%; $C_{max}$ decreased by 31%. Digoxin median ( $t_{max}$ ) was delayed from 1 h to 1.5 h.	No dose adjustment of digoxin is required based on these results.
Lisinopril	CT	A single dose administration of lisinopril 20 mg with Victoza <sup>®</sup> 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 Victoza <sup>®</sup> .	No dose adjustment of lisinopril is required based on these results.
Oral contra ceptiv es	CT	liraglutide 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 Victoza <sup>®</sup> for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel.	The contraceptive effect is therefore anticipated to be unaffected when co-administered with Victoza <sup>®</sup>

Warfarin and other coumarin derivatives	T	A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded	Upon initiation of Victoza® treatment in patients on warfarin or other coumarin derivatives, more frequent monitoring of international normalised ratio (INR) is recommended.
Combination with Insulin	CT	No pharmacokinetic or pharmacodynamic interactions were observed	No PK or PD interactions were observed between liraglutide and insulin detemir when administering a single dose of insulin detemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### Drugs that Increase Heart Rate

Victoza® causes an increase in heart rate (see [10 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 [10 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.



## 9.5 Drug-Food Interactions

There are no known interactions with food.

## 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

Victoza<sup>®</sup> contains liraglutide, an analog of human Glucagon-Like Peptide-1 (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.

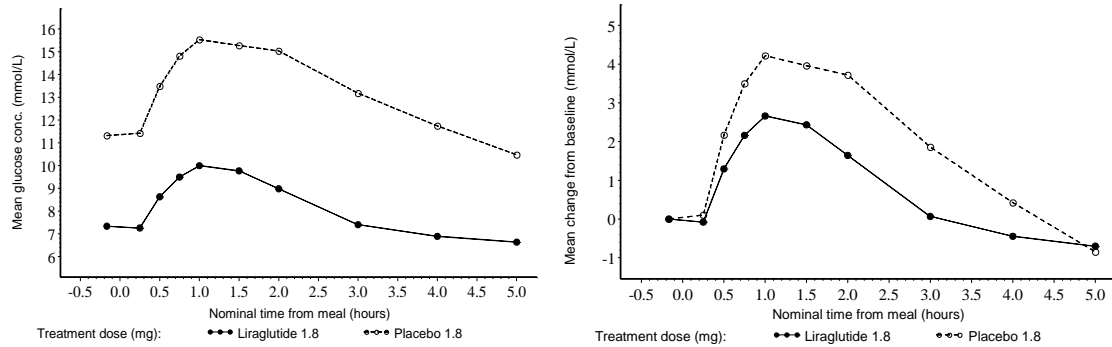
Liraglutide binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a pharmacokinetic profile in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, binding to albumin and enzymatic stability towards the dipeptidyl peptidase (DPP-IV) and neutral endopeptidase (NEP) enzymes resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, liraglutide lowers glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, when blood glucose is low, liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

## 10.2 Pharmacodynamics

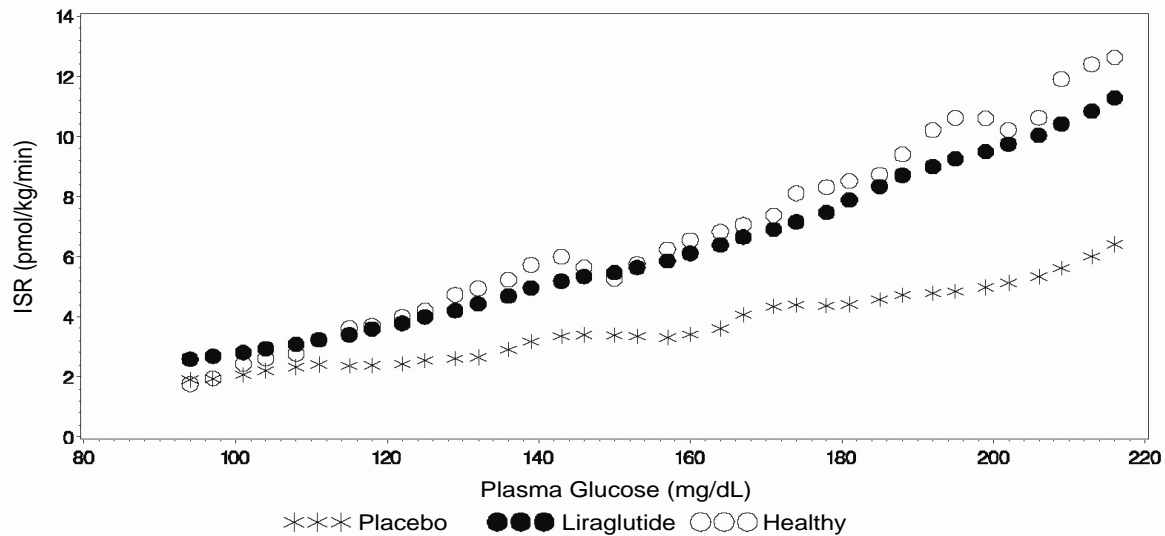
Victoza<sup>®</sup> has 24-hour duration of action and improves long-term glycemic control by lowering fasting and postprandial blood glucose in patients with type 2 diabetes mellitus. Inadequately controlled hyperglycemia is associated with an increased risk of diabetic complications, including cardiovascular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

Victoza<sup>®</sup> 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<sup>®</sup> 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 (**Figure 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)**

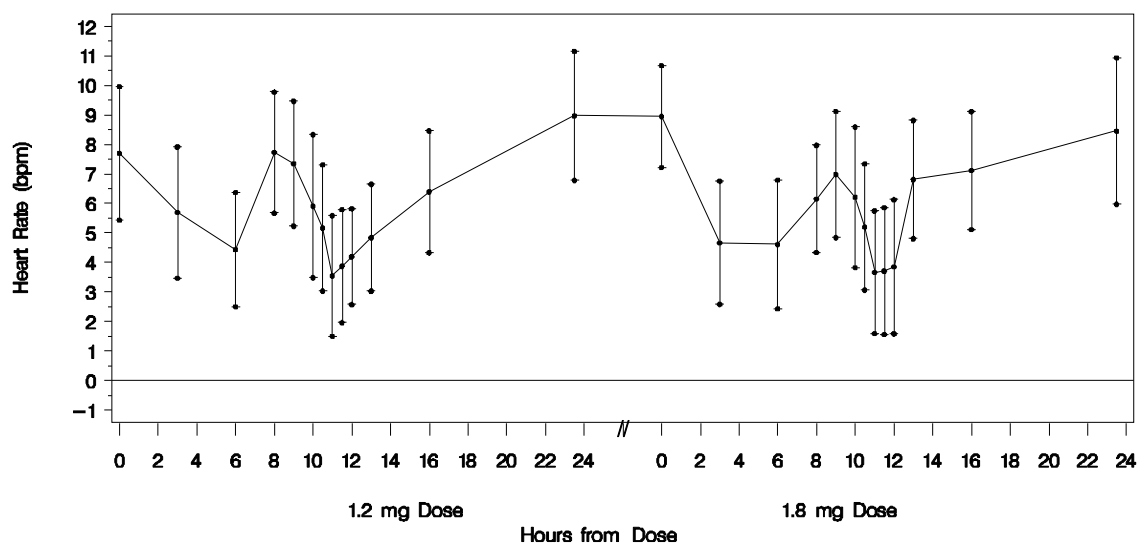
**Glucagon secretion:** Victoza® lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of Victoza® of ~0.7 mg did not impair glucagon response to low glucose concentrations. Furthermore, due to increased insulin and lower glucagon secretion, a lower endogenous glucose release was 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 randomized, double-blind, 2-period crossover, placebo-controlled trial was performed in 51 healthy volunteers (25 M/26 F, 18-44 years). Following randomization, 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 randomized 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.

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

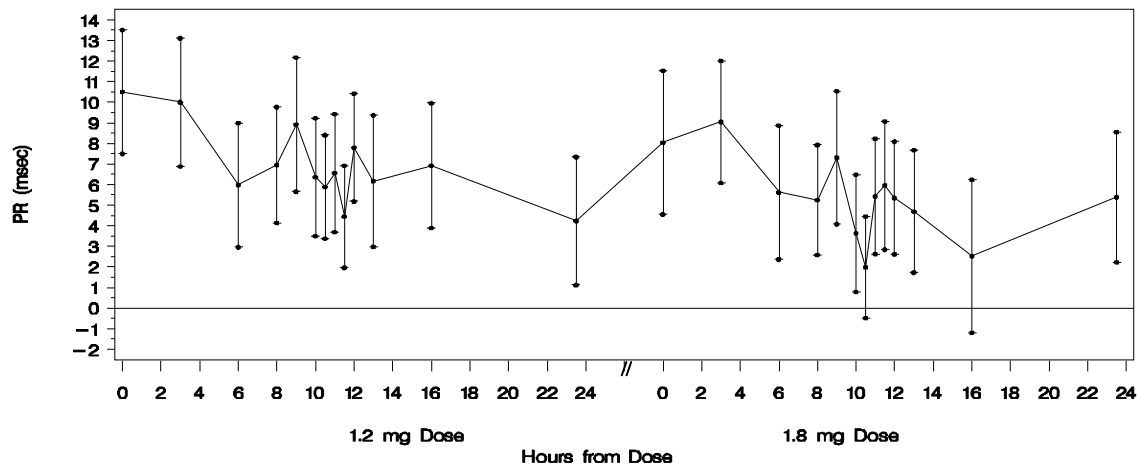


Delta: The difference between HR at current time and HR at baseline for each patient  
 LCL: Lower Confidence Limit UCL: Upper Confidence Limit

**Figure 5**

**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.

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

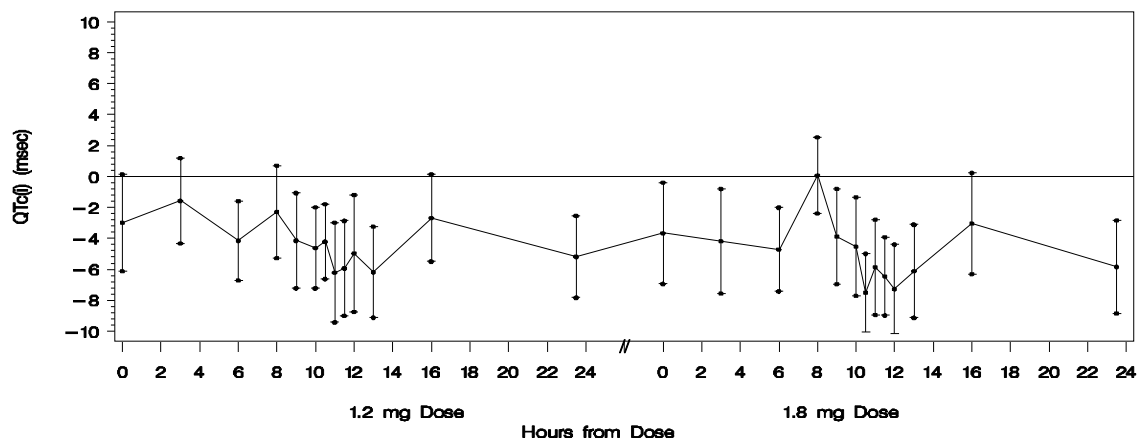


Delta: The difference between PR at current time and PR at baseline for each patient  
 LCL: Lower Confidence Limit UCL: Upper Confidence Limit

**Figure 6**

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.

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



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

**Figure 7**

**Combination with Insulin**

No pharmacodynamic interactions were observed between Victoza® and insulin detemir when

administering a single dose of insulin detemir 0.5 U/kg with Victoza® 1.8 mg at steady state in patients with type 2 diabetes.

### Non-Clinical Pharmacodynamics

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 hypoglycemic 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).

### 10.3 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<sub>τ/24</sub>) 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 a 24 h period following administration of a single [<sup>3</sup>H]-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.

**Elimination:** Following a [<sup>1</sup>H]-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 were 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:** Pharmacokinetic properties were assessed in clinical studies in the pediatric population with type 2 diabetes aged 10-17. Based on the population pharmacokinetic analysis, the liraglutide exposure in pediatric subjects was comparable to that in adults.

**Geriatrics:** Exposure (AUC) to Victoza® is independent of age (see [4 DOSAGE AND ADMINISTRATION](#) and [10 CLINICAL PHARMACOLOGY](#)).

**Sex:** After adjusting for body weight, AUC(0-t), C<sub>max</sub>, t<sub>max</sub>, AUC (0-∞), CL/F, Vz/F, and t<sub>1/2</sub> 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®.

**Ethnic origin:** 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.

## 11 STORAGE, STABILITY AND DISPOSAL

Victoza® should be stored in a refrigerator (2-8°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).

## 12 SPECIAL HANDLING INSTRUCTIONS

Victoza® should be kept with the pen cap on when the 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.

Each Victoza<sup>®</sup> pen is for use by a single patient. The Victoza<sup>®</sup> pen should never be shared between patients, even if the needle is changed.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Victoza<sup>®</sup>

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<sup>®</sup> (liraglutide injection) is a clear, colourless solution.

### 14 CLINICAL TRIALS

#### 14.1 Trial Design and Study Demographics

The efficacy and safety of Victoza<sup>®</sup> in adults were evaluated in five randomized double-blind, controlled clinical trials 1572 (LEAD<sup>™</sup> 2), 1697 (LEAD<sup>™</sup> 5), 1860, 1842, 1573 (monotherapy LEAD<sup>™</sup> 3), and 4315 (LIRA-ADD2SGLT2i). The long-term safety of Victoza<sup>®</sup> in subjects with high cardiovascular risk was evaluated in the large cardiovascular outcome trial (CVOT) EX2211-3748 (LEADER<sup>®</sup>).

The efficacy and safety of Victoza<sup>®</sup> in adolescents and children aged 10 years and above were evaluated in a randomized, double-blind, controlled clinical trial 3659 (Ellipse<sup>™</sup>).



**Table 9 Summary of baseline demographics and study design for trials 1572, 1697, 1860, 1842, 1573, 4315, the cardiovascular outcome trial (CVOT) EX2211-3748 (LEADER), and the pediatric trial 3659**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex	
					Male	Female
1572 (LEAD™ 2)	Multicentre, randomized, 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*	Mean (SD) 56.7 (9.5) Range 25-79	633 (58.2 %)	454 (41.8 %)
1697 (LEAD™ 5)	Multicentre, randomized, 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*	Mean (SD) 57.6 (9.9) Range 24-80	325 (56.4 %)	251 (43.6 %)
1860	Multicentre, 26-week, randomized, 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*	Mean (SD) 55.3 (9.2) Range 23-79	352 (53.9 %)	313 (37.1 %)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex	
					Male	Female
1842	Multicentre, 26 week randomized, open-label, parallel-group, multinational trial with a 26 week extension	Victoza® 1.8 mg once daily + metformin or Victoza® 1.8 mg + Levemir® (insulin detemir) + metformin or Non-randomized Victoza® 1.8 mg + metformin	987	Mean (SD) 57.1 (9.7) Range 18-80	550 (56.6 %)	437 (43.4 %)
1573 (LEAD™ 3)	Multicentre, double-blind, double-dummy, randomized, parallel, active-controlled clinical trial of 52 weeks treatment duration followed by a 52-week, open-label extension	Victoza® 1.2 mg or 1.8 mg once daily with a 1-2 week period of forced titration with liraglutide (or placebo) for reaching the intended daily dose. or Glimepiride (or placebo) titrated up to the 8-mg dose during a 4-week period.	745	Mean (SD) 53.0 (10.9) Range 19-79	371 (49.8 %)	374 (50.2 %)
EX2211-3748 (LEADER®)	Multicentre, international, randomized, double-blind, placebo controlled Cardiovascular Outcome Trial (CVOT)	Victoza® 1.8 mg once daily + standard of care or Placebo once daily + standard of care Victoza® and placebo were administered subcutaneously in a event and time-driven treatment period of 42 to 60 months	9340	Mean (SD) 64.3 (7.2) Range 49-91	6003 (64.3 %)	3337 (35.7 %)
4315 (LIRA-ADD 2SGLT2i)	Multicentre, international, randomized, double-blind, placebo controlled, two-arm, parallel-group trial	Victoza® 1.8 mg once daily + SGLT2i ± metformin or Placebo once daily + SGLT2i ± metformin	303	Mean (SD) 55.15 (10.02) Range 25-79	183 (60.4 %)	120 (39.6 %)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex	
					Male	Female
3659 (Ellipse™)	Multicentre, international, randomized, parallel-group, placebo controlled, 26 weeks double-blind followed by a 26-week open-label extension in subjects with T2D aged 10-17 years	Victoza® 1.8 mg once daily + metformin ± insulin or Placebo once daily + metformin ± insulin	134	Mean (SD) 14.57 (1.72) Range 10-16.9	51 (38.1 %)	83 (61.9 %)

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 years (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 2 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/m<sup>2</sup>, a mean duration of diabetes of 6.2 years and a mean baseline HbA<sub>1c</sub> 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.

## 14.2 Study Results

### 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 (8 mg), 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.

The percentage of patients who discontinued due to ineffective therapy was 5.4% in the Victoza® 1.8 mg *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<sub>1c</sub> that were non-inferior to treatment with glimepiride in combination with metformin (**Table 10**).

**Table 10 Results of a 26-week trial of Victoza® in combination with metformin**

	Victoza® 1.8 mg + metformin	Victoza® 1.2 mg + metformin	Placebo + metformin	Glimepiride 4 mg + metformin
<b>Intent-to-Treat Population (N)</b>	242	240	121	242
<b>HbA<sub>1c</sub> (%) (Mean)</b>				
Baseline	8.4	8.3	8.4	8.4
Change from baseline (adjusted mean) <sup>b</sup>	-1.0	-1.0	+0.1	-1.0
Difference from glimepiride + metformin arm (adjusted mean) <sup>b</sup>	0.0	0.0		
95% Confidence Interval	(-0.2, 0.2)	(-0.2, 0.2)		
Patients (%) achieving A <sub>1c</sub> <7%	42	35	11	36
<b>Fasting Plasma Glucose (mmol/L) (Mean)</b>				
Baseline	10.05	9.94	10.11	10
Change from baseline (adjusted mean) <sup>b</sup>	-1.68	-1.63	+0.40	-1.31
Difference from glimepiride + metformin arm (adjusted mean) <sup>b</sup>	-0.38	-0.33		
<b>Body Weight (kg) (Mean)</b>				
Baseline	88.0	88.5	91.0	89.0
Change from baseline (adjusted mean) <sup>b</sup>	-2.8	-2.6	-1.5	+1.0
Difference from glimepiride + metformin arm (adjusted mean) <sup>b</sup>	-3.8**	-3.5**		
95% Confidence Interval	(-4.5, -3.0)	(-4.3, -2.8)		

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least 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 randomized 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® 1.2 mg + metformin group, 1.4% in the Victoza® 1.8 mg + 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<sub>1c</sub> compared to Sitagliptin + metformin (See **Table 11**) at Weeks 26.

**Table 11 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
<b>Full Analysis Set Population (N)</b>	221	218	219
<b>HbA<sub>1c</sub> (%) (Mean)</b>			
N	211	214	210
Baseline	8.4	8.4	8.5
Change from baseline (adjusted mean) <sup>b</sup>	-1.24	-1.50	-0.9
Difference from sitagliptin + metformin arm (adjusted mean) <sup>b</sup>	-0.34**	-0.60	
95% Confidence Interval	-0.51; -0.16	-0.77; -0.43	
Patients (%) achieving A <sub>1c</sub> <7%	43.4	54.6	22.4
<b>FPG (mmol/L) (Mean)</b>			
N	210	212	210
Baseline	10.1	10.0	10.0
Change from baseline (adjusted mean) <sup>b</sup>	-1.87	-2.14	-0.83
<b>Body Weight (kg) (Mean)</b>			
N	215	214	215
Baseline	93.9	94.9	93.1
Change from baseline (adjusted mean) <sup>b</sup>	-2.86	-3.38	-0.96

<sup>a</sup>Intent-to-treat population using last observation carried forward

<sup>b</sup>Least 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<sub>1c</sub> observed after the first 6 months with both liraglutide doses in combination with metformin were sustained. The estimated mean changes in HbA<sub>1c</sub> 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<sub>1c</sub> < 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.

### **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® 1.8 mg, 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 (8 mg) 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.

Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of  $\leq 5.5$  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<sup>®</sup> 1.8 mg *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<sup>®</sup> 1.8 mg in combination with glimepiride and metformin resulted in a statistically significant mean reduction in HbA<sub>1c</sub> compared to placebo in combination with glimepiride and metformin, (See **Table 12**).

**Table 12 Results of a 26-week trial of Victoza<sup>®</sup> in combination with metformin and sulfonylurea**

	Victoza <sup>®</sup> 1.8 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Insulin glargine + Metformin + Glimepiride
<b>Intent-to-Treat Population (N)</b>	230	114	232
<b>HbA<sub>1c</sub> (%) (Mean)</b>			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean) <sup>b</sup>	-1.3	-0.2	-1.1
Difference from placebo + metformin +glimepiride arm (adjusted mean) <sup>b</sup>	-1.1**		
95% Confidence Interval	(-1.3, -0.9)		
Patients (%) achieving A1c <7%	53	15	46
<b>Fasting Plasma Glucose (mmol/l) (Mean)</b>			
Baseline	9.17	9.44	9.11
Change from baseline (adjusted mean) <sup>b</sup>	-1.55	+0.55	-1.77
<b>Body Weight (kg) (Mean)</b>			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean) <sup>b</sup>	-1.8	-0.4	1.6

<sup>a</sup> Intent-to-treat population using last observation on study

<sup>b</sup> Least squares mean adjusted for baseline value

\*\*p-value <0.0001

### Combination Therapy with Metformin and SGLT2i (4315)

Study 4315 was a confirmatory, randomized, double-blind, placebo-controlled, multicentre, multinational, two-arm, parallel-group trial investigating the efficacy and safety of adding Victoza<sup>®</sup> 1.8 mg/day to pre-trial treatment with any SGLT2 inhibitor (as monotherapy or in combination with metformin) in adults with T2DM inadequately controlled on stable treatment with SGLT2 inhibitor  $\pm$  metformin (HbA<sub>1c</sub> of 7.0-9.5%). Eligible subjects were randomized in a 2:1 manner to receive a once-daily dose of either liraglutide (1.8 mg) or placebo. The randomization was stratified by metformin use at baseline (yes versus no). The trial period consisted of a 2-week screening period, a 26-week treatment period and a 1-week follow-up period.

A total of 303 subjects were randomized to receive Victoza<sup>®</sup> 1.8 mg/day (203 subjects) or placebo (100 subjects). All patients were taking SGLT2 inhibitors: 25.7% taking empagliflozin, 49.5% taking dapagliflozin, and 24.8% taking canagliflozin. Overall, 94.4% of randomized subjects were taking metformin.

Treatment with Victoza® 1.8 mg/day resulted in a statistically significant greater reduction of HbA<sub>1c</sub> from baseline compared to placebo, each in combination with SGLT2 inhibitors with or without metformin (**Table 13**).

**Table 13 Results of a 26-week trial of Victoza® in combination with metformin and sodium glucose cotransporter 2 inhibitor (SGLT2i)**

	Victoza® 1.8 mg + SGLT2i* ± Metformin	Placebo + SGLT2i* ± Metformin
<b>Intent-to-Treat Population (N)</b>	203	100
<b>HbA<sub>1c</sub> (%) (Mean)</b>		
Baseline	8.00	7.96
Change from baseline (adjusted mean) <sup>a</sup>	-0.98	-0.30
Treatment difference	-0.68**	
95% Confidence Interval	(-0.89, -0.48)	
Patients (%) achieving A1c <7% <sup>b</sup>	51.8	23.2
<b>Body Weight (kg) (Mean)</b>		
Baseline	91.0	91.4
Change from baseline (adjusted mean) <sup>a</sup>	-2.81	-1.99

<sup>a</sup> Analysis using a pattern mixture model (PMM) of in-trial observation period data with missing observations imputed 1000 times based on patients who discontinue or initiate rescue therapy within each randomized treatment arm, respectively. For each of the 1000 imputed data sets the change in HbA<sub>1c</sub> from baseline to week 26 were analysed using an ANCOVA with treatment, country and the stratification factor (metformin use at baseline: yes vs no) as categorical fixed effects and baseline HbA<sub>1c</sub> as covariate.

<sup>b</sup> The response status is derived from the continuous endpoint (HbA<sub>1c</sub>) using a PMM with multiple imputation for missing observations.

\*Victoza® add on to SGLT2i was investigated at all doses approved of SGLT2i.

\*\*p-value <0.001

### Combination Therapy with Metformin and Insulin

This 26-week open-label trial enrolled 987 patients with inadequate glycemic control (HbA<sub>1c</sub> 7-10%) on metformin (≥1500 mg/day) alone or inadequate glycemic control (HbA<sub>1c</sub> 7-8.5%) on metformin (≥1500 mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea at start of run-in (Week -12). All patients entered a 12-week run-in period during which they received add-on therapy with Victoza® titrated to 1.8 mg once-daily. The greatest change in HbA<sub>1c</sub> and body weight was observed during the 12-week run-in period; subjects in the randomized groups had a mean screening HbA<sub>1c</sub> of 8.3% which decreased to 7.6% and observed change in body weight was 3.5 kg. At the end of the run-in period, 498 patients (50%) achieved HbA<sub>1c</sub> <7% with Victoza® 1.8 mg and metformin and continued treatment in a nonrandomized, observational arm. Another 167 patients (17%) withdrew from the trial during the run-in period with approximately one-half of these patients doing so because of gastrointestinal adverse reactions (see [8 ADVERSE REACTIONS](#)). The remaining 323 patients with HbA<sub>1c</sub> ≥7% (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily insulin detemir administered in the evening as add-on therapy (N=162) or to continued, unchanged treatment with Victoza® 1.8 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day (0.41 U/kg). During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 3.1% in the group randomized to continued treatment with Victoza® 1.8 mg and metformin and 1.2% in the group randomized to add on therapy with insulin detemir. The total percentage of withdrawals was 21.1% (N=34) in the group randomized to continued treatment with Victoza® 1.8 mg and metformin and 11.1% (N=18) in the group randomized to add on therapy with insulin

detemir.

Treatment with insulin detemir as add-on to Victoza® 1.8 mg + metformin resulted in a statistically significant reduction in HbA<sub>1c</sub> compared to continued, unchanged treatment with Victoza® 1.8 mg + metformin alone (see **Table 14**).

**Table 14 Results of a 26-week open-label trial of insulin detemir as add on to Victoza® + metformin compared to continued treatment with Victoza® + metformin alone in patients not achieving HbA<sub>1c</sub> < 7% after 12 weeks of metformin and Victoza® (Week -12 to 0)**

	Victoza® + metformin + Insulin	Victoza® +metformin
<b>Intent-to-Treat Population (N)</b>	162	157
<b>HbA<sub>1c</sub> (%)</b>		
N <sup>a</sup>	160	149
Mean at baseline (after randomization, Week 0)	7.6	7.6
Change from baseline (adjusted mean)	-0.5	0.0
Difference from Victoza® + metformin arm (adjusted mean) <sup>b</sup>	-0.5*	
95% Confidence Interval	(-0.7, -0.4)	
N <sup>a</sup>	160	149
Estimated proportion of patients achieving HbA <sub>1c</sub> <7% <sup>c</sup>	43%	17%
<b>Fasting Plasma Glucose (mmol/L)</b>		
N <sup>a</sup>	160	154
Mean as baseline (after randomization, Week 0)	9.23	8.81
Change from baseline (adjusted mean) <sup>b</sup>	-2.12	-0.39
<b>Body Weight (kg)</b>		
N <sup>a</sup>	162	157
Baseline (after randomization, Week 0)	6	95.3
Change from baseline (adjusted mean) <sup>b</sup>	-0.16	-0.95

<sup>a</sup> Intent-to-treat population using last observation on study. Subjects with no post-baseline measurements are excluded from analysis.

<sup>b</sup> Least squares mean from an ANCOVA with treatment, country and previous OAD as factors and baseline value as a covariate

<sup>c</sup> Estimates from a logistic regression model with treatment as fixed effect and baseline HbA<sub>1c</sub> as covariate

\*p-value <0.0001

### Monotherapy (LEAD™ 3)

In this 52-week trial, 746 patients were randomized to Victoza® 1.2 mg (N=251), Victoza® 1.8 mg (N=247), or glimepiride 8 mg (N=248). Patients enrolled in this study were diagnosed with type 2 diabetes mellitus and previously treated with diet/exercise (N=272; 36.5%) or not more than half-maximal OAD monotherapy (N=474; 63.5%) for at least 2 months. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily; patients who were randomized to Victoza® 1.2 mg or Victoza® 1.8 mg were initially treated with 0.6 mg daily and the dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg. After the titration period, Victoza® and glimepiride doses remained fixed. Treatment with Victoza® 1.8 mg and 1.2 mg resulted in statistically significant mean reductions in HbA<sub>1c</sub> compared to glimepiride (**Table 15**).

The mean age of the randomized subjects at baseline was 53 years and mean duration of diabetes was 5.4 years, 49.7% were male. 77.5% were Caucasian and 12.6% African



American. The mean BMI at baseline was 33.1 kg/m<sup>2</sup>.

**Table 15 Results of a 52-week monotherapy trial<sup>a</sup>**

	<b>Victoza<sup>®</sup> 1.8 mg</b>	<b>Victoza<sup>®</sup> 1.2 mg</b>	<b>Glimepiride 8 mg</b>
<b>Intent-to-Treat Population (N)</b>	246	251	248
<b>HbA<sub>1c</sub> (%) (Mean)</b>			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean) <sup>b</sup>	-1.1	-0.8	
Difference from glimepiride arm (adjusted mean) <sup>b</sup>	-0.6**	-0.3*	-0.5
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.1)	
Percentage of patients achieving A1c <7%	51	43	28
<b>Fasting Plasma Glucose (mmol/L) (Mean)</b>			
Baseline	9.54	9.24	9.53
Change from baseline (adjusted mean) <sup>b</sup>	-1.42	-0.84	-0.29
<b>Body Weight (kg) (Mean)</b>			
Baseline	92.6	92.1	93.3
Change from baseline (adjusted mean) <sup>b</sup>	-2.5	-2.1	+1.1

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

\*p-value <0.05

\*\*p-value <0.0001

### **Use in Patients with Type 2 Diabetes and Established Cardiovascular Disease (LEADER EX2211-3748)**

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results trial (LEADER) was a large, long-term, multicentre, multi-national, randomized, double-blind, placebo-controlled, time and event-driven trial in adults with type 2 diabetes mellitus (T2DM) at high risk of cardiovascular disease. LEADER was a non-inferiority trial aimed to demonstrate that liraglutide compared to placebo did not contribute to a significant increase in cardiovascular risk in patients with T2DM. A total of 9,340 patients were randomized equally to Victoza<sup>®</sup> 1.8 mg or placebo in addition to standard of care. At baseline, patients were to be at least 50 years of age with established cardiovascular disease or chronic kidney disease (n=7,598; (81.3%); or 60 years of age with only risk factors of vascular disease (n=1,742; (18.7%).

At baseline, patients were allowed to be anti-diabetic drug naïve or treated with one or more oral anti-diabetic drugs (OAD) or insulin (either alone or in combination with OAD(s)). The Victoza<sup>®</sup> and placebo groups were generally balanced in terms of concomitant medications (anti-diabetic and cardiovascular medications including antihypertensives, diuretics, lipid-lowering, and platelet aggregation inhibitors). During the trial, additional anti-diabetic and cardiovascular medications were to be added according to standard of care to achieve individualized guideline targets for glycemic control, blood pressure, and lipids.

The primary endpoint was the time from randomization to first occurrence of any major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. If non-inferiority was met for the primary endpoint, statistical superiority was subsequently tested.

Primary outcome or vital status at end of trial was available for 99.7% and 99.6% of participants randomized to Victoza<sup>®</sup> and placebo, respectively. The median duration of exposure was 3.5

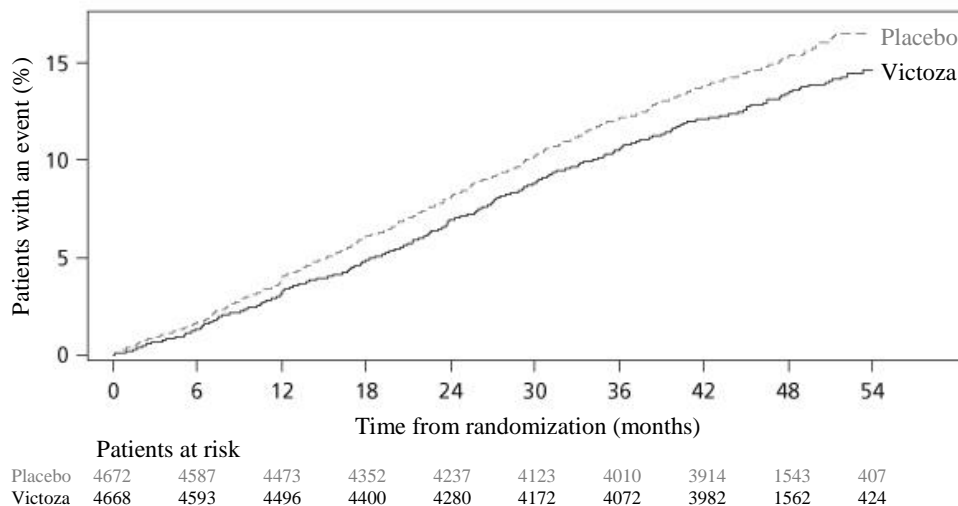
years and up to a maximum of 5 years. The mean age was 64 years and the mean BMI was 32.5 kg/m<sup>2</sup>. The population was primarily male (64.3%), Caucasian (77.5%), with a mean duration of diabetes of 12.8 years and mean HbA<sub>1c</sub> of 8.7%. Concomitant cardiovascular diseases of randomized patients primarily included history of myocardial infarction (30.1%), history of ischemic stroke (11.1%), NYHA class I (3.7%), NYHA class II (11.7%), NYHA class III (2.3%), hypertension/left ventricular hypertrophy (91.1%), and arrhythmia (15.4%). At baseline, 41.8% of patients had mild renal impairment, 20.7% had moderate renal impairment, and 2.4% had severe renal impairment.

According to hierarchical testing for non-inferiority and superiority for MACE, Victoza<sup>®</sup> was found to be:

- Non-inferior to placebo, since the upper bound of the 95% CI was below 1.3; and
- Statistically superior to placebo, since the upper bound of the 95% CI was also below 1.0.

The estimated hazard ratio was below 1.0 for MACE and all 3 individual components (**Figure 10**):

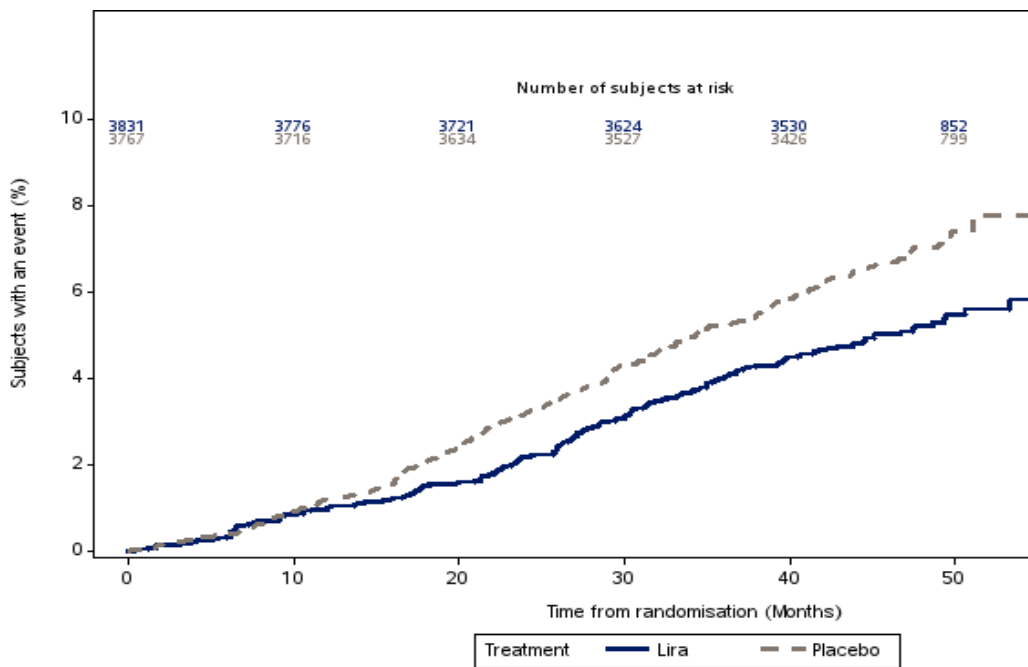
1. MACE (HR 0.87 [95% Confidence Interval (CI); 0.78, 0.97] ( $p < 0.001$  for non-inferiority and  $p = 0.005$  for superiority) (see **Figure 8** and **Figure 10**)
  - Cardiovascular death (HR 0.78 [95% CI; 0.66, 0.93])
  - Non-fatal myocardial infarction (HR 0.88 [95% CI; 0.75, 1.03])
  - Non-fatal stroke (HR 0.89 [95% CI; 0.72, 1.11]).



FAS: full analysis set.

**Figure 8 Kaplan-Meier Plot Time to First MACE in subjects with T2DM at high risk of cardiovascular disease**

The results for the primary endpoint stratified by the baseline cardiovascular risk demonstrated that for time to first MACE, subjects with established cardiovascular disease at baseline had an estimated hazard ratio of 0.83 [95% CI; 0.74, 0.93]; while subjects with only risk factors for cardiovascular disease at baseline had an estimated hazard ratio of 1.20 [95% CI; 0.86, 1.67]. In the subgroup with established cardiovascular disease, the treatment effect reflected a significant reduction in the incidence of cardiovascular death (HR 0.74 [95% CI; 0.61, 0.89]) (see **Figure 9**).

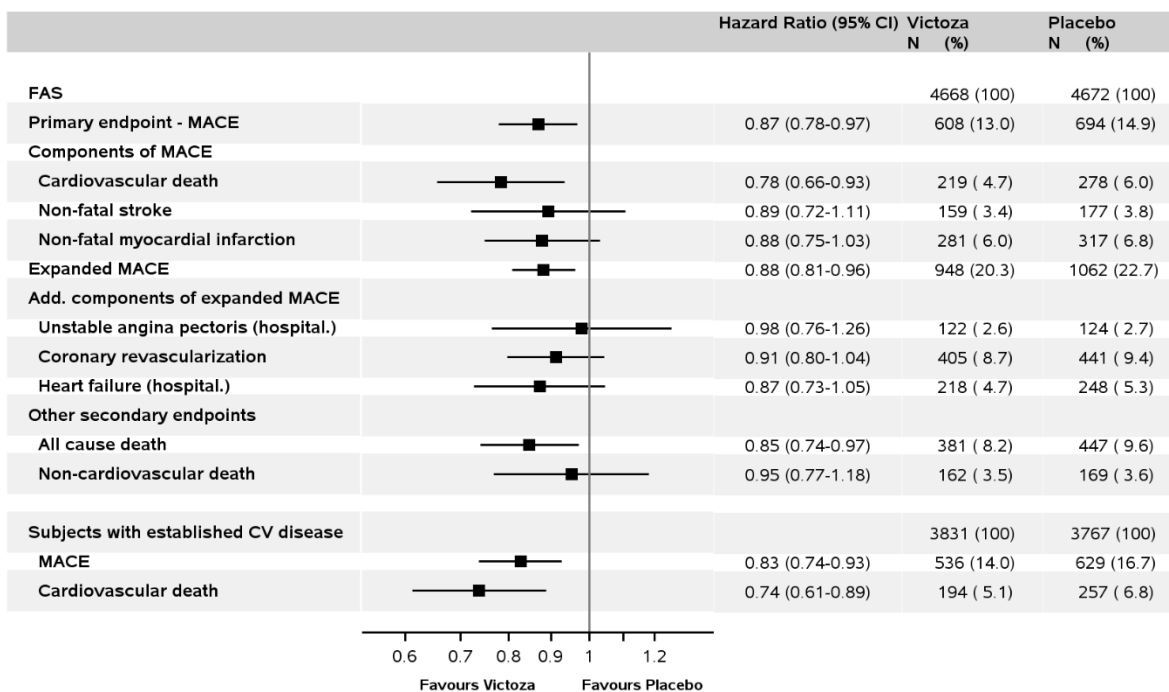


EAC: event adjudication committee, CV: Cardiovascular  
Lira: Liraglutide.

**Figure 9** Kaplan-Meier plot of time to EAC confirmed cardiovascular death - subjects with established CV disease

Victoza<sup>®</sup> also significantly reduced the risk of expanded MACE (including MACE components, unstable angina pectoris leading to hospitalization, coronary revascularization, and hospitalization due to heart failure) in subjects with T2DM at high risk of cardiovascular disease, with an estimated hazard ratio of 0.88 [95% CI; 0.81, 0.96] ( $p = 0.005$ ) (see **Figure 10**). The estimated hazard ratio of time to all-cause death for Victoza<sup>®</sup> compared to placebo was 0.85 [95% CI; 0.74, 0.96] ( $p = 0.017$ ).

The change from baseline to month 36 for HbA<sub>1c</sub> was -1.2% for Victoza<sup>®</sup>-treated patients and -0.8% for placebo-treated patients, corresponding to an estimated treatment difference of -0.4 [95% CI; -0.5, -0.3].



FAS: full analysis set, CI: confidence interval, MACE: major cardiovascular event, N: number of subjects with an event, %: percent of subjects with an event.

**Figure 10 Forest Plot of Cardiovascular Endpoints**

**Type 2 Diabetes Mellitus patients with renal insufficiency:**

In a double-blind trial comparing the efficacy and safety of liraglutide 1.8 mg versus placebo as add-on to insulin and/or OAD in patients with type 2 diabetes and moderate renal insufficiency, liraglutide was superior to placebo treatment in reducing HbA<sub>1c</sub> after 26 weeks (-1.05% vs -0.38%). The estimated treatment difference was -0.66 (95% CI [-0.90, -0.43]), p<0.0001. The estimated mean change from baseline to Week 26 in body weight for the liraglutide group was -2.41 kg and for the placebo group was -1.09 kg.

**Glycemic Control Trial in Patients 10 Years of Age and Above with Type 2 Diabetes Mellitus:**

Victoza<sup>®</sup> was evaluated in a 26-week, double-blind, randomized, parallel group, placebo controlled multi-center trial in 134 pediatric patients with type 2 diabetes aged 10 years and above. Patients were randomized to Victoza<sup>®</sup> once-daily or placebo once-daily in combination with metformin with or without basal insulin treatment. Overall, 18.7% of patients were using basal insulin at baseline. All patients were on a metformin dose of 1000 to 2000 mg prior to randomization. The basal insulin dose was decreased by 20% at randomization and Victoza<sup>®</sup> was titrated weekly by 0.6 mg for 2 to 3 weeks based on tolerability and an average fasting plasma glucose goal of < 6.1 mmol/L. Based on adequate glycaemic control or tolerability, 30% of trial subjects remained on a dose of 0.6 mg and 70% of trial subjects remained on 1.2 mg or 1.8 mg.

At week 26, treatment with Victoza<sup>®</sup> was superior in reducing HbA<sub>1c</sub> from baseline versus placebo. The estimated treatment difference in HbA<sub>1c</sub> reduction from baseline between Victoza<sup>®</sup> and placebo was -1.06% with a 95% confidence interval of [-1.65%; -0.46%] (see **Table 16**).

**Table 16 Results at Week 26 in a Trial Comparing Victoza® in combination with metformin with or without basal insulin to Placebo in combination with metformin with or without basal insulin in Pediatric Patients 10 Years of Age and Above with Type 2 Diabetes Mellitus**

	Victoza® + metformin ± basal insulin	Placebo + metformin ± basal insulin
<b>N</b>	66	68
<b>HbA<sub>1c</sub> (%)</b>		
Baseline	7.9	7.7
End of 26 weeks (LOCF)	7.1	8.2
Adjustment mean change from baseline after 26 weeks <sup>a</sup>	-0.64	0.42
Treatment difference [95% CI] Liraglutide 1.8 mg vs Placebo	-1.06 [-1.65; -0.46]*	
Percentage of patients achieving A1c <7% <sup>b</sup>	63.7	36.5
<b>FPG (mmo/L)(Mean)</b>		
Baseline	8.70	8.15
End of 26 weeks	7.342	9.220
Adjustment mean change from baseline after 26 weeks <sup>a</sup>	-1.076	0.801
Treatment difference [95% CI] Liraglutide 1.8 mg vs Placebo	-1.878 [-3.093; -0.662]	

<sup>a</sup> The change from baseline to end of treatment visit in HbA<sub>1c</sub> and FPG was analysed using a pattern mixed model (PMM) of observed data with missing observations imputed from the placebo arm based on multiple (x10,000) imputations. The data for week 26 were then analysed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate.

<sup>b</sup>The response status is derived from the continuous endpoint (HbA<sub>1c</sub>) using a PMM with multiple imputation for missing observations.

\* p-value <0.001

## 16 NON-CLINICAL TOXICOLOGY

### General 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 s.c. 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 17**

Study ID	NN203261	NN204082
Species/strain	CD-1 mice	CD-1 mice
Drug	Liraglutide	Liraglutide
Dose Route	s.c.	s.c.
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	s.c	s.c.	s.c.
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	s.c.	s.c.	s.c.
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 < 0.05 mg/kg NOAEL 5 mg/kg	NOEL < 0.05 mg/kg NOAEL 5 mg/kg	NOEL 0.05 mg/kg NOAEL 5 mg/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 of 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 4 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 AUC<sub>0-24</sub> comparison) values for the 0.03, 0.2, 1 and 3 mg/kg/day doses were 0.2, 1.8, 10.0 and 45.0, respectively. 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 0.2 mg/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 3.0 mg/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 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0mg/kg/day group. Thyroid C-cell tumours 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 3 mg/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 (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/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 AUC<sub>0-24</sub> 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 [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#); and [7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis](#)).

### **Genotoxicity**

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.

### **Reproductive and Developmental Toxicology**

In a 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 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, or 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 F<sub>0</sub> 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 F<sub>1</sub> pups prior to weaning, at all dose levels.

The reduced body weight of F<sub>1</sub> 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 F<sub>1</sub> animals, except for a slight reduction in body weights of F<sub>2</sub> pups at 1.0 mg/kg/day.

### **Juvenile Toxicity**

In a juvenile toxicity study, subcutaneous doses of 0, 0.05, 0.25 or 1.0 mg/kg/day of liraglutide (0.4, 2.7 and 8.5 fold the human exposure of that in pediatric patients 10-17 years of age) were administered to rats from postnatal day 21 to day 90. As in other studies, lower body weight gain, body weights, and food consumption were observed in juvenile animals administered liraglutide when compared to control animals. Liraglutide also caused a decrease in ulna growth and ulna length which completely recovered off treatment and a delay in sexual maturation in both sexes at 0.25 and 1.0 mg/kg/day. Slightly longer estrous cycles which recovered off treatment, slightly lower implantation counts and post-partum litter size following mating were also observed at 1 mg/kg/day in females, for which a relationship to treatment could not be discounted. The NOAEL for juvenile rats was therefore considered to be 0.05 mg/kg/day.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### **PrVictoza<sup>®</sup>** **liraglutide injection**

Read this carefully before you start taking **Victoza<sup>®</sup>** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Victoza<sup>®</sup>**.

#### **Serious Warnings and Precautions**

##### **Possible Risk of thyroid tumours, including cancer**

As part of drug testing, liraglutide, the active ingredient in **Victoza<sup>®</sup>** 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<sup>®</sup>** 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<sup>®</sup>** with your doctor.

#### **What is **Victoza<sup>®</sup>** used for?**

- **Victoza<sup>®</sup>** is used in combination with metformin, with metformin and a sulfonylurea, with metformin and a sodium glucose cotransporter 2 inhibitor (SGLT2i), or basal insulin to improve blood sugar levels in adults with type 2 diabetes.
- **Victoza<sup>®</sup>** is used in combination with metformin with or without basal insulin to improve blood sugar levels in adolescents and children aged 10 years and above with type 2 diabetes.
- **Victoza<sup>®</sup>** may be used on its own if your blood sugar is not properly controlled by diet and exercise alone and you cannot use metformin.
- If you have type 2 diabetes and have a history of heart disease (such as a past heart attack, heart failure, or stroke), **Victoza<sup>®</sup>** can be used along with diet and exercise to lower your risk of dying from events related to your heart or blood vessels.
- **Victoza<sup>®</sup>** should not be used in type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM).

#### **How does **Victoza<sup>®</sup>** work?**

**Victoza<sup>®</sup>** belongs to a class of medicines called GLP-1 analogue. **Victoza<sup>®</sup>** 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.

#### **What are the ingredients in **Victoza<sup>®</sup>**?**

Medicinal ingredients: Liraglutide

Non-medicinal ingredients: Disodium phosphate dihydrate, propylene glycol, phenol and water for injections

**Victoza® comes in the following dosage forms:**

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

**Do not use Victoza® if:**

- You or a member of your family has 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.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Victoza®. Talk about any health conditions or problems you may have, including 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).
- Have type 1 diabetes.
- Have ever had diabetic ketoacidosis (increased ketones in the blood or urine).
- Have ever had an allergic reaction to Victoza®.
- Have a high heart rate (fast pulse).
- Have a condition called heart block.
- 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).
- Have kidney problems.
- Have liver problems.
- Have gastrointestinal (digestive) problems.
- Have ever had pancreatitis.
- Are breastfeeding or plan to breastfeed.
- Are pregnant or plan to become pregnant.
- Have severe vomiting and/or diarrhea and/or dehydration.

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. Worsening of renal function may sometimes require hemodialysis. 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 '*What are possible side effects from using Victoza®?*'

Victoza® is not recommended for use in children under 10 years of age.

**Driving and Using Machines**

While you are driving or using tools or machines, you should avoid getting low blood sugar (hypoglycemia), because this may reduce your ability to concentrate. Talk to your doctor for further information. Do not drive or operate machinery if you feel dizzy.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

In particular, tell your doctor, Diabetes Nurse Educator or pharmacist if you are using any of the following medicines for diabetes:

- A sulfonylurea medicine (such as glibenclamide or glimepiride). This is because using Victoza<sup>®</sup> 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.
- Insulin. You may get hypoglycemia (low blood sugar) when using Victoza<sup>®</sup> with insulin as insulin increases the risk of hypoglycemia. See '*What are possible side effects from using Victoza<sup>®</sup>?*'
- If you are not sure if the medicines you are taking contain a sulfonylurea, ask your doctor, Diabetes Nurse Educator or pharmacist.

**The following may interact with Victoza<sup>®</sup>:**

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

- 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

**How to take Victoza<sup>®</sup>:**

Take Victoza<sup>®</sup> exactly as your doctor has prescribed.

Victoza<sup>®</sup> 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 Educator 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. Change the place within the area where you inject each day to reduce the risk of developing lumps under the skin. You can give yourself the injection at any time of the day. (See '*Instructions for using the Victoza<sup>®</sup> (liraglutide injection) pen*').

Do not share your Victoza<sup>®</sup> pen with anyone else, even if the needle is changed. Do not reuse or share needles with another person including family members. You may give another person an infection or get an infection from them.

**Usual dose:**

Victoza<sup>®</sup> can be taken at any time of the 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 may be increased to 1.2 mg once a day if your blood glucose is not under control. 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<sup>®</sup>. However, if you are taking a sulfonylurea medicine as well as Victoza<sup>®</sup>, 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.

For children and adolescents starting Victoza<sup>®</sup>, your doctor may advise you to test your blood sugar levels to monitor for hypoglycemia (low blood sugar).

#### **Overdose:**

If you think you have taken too much Victoza<sup>®</sup>, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you use more Victoza<sup>®</sup> than you should, talk to your doctor straight away. You may need medical treatment. If you use too much Victoza<sup>®</sup> you may feel sick (have nausea), become sick (vomit), or experience low blood sugar (hypoglycemia). Please refer to '*Common (affects less than 1 in 10 people)*' for early warning signs of low blood sugar.

#### **Missed Dose:**

If a dose of Victoza<sup>®</sup> 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<sup>®</sup> without talking to your doctor. If you stop using it, your blood sugar levels may increase.

#### **What are possible side effects from using Victoza<sup>®</sup>?**

These are not all the possible side effects you may feel when taking Victoza<sup>®</sup>. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, Victoza<sup>®</sup> can cause side effects. The following side effects may happen with this medicine.

#### **Very common (affects 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<sup>®</sup>, your doctor may tell you to reduce the dose of the sulfonylurea.
- Anorexia
- Decreased appetite
- Headache
- Feeling dizzy
- 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
- Injection site reactions (such as bruising, pain irritation, itching and rash)
- Increased heart rate
- Gallstones
- Inflamed gallbladder (upper abdominal pain after eating, nausea, bloating and indigestion, especially after consuming a fatty meal)

**Uncommon (affects less than 1 in 100)**

- Urticaria (a type of skin rash)
- Change in how things taste

**Unknown**

- Delay in the emptying of the stomach
- Ileus: A condition where your intestine can't push food and waste out of your body (can cause constipation, with additional symptoms such as stomach ache, bloating, vomiting, etc.)
- Lumps under the skin may be caused by build-up of a protein called amyloid (cutaneous amyloidosis). Victoza<sup>®</sup> may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent this skin change.

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 doctor, Diabetes Nurse Educator or pharmacist.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>UNCOMMON</b> Chest pain or symptoms of a possible heart rhythm disturbance / dizziness, palpitations, fainting or seizures, you should seek immediate medical attention		✓	✓
<b>RARE</b> Pancreatitis / persistent, severe abdominal pain with or without vomiting		✓	
Severe hypoglycemia / disorientation, loss of consciousness, and seizures		✓	✓
Severe form of allergic reaction (anaphylactic reaction) with symptoms of breathing problems, swelling of throat and face, and fast heart beat. You should seek immediate medical attention		✓	✓
Cases of inflammation of the pancreas (pancreatitis). Pancreatitis can be a serious, potentially life-threatening medical condition. Stop taking Victoza® and contact your doctor immediately, if you notice any of the following serious side effects: severe and persistent pain in the abdomen (stomach area) which might reach through your back, as well as nausea and vomiting, as it could be a sign of an inflamed pancreas (pancreatitis).		✓	✓
<b>VERY RARE</b> Thyroid tumour / lump in the neck, difficulty in swallowing, difficulty in breathing or persistent hoarseness		✓	
<b>UNKNOWN</b> Cutaneous amyloidosis: lumps under the skin		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough

to interfere with your daily activities, talk to your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

Keep out of reach and sight of children.

Do not use Victoza<sup>®</sup> 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<sup>®</sup>, store it in a refrigerator (2°C-8°C) away from the freezer compartment. Do not freeze it.
- When Victoza<sup>®</sup> is being used, you can keep it for 1 month either at room temperature (not above 30°C) or in a refrigerator (2°C-8°C).
- Do not use Victoza<sup>®</sup> if it has been frozen.
- Do not use Victoza<sup>®</sup> if it is not clear and colourless.
- Always remove the injection needle after each injection and store your Victoza<sup>®</sup> 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<sup>®</sup> from high temperatures and sunlight.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

### If you want more information about Victoza<sup>®</sup>:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.novonordisk.ca>), or by calling Novo Nordisk Canada Inc., at 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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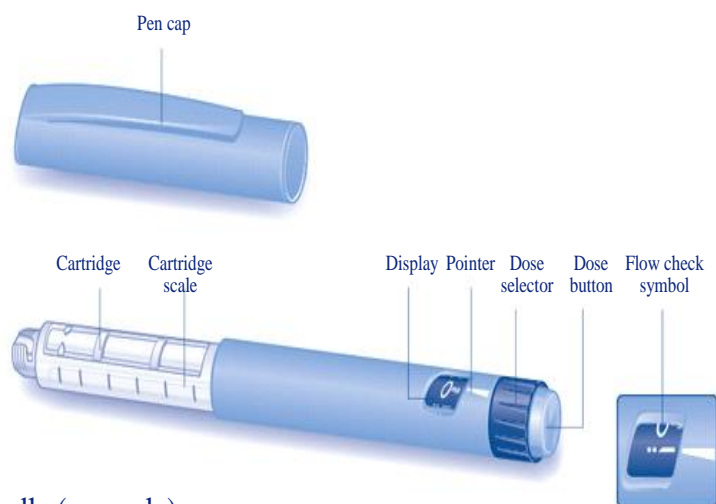
## Instructions for using the Victoza® (liraglutide injection) pen

Please read these instructions carefully before using your Victoza® pen.

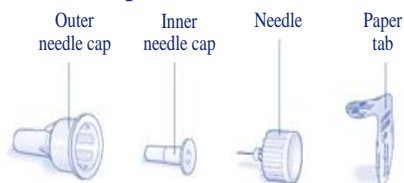
Your Victoza® pen comes with 18 mg of liraglutide. You can select doses of 0.6 mg, 1.2 mg and 1.8 mg. Victoza® pen is designed to be used with NovoFine® disposable needles up to a length of 8 mm and as thin as 32G.

Do not share your Victoza® pen with another person, even if the needle is changed. Do not reuse or share needles with another person including family members. You may give another person an infection, or get an infection from them.

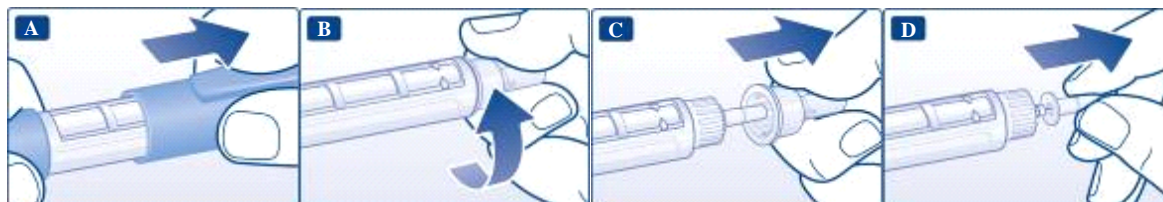
### Victoza® pen



### Needle (example)



## Preparing your Victoza® pen



**Check the name and coloured label** of your pen to make sure that it contains liraglutide. Using the wrong medicine could cause severe harm.

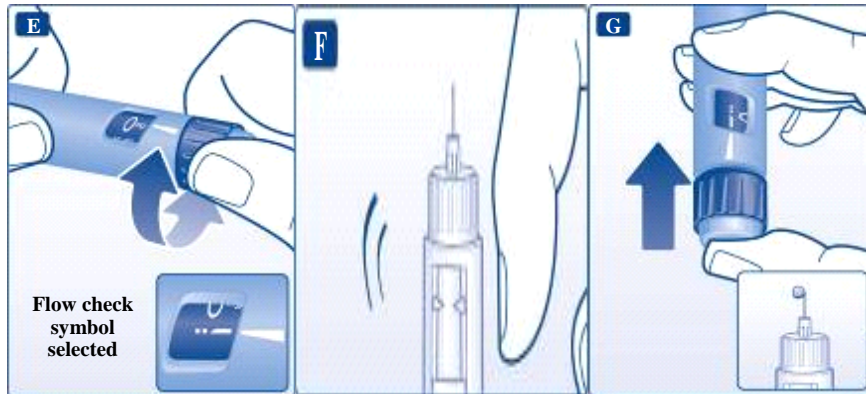
**A.** Pull off the pen cap.

- B. Pull off the paper tab from a new disposable needle. Screw the needle straight and tightly onto your pen.
- C. Pull off the outer needle cap and keep it for later.
- D. Pull off the inner needle cap and throw it away.

- **Always use a new needle for each injection. This reduces the risk of** contamination, infection, leakage of liraglutide, blocked needles and inaccurate dosing. Do not reuse or share needles with another person.
- Be careful not to bend or damage the needle.
- Never put the inner needle cap back on when you have removed it from the needle. This reduces the risk of hurting yourself with the needle.

### With each new pen, check the liraglutide flow

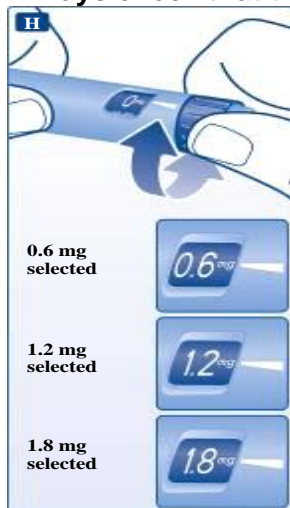
**Always check the liraglutide flow before your first injection with each new pen as follows. If your pen is already in use, go to “Select your dose” Step H.**



- E. Turn the dose selector until the flow check symbol lines up with the pointer.
  - F. Hold the pen with the needle pointing up. Tap the cartridge gently with your finger a few times. This will make any air bubbles collect at the top of the cartridge.
  - G. Keep the needle pointing up and press the dose button until 0 mg lines up with the pointer. A drop of liraglutide should appear at the needle tip. If no drop appears, repeat steps E to G up to four times. If there is still no drop of liraglutide, change the needle and repeat steps E to G once more. Do not use the pen if a drop of liraglutide still does not appear. This indicates the pen is defective and you must use a new one.
- If you have dropped your pen against a hard surface or suspect that something is wrong with it, always put on a new disposable needle and check the flow before you inject.

## Selecting your dose

Always check that the pointer lines up with 0 mg.



- H. Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg).

If you selected a wrong dose by mistake, simply change it by turning the dose selector backwards or forwards until the right dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector backwards, as liraglutide may come out.

If the dose selector stops before your needed dose lines up with the pointer, there is not enough liraglutide left for a full dose. Then you can either:

### *Divide your dose into two injections:*

Turn the dose selector in either direction until 0.6 mg or 1.2 mg lines up with the pointer. Inject the dose. Prepare a new pen for injection and inject the remaining number of mg to complete your dose.

You may only split your dose between your current pen and a new pen if trained or advised by your healthcare professional. Use a calculator to plan the doses. If you split the dose wrong, you may inject too much or too little liraglutide.

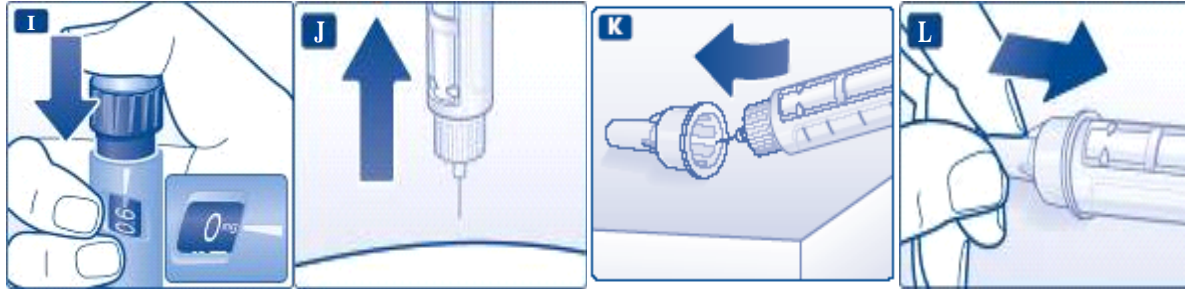
### *Inject the full dose with a new pen:*

If the dose selector stops before 0.6 mg lines up with the pointer, prepare a new pen and inject the full dose with the new pen.

- The dose selector clicks when you turn it. You must not use these clicks to select the amount of liraglutide to inject.
- Do not use the cartridge scale to measure how much liraglutide to inject – it is not accurate enough.
- Do not try to select other doses than 0.6 mg, 1.2 mg or 1.8 mg. The numbers in the display must line up precisely with the pointer to ensure that you get a correct dose.

## Using your injection

Insert the needle into your skin using the injection technique shown by your doctor or nurse. Then follow the instructions below:



- I. Press the dose button to inject until 0 mg lines up with the pointer. Be careful not to touch the display with your other fingers or press the dose selector sideways when you inject. This is because it may block the injection. Keep the dose button pressed down and leave the needle under the skin for at least six seconds. This is to make sure that you get your full dose.
  - J. Pull out the needle.  
After that, you may see a drop of liraglutide at the needle tip.  
This is normal and has no effect on the dose you have just had.
  - K. Guide the needle tip into the outer needle cap without touching the outer needle cap.
  - L. When the needle is covered, carefully push the outer needle cap completely on. Then unscrew the needle. Dispose of it carefully and put the pen cap back on. When the pen is empty, carefully dispose of it without a needle attached. Please dispose of the pen and needle in accordance with local requirements.
- Always remove the needle after each injection and store your Victoza<sup>®</sup> pen without a needle attached.
  - This prevents contamination or infection or leakage of liraglutide. It also ensures that the dosing is accurate.
  - Caregivers should be very careful when handling used needles to avoid hurting themselves with the needles.

### Caring for your Victoza<sup>®</sup> pen

Your Victoza<sup>®</sup> pen is accurate and safe to use. But you must take care of it:

- Do not try to repair your pen or pull it apart.
- Keep your pen away from dust, dirt and all kinds of liquids.
- Clean the pen with a cloth moistened with a mild detergent. Do not try to wash it, soak it or lubricate it – this can harm the pen.

### Important information

- Do not share your Victoza<sup>®</sup> pen with anyone else.  
Keep your Victoza<sup>®</sup> pen out of reach of others, especially children.