**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use VICTOZA safely and effectively. See full prescribing information for VICTOZA.**

**VICTOZA® (liraglutide) injection, for subcutaneous use**
**Initial U.S. Approval: 2010**

**WARNING: RISK OF THYROID C-CELL TUMORS**
***See full prescribing information for complete boxed warning.***

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1)**.
- **VICTOZA is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage ( 1) ---------- | 8/2017 |
| Contraindications (4) ---------- | 8/2017 |
| Warnings and Precautions (5.2, 5.6, 5.7) ---------- | 8/2017 |

**·····INDICATIONS AND USAGE·····**

VICTOZA is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

Limitations of Use**:**

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with prandial insulin.

**·····DOSAGE AND ADMINISTRATION·····**

- Inject subcutaneously in the abdomen, thigh or upper arm (2.1).
- Administer once daily at any time of day, independently of meals (2.2).
- Initiate at 0.6 mg per day for one week then increase to 1.2 mg. Dose can be increased to 1.8 mg for additional glycemic control (2.2).

**·····DOSAGE FORMS AND STRENGTHS·····**

Injection: 6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (3).

**·····CONTRAINDICATIONS·····**

VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).

VICTOZA is contraindicated in patients with a prior serious hypersensitivity reaction to VICTOZA or any of the product components (4).

**·····WARNINGS AND PRECAUTIONS·····**

- Thyroid C-cell Tumors: See Boxed Warning (5.1).
- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Never share a VICTOZA pen between patients, even if the needle is changed (5.3).
- Serious Hypoglycemia: When VICTOZA is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (5.4).
- Renal Impairment: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of VICTOZA in patients with renal impairment (5.5).
- Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue VICTOZA and promptly seek medical advice (5.6).
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7)

**·····ADVERSE REACTIONS·····**

- The most common adverse reactions, reported in ≥5% of patients treated with VICTOZA are: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation (6.1).
- Immunogenicity-related events, including urticaria, were more common among VICTOZA-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (6.2).

**To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-484-2869 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**

VICTOZA delays gastric emptying. May impact absorption of concomitantly administered oral medications. (7).

**·····USE IN SPECIFIC POPULATIONS·····**

- Renal Impairment: No dose adjustment recommended (2.4, 8.6, 12.3).
- Pregnancy: Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

**See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.**

**Revised: 08/2017**

**FULL PRESCRIBING INFORMATION: CONTENTS***


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**FULL PRESCRIBING INFORMATION**

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

- **Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **VICTOZA is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of VICTOZA and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

## 1 INDICATIONS AND USAGE

VICTOZA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease *[see Clinical Studies (14.2)]*.

Limitations of Use**:**

- VICTOZA is not a substitute for insulin. VICTOZA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of VICTOZA and prandial insulin has not been studied.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

- Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Inject VICTOZA subcutaneously in the abdomen, thigh or upper arm. No dose adjustment is needed if changing the injection site and/or timing.
- 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.

### 2.2 General Dosing and Administration

- Inject VICTOZA subcutaneously once-daily at any time of day, independently of meals.
- Initiate VICTOZA with a dose of 0.6 mg per day for one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg. If a dose is

missed, resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase in dose to make up for the missed dose.

- If more than 3 days have elapsed since the last VICTOZA dose, reinitiate VICTOZA at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Upon reinitiation, VICTOZA should be titrated at the discretion of the prescriber.

### 2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating VICTOZA, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]*.

### 2.4 Dosage in Patients with Renal Impairment

No dose adjustment is recommended for patients with renal impairment.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/mL solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg.

## 4 CONTRAINDICATIONS

- **Medullary Thyroid Carcinoma**

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

- **Hypersensitivity**

VICTOZA is contraindicated in patients with a prior serious hypersensitivity reaction to VICTOZA or to any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with VICTOZA *[see Warnings and Precautions (5.6)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice *[see Nonclinical Toxicology (13.1)]*. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether VICTOZA will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with VICTOZA have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and VICTOZA use in humans.

VICTOZA is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of VICTOZA and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC

usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

### 5.2 Pancreatitis

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with VICTOZA. After initiation of VICTOZA, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, VICTOZA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, VICTOZA should not be restarted.

In glycemic control trials of VICTOZA, there have been 13 cases of pancreatitis among VICTOZA-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with VICTOZA were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a VICTOZA-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

VICTOZA 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.

### 5.3 Never Share a VICTOZA Pen Between Patients

VICTOZA pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

### 5.4 Use with Medications Known to Cause Hypoglycemia

Patients receiving VICTOZA in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Dosage and Administration (2.2), Adverse Reactions (6.1)]*.

### 5.5 Renal Impairment

VICTOZA has not been found to be directly nephrotoxic in animal studies or clinical trials.
There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA-treated patients *[see Adverse Reactions (6.2)]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions (6.1)]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including VICTOZA. Use caution when initiating or escalating doses of VICTOZA in patients with renal impairment *[see Use in Specific Populations (8.6)]*.

### 5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with VICTOZA. If a hypersensitivity reaction occurs, discontinue

VICTOZA; 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 *[see Contraindications (4)]*.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-receptor agonist because it is unknown whether such patients will be predisposed to these reactions with VICTOZA.

**5.7 Acute Gallbladder Disease**

In the LEADER trial *[see Clinical Studies (14.2)]*, 3.1% of Victoza-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.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions (5.4)]*
- Renal Impairment *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions

The data in Table 1 are derived from 5 glycemic control, placebo-controlled trials *[see Clinical Studies (14.1)]*. These data reflect exposure of 1673 patients to VICTOZA and a mean duration of exposure to VICTOZA of 37.3 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9.1 years and a mean $HbA_{1c}$ of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88.1% and moderately impaired in 11.9% of the pooled population.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of VICTOZA. These adverse reactions occurred more commonly on VICTOZA than on placebo and occurred in at least 5% of patients treated with VICTOZA.

**Table 1 Adverse reactions reported in ≥ 5% of VICTOZA-treated patients**

| | **Placebo N=661** | **Liraglutide 1.2 mg N= 645** | **Liraglutide 1.8 mg N= 1024** |
|---|---|---|---|
| **Adverse Reaction** | (%) | (%) | (%) |
| Nausea | 5 | 18 | 20 |
| Diarrhea | 4 | 10 | 12 |
| Headache | 7 | 11 | 10 |
| Nasopharyngitis | 8 | 9 | 10 |
| Vomiting | 2 | 6 | 9 |
| Decreased appetite | 1 | 10 | 9 |

| | | | |
|---|---|---|---|
| Dyspepsia | 1 | 4 | 7 |
| Upper Respiratory Tract Infection | 6 | 7 | 6 |
| Constipation | 1 | 5 | 5 |
| Back Pain | 3 | 4 | 5 |

Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights

In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Other Adverse Reactions

*Gastrointestinal Adverse Reactions*

In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of VICTOZA-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

*Injection site reactions*

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of VICTOZA-treated patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of VICTOZA-treated patients discontinued due to injection site reactions.

*Hypoglycemia*

Hypoglycemia requiring the assistance of another person in placebo-controlled trials

In 5 glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 VICTOZA-treated patients (7.5 events per 1000 patient-years). Of these 8 VICTOZA-treated patients, 7 patients were concomitantly using a sulfonylurea.

**Table 2 Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in 26-Week Combination Therapy Placebo-controlled Trials**

| | **Placebo Comparator** | **VICTOZA Treatment** |
|---|---|---|
| **Add-on to Metformin** | **Placebo + Metformin** (N = 121) | **VICTOZA + Metformin** (N = 724) |
| Patient not able to self-treat | 0 | 0.1 (0.001) |
| Patient able to self-treat | 2.5 (0.06) | 3.6 (0.05) |
| **Add-on to Glimepiride** | **Placebo + Glimepiride** (N = 114) | **VICTOZA + Glimepiride** (N = 695) |
| Patient not able to self-treat | 0 | 0.1 (0.003) |
| Patient able to self-treat | 2.6 (0.17) | 7.5 (0.38) |
| Not classified | 0 | 0.9 (0.05) |
| **Add-on to Metformin + Rosiglitazone** | **Placebo + Metformin + Rosiglitazone** (N = 175) | **VICTOZA + Metformin + Rosiglitazone** (N = 355) |
| Patient not able to self-treat | 0 | 0 |
| Patient able to self-treat | 4.6 (0.15) | 7.9 (0.49) |
| Not classified | 1.1 (0.03) | 0.6 (0.01) |

| **Add-on to Metformin + Glimepiride** | **Placebo + Metformin + Glimepiride** (N = 114) | **VICTOZA + Metformin + Glimepiride** (N = 230) |
|---|---|---|
| Patient not able to self-treat | 0 | 2.2 (0.06) |
| Patient able to self-treat | 16.7 (0.95) | 27.4 (1.16) |
| Not classified | 0 | 0 |

"Patient not able to self-treat" is defined as an event requiring the assistance of another person for treatment

*Papillary thyroid carcinoma*
In glycemic control trials of VICTOZA, there were 7 reported cases of papillary thyroid carcinoma in patients treated with VICTOZA and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

*Cholelithiasis and cholecystitis*
In glycemic control trials of VICTOZA, the incidence of cholelithiasis was 0.3% in both VICTOZA-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both VICTOZA-treated and placebo-treated patients.

In the LEADER trial *[see Clinical Studies (14.2)]*, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in VICTOZA-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) n VICTOZA-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients.

**Laboratory Tests**
*Bilirubin*
In the five glycemic control trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of VICTOZA-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

*Calcitonin*
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-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-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown.

*Lipase and Amylase*
In one glycemic control trial in renal impairment patients, a mean increase of 33% for lipase and 15% for amylase from baseline was observed for VICTOZA-treated patients while placebo-treated patients had a mean decrease in lipase of 3% and a mean increase in amylase of 1%.

In the LEADER trial, serum lipase and amylase were routinely measured. Among VICTOZA-treated patients, 7.9% had a lipase value at any time during treatment of greater than or equal to 3 times the upper limit of normal compared with 4.5% of placebo-treated patients, and 1% of VICTOZA-treated patients had an amylase value at any time during treatment of greater than or equal to 3 times the upper limit of normal versus 0.7% of placebo-treated patients.

The clinical significance of elevations in lipase or amylase with VICTOZA is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions (5.2)]*.

**Vital signs**
VICTOZA did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with VICTOZA compared to placebo.

### 6.2 Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with VICTOZA 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-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-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the VICTOZA-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the VICTOZA-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-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the VICTOZA-treated patients in the double-blind 26-week add-on combination therapy trials.

Antibody formation was not associated with reduced efficacy of VICTOZA when comparing mean $HbA_{1c}$ 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 $HbA_{1c}$ with VICTOZA treatment.

In five double-blind glycemic control trials of VICTOZA, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of VICTOZA-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for VICTOZA-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 *[see Clinical Studies (14.2)]*, anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) VICTOZA-treated patients with antibody measurements.

Of the 11 VICTOZA-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies against native GLP-1.

### 6.3 Post-Marketing Experience

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.

- Medullary thyroid carcinoma *[see Warnings and Precautions (5.1)]*
- Dehydration resulting from nausea, vomiting and diarrhea. *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis. *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*
- Angioedema and anaphylactic reactions. *[see Contraindications (4), Warnings and Precautions (5.6), Patient Counseling Information (17)]*
- Allergic reactions: rash and pruritus
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Warnings and Precautions (5.2)]*
- Hepatobiliary disorders: elevations of liver enzymes, hyperbilirubinemia, cholestasis, hepatitis *[see Adverse Reactions (6.1)]*

## 7 DRUG INTERACTIONS

### 7.1 Oral Medications

VICTOZA causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, VICTOZA did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to VICTOZA during pregnancy. VICTOZA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that

approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Animal Data]*.

The estimated background risk of major birth defects for women with uncontrolled pre-gestational diabetes (Hemoglobin $A_{1C}$ >7) is 6 to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin $A_{1C}$ >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

*Disease-associated maternal and/or embryo/fetal risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications due to fetal macrosomia (e.g., perineal injury and lacerations, need for cesarean section, and post-partum hemorrhage). Poorly controlled diabetes increases the fetal risk for neural tube defects, cardiovascular malformations, oral clefts, still birth, macrosomia related morbidity (e.g., brachial plexus injury, hypoxia), and neonatal hyperglycemia.

Animal Data

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given 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 at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams.

Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in $F_2$ generation rats descended from liraglutide-treated rats compared to $F_2$ generation rats descended from controls, but differences did not reach statistical significance for any group.

### 8.2 Lactation

Risk Summary

There are no data on the presence of VICTOZA in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats *[see Data]*.

Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VICTOZA and any potential adverse effects on the breastfed infant from VICTOZA or from the underlying maternal condition.

Data

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

### 8.4 Pediatric Use

Safety and effectiveness of VICTOZA have not been established in pediatric patients. VICTOZA is not recommended for use in pediatric patients.

### 8.5 Geriatric Use

In the VICTOZA treatment arms of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In the VICTOZA treatment arm of the LEADER trial *[see Clinical Studies (14.2)]*, a total of 1738 (37.2%) patients were 65 to 74 years of age, 401 (8.6%) were 75 to 84 years of age, and 17 (0.4%) were 85 years of age or older at baseline. No overall differences in safety or efficacy were observed between these patients and younger patients.

### 8.6 Renal Impairment

No dose adjustment of VICTOZA is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*. The safety and efficacy of VICTOZA was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m$^2$) *[see Clinical Studies (14.1)]*.

In the VICTOZA treatment arm of the LEADER trial *[see Clinical Studies (14.2)]*, 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.

There is limited experience with VICTOZA in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis *[see Warnings and Precautions (5.5) and Adverse Reactions (6.2)]*. Use caution in patients who experience dehydration.

### 8.7 Hepatic Impairment
There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, VICTOZA should be used with caution in this patient population. No dose adjustment of VICTOZA is recommended for patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

### 8.8 Gastroparesis
VICTOZA slows gastric emptying. VICTOZA has not been studied in patients with pre-existing gastroparesis.

## 10 OVERDOSAGE
Overdoses have been reported in clinical trials and post-marketing use of VICTOZA. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

## 11 DESCRIPTION
VICTOZA contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae,* has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

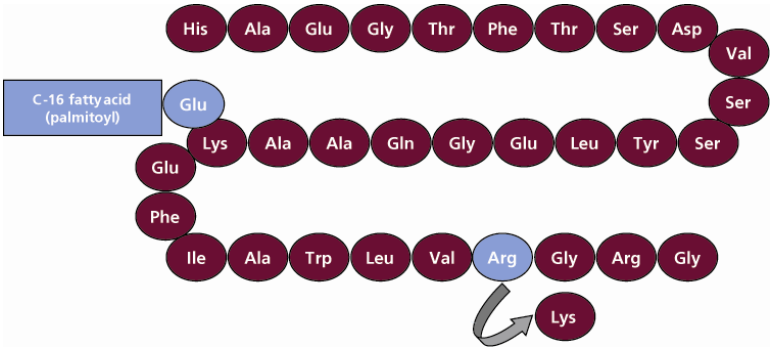



**Figure 1 Structural Formula of liraglutide**

VICTOZA is a clear, colorless or almost colorless solution. Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).

## 12 CLINICAL PHARMACOLOGY
### 12.1 Mechanism of Action
Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose

concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

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

### 12.2 Pharmacodynamics

VICTOZA's pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as VICTOZA lowered fasting, premeal and postprandial glucose throughout the day *[see Clinical Pharmacology (12.3)]*.

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg VICTOZA or placebo. Compared to placebo, the postprandial plasma glucose $AUC_{0\text{-}300min}$ was 35% lower after VICTOZA 1.2 mg and 38% lower after VICTOZA 1.8 mg.

*Glucose-dependent insulin secretion*

The effect of a single dose of 7.5 mcg/kg (~ 0.7 mg) VICTOZA on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

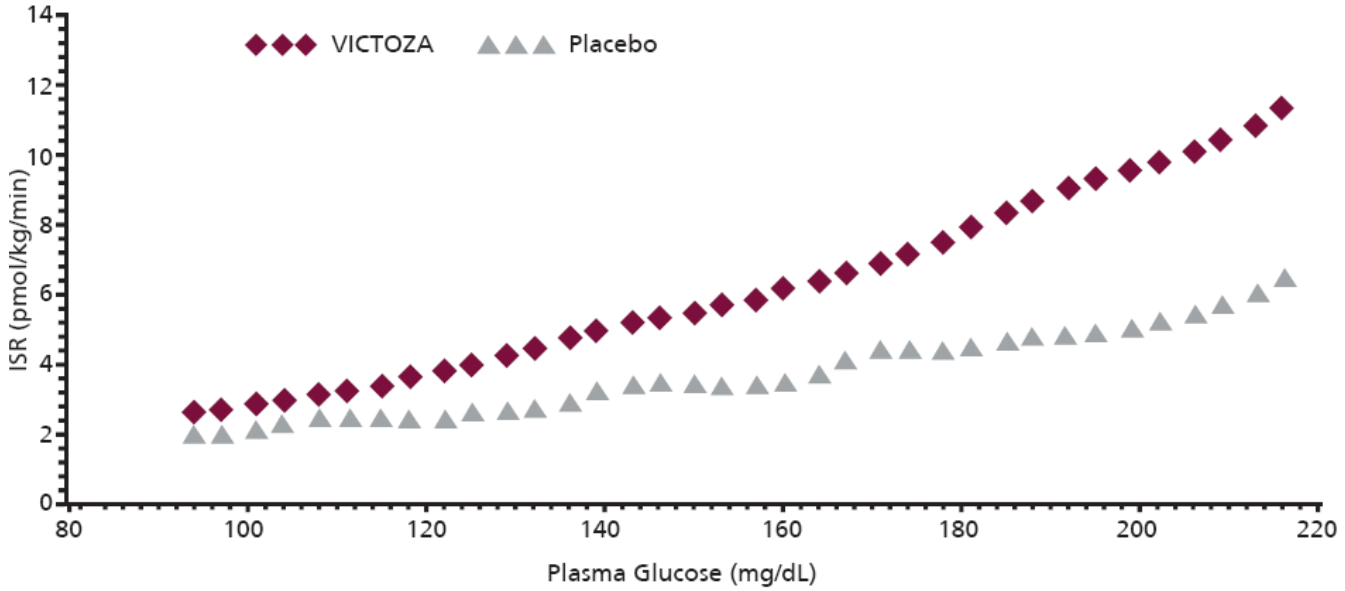



**Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose VICTOZA 7.5 mcg/kg (~ 0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion**

*Glucagon secretion*

VICTOZA lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of VICTOZA 7.5 mcg/kg (~ 0.7 mg) did not impair glucagon response to low glucose concentrations.

*Gastric emptying*
VICTOZA causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

*Cardiac Electrophysiology (QTc)*
The effect of VICTOZA on cardiac repolarization was tested in a QTc study. VICTOZA at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

**12.3 Pharmacokinetics**
*Absorption* - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak ($C_{max}$) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, $C_{max}$ and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg VICTOZA, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. $AUC_{0-\infty}$ was equivalent between upper arm and abdomen, and between upper arm and thigh. $AUC_{0-\infty}$ from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

*Distribution* - The mean apparent volume of distribution after subcutaneous administration of VICTOZA 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of VICTOZA is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

*Metabolism* - During the initial 24 hours following administration of a single [$^3$H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

*Elimination* - Following a [$^3$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 majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making VICTOZA suitable for once daily administration.

**Specific Populations**
*Elderly* - Age had no effect on the pharmacokinetics of VICTOZA based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age *[see Use in Specific Populations (8.5)]*.

*Gender* - Based on the results of population pharmacokinetic analyses, females have 25% lower weight-adjusted clearance of VICTOZA compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Treatment with insulin detemir as add-on to VICTOZA 1.8 mg + metformin resulted in statistically significant reductions in $HbA_{1c}$ and FPG compared to continued, unchanged treatment with VICTOZA 1.8 mg + metformin alone (Table 6). From a mean baseline body weight of 96 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received insulin detemir add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with VICTOZA 1.8 mg + metformin alone.

**Table 6 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 $HbA_{1c}$ < 7% after 12 weeks of Metformin and VICTOZA[a]**

| | **Insulin detemir + VICTOZA + Metformin** | **VICTOZA + Metformin** |
|---|---|---|
| **Intent-to-Treat Population (N)** | 162 | 157 |
| **$HbA_{1c}$ (%) (Mean)** | | |
| Baseline (week 0) | 7.6 | 7.6 |
| Change from baseline (adjusted mean) | -0.5 | 0 |
| Difference from VICTOZA + metformin arm (LS mean)[b] | -0.5** | |
| 95% Confidence Interval | (-0.7, -0.4) | |
| Percentage of patients achieving $A_{1c}$ <7% | 43 | 17 |
| **Fasting Plasma Glucose (mg/dL) (Mean)** | | |
| Baseline (week 0) | 166 | 159 |
| Change from baseline (adjusted mean) | -39 | -7 |
| Difference from VICTOZA + metformin arm (LS mean)[b] | -31** | |
| 95% Confidence Interval | (-39, -23) | |

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
**p-value <0.0001

*Add-on to Sulfonylurea*

In this 26-week trial, 1041 patients were randomized to VICTOZA 0.6 mg, VICTOZA 1.2 mg, VICTOZA 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

The mean age of participants was 56 years, and the mean duration of diabetes was 8 years. Participants were 49.4% male, 64.4% White and 2.8% Black or African American. The mean BMI was 29.9 $kg/m^2$.

Treatment with VICTOZA 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean $HbA_{1c}$ compared to placebo add-on to glimepiride (Table 7). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the VICTOZA 1.8 mg + glimepiride treatment group, 3.5% in the VICTOZA 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

**Table 7 Results of a 26-week trial of VICTOZA as add-on to sulfonylurea[a]**

| | VICTOZA 1.8 mg + Glimepiride | VICTOZA 1.2 mg + Glimepiride | Placebo + Glimepiride | Rosiglitazone 4 mg[†] + Glimepiride |
|---|---|---|---|---|
| **Intent-to-Treat Population (N)** | 234 | 228 | 114 | 231 |
| **$HbA_{1c}$ (%) (Mean)** | | | | |
| Baseline | 8.5 | 8.5 | 8.4 | 8.4 |
| Change from baseline (adjusted mean)[b] | -1.1 | -1.1 | +0.2 | -0.4 |
| Difference from placebo + glimepiride arm (adjusted mean)[b] | -1.4** | -1.3** | | |
| 95% Confidence Interval | (-1.6, -1.1) | (-1.5, -1.1) | | |
| Percentage of patients achieving $A_{1c}$ <7% | 42 | 35 | 7 | 22 |
| **Fasting Plasma Glucose (mg/dL) (Mean)** | | | | |
| Baseline | 174 | 177 | 171 | 179 |
| Change from baseline (adjusted mean)[b] | -29 | -28 | +18 | -16 |
| Difference from placebo + glimepiride arm (adjusted mean)[b] | -47** | -46** | | |
| 95% Confidence Interval | (-58, -35) | (-58, -35) | | |
| **Body Weight (kg) (Mean)** | | | | |
| Baseline | 83.0 | 80.0 | 81.9 | 80.6 |
| Change from baseline (adjusted mean)[b] | -0.2 | +0.3 | -0.1 | +2.1 |
| Difference from placebo + glimepiride arm (adjusted mean)[b] | -0.1 | 0.4 | | |
| 95% Confidence Interval | (-0.9, 0.6) | (-0.4, 1.2) | | |

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
[†] For rosiglitazone, one-half of the maximal approved United States dose.
**p-value <0.0001

*Add-on to Metformin and Sulfonylurea*

In this 26-week trial, 581 patients were randomized to VICTOZA 1.8 mg, placebo, or insulin glargine, 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, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. 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, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine 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 ≤100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

The mean age of participants was 58 years, and the mean duration of diabetes was 9 years. Participants were 56.5% male, 75.0% White and 3.6% Black or African American. The mean BMI was 30.5 $kg/m^2$.

Treatment with VICTOZA as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in $HbA_{1c}$ compared to placebo add-on to glimepiride and metformin (Table 8). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the VICTOZA 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

**Table 8 Results of a 26-week trial of VICTOZA as add-on to metformin and sulfonylurea[a]**

| | VICTOZA 1.8 mg + Metformin + Glimepiride | Placebo + Metformin + Glimepiride | Insulin glargine[†] + Metformin + Glimepiride |
|---|---|---|---|
| **Intent-to-Treat Population (N)** | 230 | 114 | 232 |
| **$HbA_{1c}$ (%) (Mean)** | | | |
| Baseline | 8.3 | 8.3 | 8.1 |
| Change from baseline (adjusted mean) [b] | -1.3 | -0.2 | -1.1 |
| Difference from placebo + metformin + glimepiride arm (adjusted mean) [b] | -1.1** | | |
| 95% Confidence Interval | (-1.3, -0.9) | | |
| Percentage of patients achieving $A_{1c}$ <7% | 53 | 15 | 46 |
| **Fasting Plasma Glucose (mg/dL) (Mean)** | | | |
| Baseline | 165 | 170 | 164 |
| Change from baseline (adjusted mean) [b] | -28 | +10 | -32 |
| Difference from placebo + metformin + glimepiride arm (adjusted mean) [b] | -38** | | |
| 95% Confidence Interval | (-46, -30) | | |
| **Body Weight (kg) (Mean)** | | | |
| Baseline | 85.8 | 85.4 | 85.2 |
| Change from baseline (adjusted mean) [b] | -1.8 | -0.4 | 1.6 |
| Difference from placebo + metformin + glimepiride arm (adjusted mean) [b] | -1.4* | | |
| 95% Confidence Interval | (-2.1, -0.7) | | |

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
[†] For insulin glargine, optimal titration regimen was not achieved for 80% of patients.
*p-value <0.05
**p-value <0.0001

*VICTOZA Compared to Exenatide, Both as Add-on to Metformin and/or Sulfonylurea Therapy*

In this 26–week, open-label trial, 464 patients on a background of metformin monotherapy, sulfonylurea monotherapy or a combination of metformin and sulfonylurea were randomized to once daily VICTOZA 1.8 mg or exenatide 10 mcg twice daily. Maximally tolerated doses of background therapy were to remain unchanged for the duration of the trial. Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily.

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 51.9% male, 91.8% White, 5.4% Black or African American and 12.3% of Hispanic ethnicity. The mean BMI was 32.9 $kg/m^2$.

Treatment with VICTOZA 1.8 mg resulted in statistically significant reductions in $HbA_{1c}$ and FPG relative to exenatide (Table 9). The percentage of patients who discontinued for ineffective therapy was 0.4% in the VICTOZA treatment group and 0% in the exenatide treatment group. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.

**Table 9 Results of a 26-week open-label trial of VICTOZA versus Exenatide (both in combination with metformin and/or sulfonylurea)[a]**

| | VICTOZA 1.8 mg once daily + metformin and/or sulfonylurea | Exenatide 10 mcg twice daily + metformin and/or sulfonylurea |
|---|---|---|

| | | |
|---|---|---|
| **Intent-to-Treat Population (N)** | 233 | 231 |
| **$HbA_{1c}$ (%) (Mean)** | | |
| Baseline | 8.2 | 8.1 |
| Change from baseline (adjusted mean) [b] | -1.1 | -0.8 |
| Difference from exenatide arm (adjusted mean) [b] | -0.3** | |
| 95% Confidence Interval | (-0.5, -0.2) | |
| Percentage of patients achieving $A_{1c}$ <7% | 54 | 43 |
| **Fasting Plasma Glucose (mg/dL) (Mean)** | | |
| Baseline | 176 | 171 |
| Change from baseline (adjusted mean) [b] | -29 | -11 |
| Difference from exenatide arm (adjusted mean) [b] | -18** | |
| 95% Confidence Interval | (-25, -12) | |

[a]Intent-to-treat population using last observation carried forward
[b]Least squares mean adjusted for baseline value
**p-value <0.0001

*Add-on to Metformin and Thiazolidinedione*

In this 26-week trial, 533 patients were randomized to VICTOZA 1.2 mg, VICTOZA 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

The mean age of participants was 55 years, and the mean duration of diabetes was 9 years. Participants were 61.6% male, 84.2% White, 10.2% Black or African American and 16.4% of Hispanic ethnicity. The mean BMI was 33.9 $kg/m^2$.

Treatment with VICTOZA as add-on to metformin and rosiglitazone produced a statistically significant reduction in mean $HbA_{1c}$ compared to placebo add-on to metformin and rosiglitazone (Table 10). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the VICTOZA 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the VICTOZA 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

**Table 10 Results of a 26-week trial of VICTOZA as add-on to metformin and thiazolidinedione[a]**

| | **VICTOZA 1.8 mg + Metformin + Rosiglitazone** | **VICTOZA 1.2 mg + Metformin + Rosiglitazone** | **Placebo + Metformin + Rosiglitazone** |
|---|---|---|---|
| **Intent-to-Treat Population (N)** | 178 | 177 | 175 |
| **$HbA_{1c}$ (%) (Mean)** | | | |
| Baseline | 8.6 | 8.5 | 8.4 |
| Change from baseline (adjusted mean) [b] | -1.5 | -1.5 | -0.5 |
| Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b] | -0.9** | -0.9** | |
| 95% Confidence Interval | (-1.1, -0.8) | (-1.1, -0.8) | |
| Percentage of patients achieving $A_{1c}$ <7% | 54 | 57 | 28 |
| **Fasting Plasma Glucose (mg/dL) (Mean)** | | | |
| Baseline | 185 | 181 | 179 |
| Change from baseline (adjusted mean) [b] | -44 | -40 | -8 |

| | | | |
|---|---|---|---|
| Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b]<br>95% Confidence Interval | -36**<br>(-44, -27) | -32**<br>(-41, -23) | |
| **Body Weight (kg) (Mean)** | | | |
| Baseline<br>Change from baseline (adjusted mean) [b]<br>Difference from placebo + metformin + rosiglitazone arm (adjusted mean) [b]<br>95% Confidence Interval | 94.9<br>-2.0<br>-2.6**<br>(-3.4, -1.8) | 95.3<br>-1.0<br>-1.6**<br>(-2.4, -1.0) | 98.5<br>+0.6 |

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
**p-value <0.0001

*VICTOZA Compared to Placebo Both With or Without metformin and/or Sulfonylurea and/or Pioglitazone and/or Basal or Premix insulin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment*

In this 26-week, double-blind, randomized, placebo-controlled, parallel-group trial, 279 patients with moderate renal impairment, as per MDRD formula (eGFR 30−59 mL/min/1.73 $m^2$), were randomized to VICTOZA or placebo once daily. VICTOZA was added to the patient's stable pre-trial antidiabetic regimen (insulin therapy and/or metformin, pioglitazone, or sulfonylurea). The dose of VICTOZA was escalated according to approved labeling to achieve a dose of 1.8 mg per day. The insulin dose was reduced by 20% at randomization for patients with baseline $HbA_{1c} \leq$ 8% and fixed until liraglutide dose escalation was complete. Dose reduction of insulin and SU was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of participants was 67 years, and the mean duration of diabetes was 15 years. Participants were 50.5% male, 92.3% White, 6.6% Black or African American, and 7.2% of Hispanic ethnicity. The mean BMI was 33.9 kg/$m^2$. Approximately half of patients had an eGFR between 30 and <45mL/min/1.73 $m^2$.

Treatment with VICTOZA resulted in a statistically significant reduction in $HbA_{1c}$ from baseline at Week 26 compared to placebo (see Table 11). 123 patients reached the 1.8 mg dose of VICTOZA.

**Table 11 Results of a 26-week trial of VICTOZA compared to placebo in Patients with Renal Impairment[a]**

| | VICTOZA 1.8 mg + insulin and/or OAD | Placebo + insulin and/or OAD |
|---|---|---|
| **Intent to Treat Population (N)** | 140 | 137 |
| **$HbA_{1c}$ (%)** | | |
| Baseline (mean)<br>Change from baseline (estimated mean) [b, c]<br>Difference from placebo[b, c]<br>95% Confidence Interval | 8.1<br>-0.9<br>-0.6*<br>(-0.8, -0.3) | 8.0<br>-0.4 |
| Proportion achieving $HbA_{1c}$ < 7% [d] | 39.3 | 19.7 |
| **FPG (mg/dL)** | | |
| Baseline (mean)<br>Change from baseline (estimated mean) [e]<br>Difference from placebo[e]<br>95% Confidence Interval | 171<br>-22<br>-12**<br>(-23, -0.8) | 167<br>-10 |

[a] Intent-to-treat population
[b] Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit. Multiple imputation method modeled "wash out" of the treatment effect for patients having missing data who discontinued treatment.
[c] Early treatment discontinuation, before week 26, occurred in 25% and 22% of VICTOZA and placebo patients, respectively.
[d] Based on the known number of subjects achieving $HbA_{1c}$ < 7%. When applying the multiple imputation method described in b) above, the estimated percents achieving $HbA_{1c}$ < 7% are 47.6% and 24.9% for VICTOZA and placebo, respectively.

[e] Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit.
*p-value <0.0001
**p-value <0.05

## 14.2 Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The LEADER trial (NCT01179048) was a multi-national, multi-center, placebo-controlled, double-blind trial. In this study, 9340 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to VICTOZA 1.8 mg or placebo for a median duration of 3.5 years. The study compared the risk of major adverse cardiovascular events between VICTOZA and placebo when these were added to, and used concomitantly with, background standard of care treatments for type 2 diabetes. The primary endpoint, MACE, was the time to first occurrence of a three part composite outcome which included; cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Patients eligible to enter the trial were; 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (80% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (20% of the enrolled population).

At baseline, demographic and disease characteristics were balanced. The mean age was 64 years and the population was 64.3% male, 77.5% Caucasian, 10.0% Asian, and 8.3% Black. In the study, 12.1% of the population identified as Hispanic or Latino. The mean duration of type 2 diabetes was 12.8 years, the mean HbA1c was 8.7% and the mean BMI was 32.5 $kg/m^2$. A history of previous myocardial infarction was reported in 31% of randomized individuals, a prior revascularization procedure in 39%, a prior ischemic stroke in 11%, documented symptomatic coronary disease in 9%, documented asymptomatic cardiac ischemia in 26%, and a diagnosis of New York Heart Association (NYHA) class II to III heart failure in 14%. The mean eGFR at baseline was 79 mL/min/1.73 $m^2$ and 41.8% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73$m^2$), 20.7% had moderate renal impairment (eGFR 30 to 60 mL/min/1.73$m^2$) and 2.4% of patients had severe renal impairment (eGFR < 30 mL/min/1.73$m^2$).

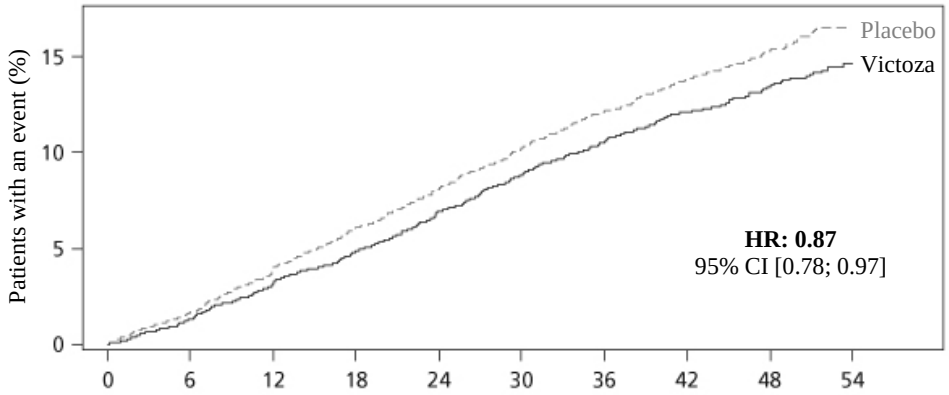
At baseline, patients treated their diabetes with; diet and exercise only (3.9%), oral antidiabetic drugs only (51.5%), oral antidiabetic drugs and insulin (36.7%) or insulin only (7.9%). The most common background antidiabetic drugs used at baseline and in the trial were metformin, sulfonylurea and insulin. Use of DPP-4 inhibitors and other GLP-1 receptor agonists was excluded by protocol and SGLT-2 inhibitors were either not approved or not widely available. At baseline, cardiovascular disease and risk factors were managed with; non-diuretic antihypertensives (92.4%), diuretics (41.8%), statin therapy (72.1%) and platelet aggregation inhibitors (66.8%). During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure, and manage patients recovering from an acute coronary syndrome or stroke event per local treatment guidelines.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and to test for superiority on MACE if non-inferiority was demonstrated. Type 1 error was controlled across multiple tests.

VICTOZA significantly reduced the time to first occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.87 (0.78, 0.97). Refer to Figure 5 and Table 12.

Vital status was available for 99.7% of subjects in the trial. A total of 828 deaths were recorded during the LEADER trial. A majority of the deaths in the trial were categorized as cardiovascular deaths and non-cardiovascular deaths were balanced between the treatment groups (3.5% in patients treated with VICTOZA and 3.6% in patients treated with placebo). The estimated hazard ratio of time to all-cause death for VICTOZA compared to placebo was 0.85 (0.74, 0.97).

**Figure 5 Kaplan-Meier: Time to First Occurrence of a MACE in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)**




Patients at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 4672 | 4587 | 4473 | 4352 | 4237 | 4123 | 4010 | 3914 | 1543 | 407 |
| Victoza | 4668 | 4593 | 4496 | 4400 | 4280 | 4172 | 4072 | 3982 | 1562 | 424 |

FAS: full analysis set.

**Table 12 Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)[a]**

| | VICTOZA N=4668 | Placebo N=4672 | Hazard Ratio (95% CI)[b] |
|---|---|---|---|
| Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (MACE) (time to first occurrence) [c] | 608 (13.0%) | 694 (14.9%) | 0.87 (0.78; 0.97) |
| Non-fatal myocardial infarction[d] | 281 (6.0%) | 317 (6.8%) | 0.88 (0.75;1.03) |
| Non-fatal stroke[d] | 159 (3.4%) | 177 (3.8%) | 0.89 (0.72;1.11) |
| Cardiovascular death[d] | 219 (4.7%) | 278 (6%) | 0.78 (0.66;0.93) |

[a]Full analysis set (all randomized patients)
[b]Cox-proportional hazards model with treatment as a factor
[c]p-value for superiority (2-sided) 0.011
[d]Number and percentage of first events

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

VICTOZA is available in the following package sizes containing disposable, pre-filled, multi-dose pens. Each individual pen delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL).

2 x VICTOZA pen NDC 0169-4060-12

3 x VICTOZA pen NDC 0169-4060-13

Each VICTOZA pen is for use by a single patient. A VICTOZA pen must never be shared between patients, even if the needle is changed.

### 16.2 Recommended Storage

Prior to first use, VICTOZA should be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC) (Table 13). 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 pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. VICTOZA should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. **Always use a new needle for each injection to prevent contamination.**

**Table 13 Recommended Storage Conditions for the VICTOZA Pen**

| **Prior to first use** | **After first use** | |
|---|---|---|
| Refrigerated<br>36°F to 46°F<br>(2°C to 8°C) | Room Temperature<br>59°F to 86°F<br>(15°C to 30°C) | Refrigerated<br>36°F to 46°F<br>(2°C to 8°C) |
| Until expiration date | 30 days | |

## 17 PATIENT COUNSELING INFORMATION

**FDA-Approved Medication Guide**

See separate leaflet.

**Risk of Thyroid C-cell Tumors**

Inform patients that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

**Dehydration and Renal Failure**

Advise patients treated with VICTOZA of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis.

**Pancreatitis**

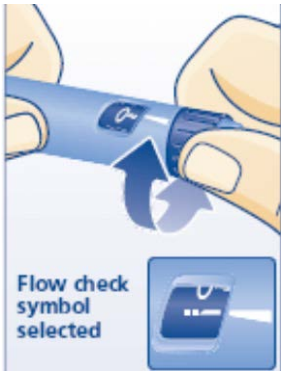
Inform patients of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue VICTOZA promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

**Acute Gallbladder Disease**

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up.

**Step C. Dial to the Flow Check Symbol**

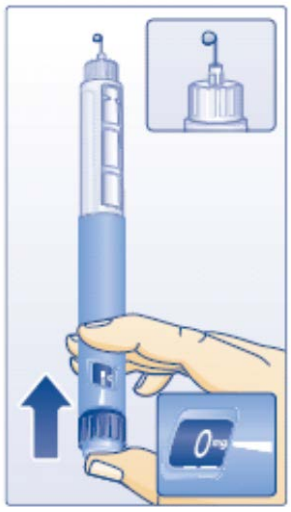
This step is done only ONCE for each new pen and is ONLY required the first time you use a new pen.




- Turn dose selector until flow check symbol (--) lines up with pointer. The flow check symbol does not administer the dose as prescribed by your healthcare provider.
- To select the dose prescribed by your healthcare provider, continue to Step G under “Routine Use”.

**Step D. Prepare the Pen**

- Hold pen with needle pointing up.
- Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge.
- Keep needle pointing up and press dose button until 0 mg lines up with pointer. Repeat steps C and D, up to 6 times, until a drop of Victoza appears at the needle tip.

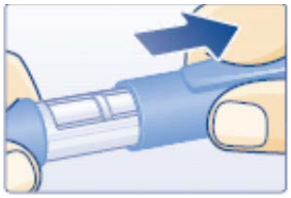


If you still see no drop of Victoza, use a new pen and contact Novo Nordisk at 1-877-484-2869.

**Continue to Step G under “Routine Use”** →

**Routine Use**

**Step E. Check the Pen**



- Take your Victoza pen from where it is stored.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your Victoza pen.

- Pull off pen cap.
- Check Victoza in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

**Step F. Attach the Needle**

- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.
- Pull off outer needle cap. Do not throw away.

- Pull off inner needle cap and throw away. A small drop of liquid may appear. This is normal.

**Step G. Dial the Dose**

- Victoza pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Victoza that is prescribed for you.
- Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg).


- You will hear a “click” every time you turn the dose selector. **Do not set the dose by counting the number of clicks you hear.**
- If you select a wrong dose, change it by turning the dose selector

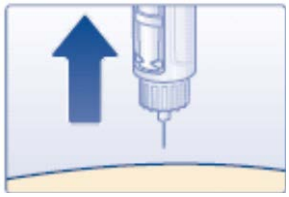
backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza to come out.

**Step H. Injecting the Dose**


- Insert needle into your skin in the stomach, thigh or upper arm. Use the injection technique shown to you by your healthcare provider. **Do not inject Victoza into a vein or muscle.**
- Press down on the center of the dose button to inject until 0 mg lines up with the pointer.
- Be careful not to touch the dose display with your other fingers. This may block the injection.

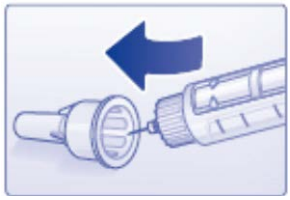

- Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin.
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

**Step I. Withdraw Needle**



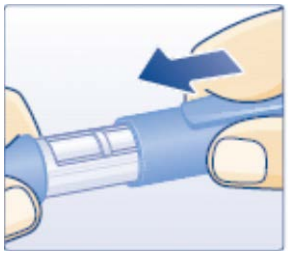
- You may see a drop of Victoza at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but **do not rub the area**.

**Step J. Remove and Dispose of the Needle**



- Carefully put the outer needle cap over the needle. Unscrew the needle.
- Safely remove the needle from your Victoza pen after each use.
- Put your used VICTOZA pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles with other people. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

**Caring for your Victoza pen**



- After removing the needle, put the pen cap on your Victoza pen and store your Victoza pen without the needle attached.
- Do not try to refill your Victoza pen – it is prefilled and is disposable.
- Do not try to repair your pen or pull it apart.
- Keep your Victoza pen away from dust, dirt and liquids.

- If cleaning is needed, wipe the outside of the pen with a clean, damp cloth.

**How should I store Victoza?**

**Before use:**

- Store your new, unused Victoza pen in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC).
- If Victoza is stored outside of refrigeration (by mistake) prior to first use, it should be used or thrown away within 30 days.
- Do not freeze Victoza or use Victoza if it has been frozen. Do not store Victoza near the refrigerator cooling element.

**Pen in use:**

- Store your Victoza pen for 30 days at 59ºF to 86ºF (15ºC to 30ºC), or in a refrigerator at 36ºF to 46ºF (2°C to 8°C).
- When carrying the pen away from home, store the pen at a temperature between 59ºF to 86ºF (15ºC to 30ºC).
- If Victoza has been exposed to temperatures above 86ºF (30°C), it should be thrown away.
- Protect your Victoza pen from heat and sunlight.
- Keep the pen cap on when your Victoza pen is not in use.
- Use a Victoza pen for only 30 days. Throw away a used Victoza pen after 30 days, even if some medicine is left in the pen.