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
• to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

**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).

**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, 6.6, 12.3).
- Pregnancy: VICTOZA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

**Full Prescribing Information: Contents**

**INDICATIONS AND USAGE**
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• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

**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).

**Recent Major Changes**
Indications and Usage (1) ——— 8/2017
Contraindications (4) ——— 8/2017
Warnings and Precautions (5.2, 5.6, 5.7) ——— 8/2017

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

**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).

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

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See 17 for PATIENT COUNSELING INFORMATION and FDA−Approved Medication Guide. Revised: 08/2017

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Warnings and Precautions (5.2, 5.6, 5.7) ——— 8/2017

**Warnings and Precautions**
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).

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See 17 for PATIENT COUNSELING INFORMATION and FDA−Approved Medication Guide. Revised: 08/2017
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 reinstatement 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 (6.6)).

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).

- Hypersensitivities

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 (5.4)).

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) in rodent studies and clinically relevant exposures in both genders of 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.

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 glyceric 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-1 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 cholecystitis or cholecystolithiasis. The majority of events required hospitalization or cholecystectomy. If cholecystitis 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 16,733 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% 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® (see Contraindications (4) and Warnings and Precautions (5.1)).
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 HbA1c 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo N = 661</th>
<th>Liraglutide 1.2 mg N = 645</th>
<th>Liraglutide 1.8 mg N = 1024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Add-on to Metformin</th>
<th>Placebo Comparator</th>
<th>VICTOZA® Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient not able to self-treat</td>
<td>0</td>
<td>0.1 (0.001)</td>
</tr>
<tr>
<td>Patient able to self-treat</td>
<td>2.5 (0.06)</td>
<td>3.6 (0.05)</td>
</tr>
</tbody>
</table>

Add-on to Glimepiride

| 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

| 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

| Patient not able to self-treat | 0                  | 0                  |
| Patient able to self-treat     | 16.7 (0.95)        | 27.4 (1.16)        |
| Not classified                  | 0                  | 0                  |

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. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in 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 6.6% 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 HbA1c of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with VICTOZA® treatment.

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®.

- 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)]
**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 A1C >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 A1C >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 based on plasma AUC comparison. The incidence 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 fetotoxic effects in liraglutide-treated groups exceeding concurrent and historical controls were misshapen orofarynx 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 increased 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, vertebræ 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 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.

**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.

**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/1.73m²) [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 Gastroparegia**

VICTOZA® slows gastric emptying. VICTOZA® has not been studied in patients with pre-existing gastroparegia.

**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 overdose, 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 C172H254N23O33 and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

![Figure 1 Structural Formula of liraglutide](image-url)

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 adenyl 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.
VICTOZA® (liraglutide) injection, for subcutaneous use

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 AUC0-120 min was 35% lower after VICTOZA® 1.2 mg and 36% 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

12.3 Pharmacokinetics

Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (Cmax) and total (AUC) exposures 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. AUC0-∞ was equivalent between upper arm and abdomen, and between upper arm and thigh. AUC0-12 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 (>88%).

Metabolism - Following the initial 24 hours following administration of a single [3H]-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 [3H]-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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, and 40- times the human exposure, respectively, at the MRHD of 1.8 mg/day based on AUC and plasma comparison. A dose-related increase in benign thyroid C-cell adenomas was seen 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 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell adenomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was 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 the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid neoplasms was seen in males and females in the 0.75 mg/kg/day liraglutide group with incidences of 8% and 24%, respectively. There were no treatment-related increases in malignant thyroid neoplasms in the 0.25 mg/kg/day liraglutide group.

In a 2-year carcinogenicity study in Fischer 344 rats administered with VICTOZA® 0.075, 0.25 and 0.75 mg/kg/day liraglutide by bolus subcutaneous injection with postprandial plasma AUC exposures 0.5-, 2-, and 8-times the human exposure, respectively, the exposure-response data demonstrated no evidence of carcinogenic potential.
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%, 4%, 6%, 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.

Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the RARα or RARβ/γ proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies [see Boxed Warning and Warnings and Precautions (5.1)]. Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose in vivo micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, 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 was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11 times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

In glycemic control trials, VICTOZA® has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin. VICTOZA® was also studied in a cardiovascular outcomes trial (LEADER trial).

In each of the placebo controlled trials, treatment with VICTOZA® produced clinically and statistically significant improvements in hemoglobin A1c and fasting plasma glucose (FPG) compared to placebo. All VICTOZA®-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. VICTOZA® 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance [see Dosage and Administration (2)].

Monotherapy

In this 52-week trial, 746 patients were randomized to VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, or glimepiride 8 mg. 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. Treatment with VICTOZA® 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA1c for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with VICTOZA® 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA1c for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily.

Table 3  Results of a 52-week monotherapy trial

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg</th>
<th>VICTOZA® 1.2 mg</th>
<th>Glimepiride 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat Population (N)</td>
<td>246</td>
<td>251</td>
</tr>
<tr>
<td>HbA1c (%) (Mean)</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.1</td>
<td>-0.8</td>
</tr>
<tr>
<td>Difference from glimepiride (adjusted mean)</td>
<td>-0.6**</td>
<td>-0.3*</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-0.8, -0.4)</td>
<td>(-0.5, -0.1)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c &lt;7%</td>
<td>51</td>
<td>43</td>
</tr>
</tbody>
</table>

Fasting Plasma Glucose (mg/dL)(Mean)

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg</th>
<th>VICTOZA® 1.2 mg</th>
<th>Glimepiride 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>172</td>
<td>168</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-2.6</td>
<td>-1.5</td>
</tr>
<tr>
<td>Difference from glimepiride (adjusted mean)</td>
<td>-0.2**</td>
<td>-0.7**</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-2.9, -1.3)</td>
<td>(-1.9, -0.1)</td>
</tr>
</tbody>
</table>

Body Weight (kg) (Mean)

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg</th>
<th>VICTOZA® 1.2 mg</th>
<th>Glimepiride 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>92.6</td>
<td>92.1</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-2.5</td>
<td>-2.1</td>
</tr>
<tr>
<td>Difference from glimepiride (adjusted mean)</td>
<td>-3.4**</td>
<td>-3.7**</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-3.8, -2.6)</td>
<td>(-3.9, -2.5)</td>
</tr>
</tbody>
</table>

Table 3  Results of a 52-week monotherapy trial

In this 26-week trial, 1091 patients were randomized to VICTOZA® 0.6 mg, VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day. Treatment with VICTOZA® 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA1c reduction relative to placebo add-on to metformin and resulted in a similar mean HbA1c reduction relative to glimepiride 4 mg add-on to metformin (Table 4). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the VICTOZA® 1.6 mg + metformin treatment group, 3.3% in the VICTOZA® 1.2 mg + metformin treatment group, and 3.7% in the glimepiride + metformin treatment group.

The mean age of participants was 57 years, and the mean duration of diabetes was 7 years. Participants were 58.2% male, 87.1% White and 2.4% Black or African American. The mean BMI was 31.0 kg/m².

Table 4  Results of a 26-week trial of VICTOZA® as add-on to metformin

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg</th>
<th>VICTOZA® 1.2 mg</th>
<th>Placebo + Metformin</th>
<th>Glimepiride 4 mg + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat Population (N)</td>
<td>242</td>
<td>121</td>
<td>242</td>
</tr>
<tr>
<td>HbA1c (%) (Mean)</td>
<td>8.4</td>
<td>8.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.0</td>
<td>-1.0</td>
<td>+0.1</td>
</tr>
<tr>
<td>Difference from placebo + metformin arm (adjusted mean)</td>
<td>-1.0**</td>
<td>-1.0**</td>
<td>-1.0*</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-1.3, -0.9)</td>
<td>(-1.3, -0.9)</td>
<td>(-1.4, -0.8)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c &lt;7%</td>
<td>42</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL) (Mean)</td>
<td>181</td>
<td>179</td>
<td>182</td>
</tr>
<tr>
<td>Baseline</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-30</td>
<td>-27</td>
<td>-7</td>
</tr>
<tr>
<td>Difference from placebo + metformin arm (adjusted mean)</td>
<td>-38**</td>
<td>-37**</td>
<td>-41*</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-48, -27)</td>
<td>(-47, -26)</td>
<td>(-54, -15)</td>
</tr>
<tr>
<td>Difference from glimepiride + metformin arm (adjusted mean)</td>
<td>-7</td>
<td>-6</td>
<td>-3</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-16, -2)</td>
<td>(-15, -3)</td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg) (Mean)</td>
<td>88.0</td>
<td>88.5</td>
<td>89.0</td>
</tr>
<tr>
<td>Baseline</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-2.8</td>
<td>-2.6</td>
<td>-1.5</td>
</tr>
<tr>
<td>Difference from placebo + metformin arm (adjusted mean)</td>
<td>-3.1**</td>
<td>-3.2**</td>
<td>-3.4**</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-4.5, -2.0)</td>
<td>(-3.9, -2.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4  Results of a 26-week trial of VICTOZA® as add-on to metformin

14.2 VICTOZA® Compared to Sitagliptin, Both as Add-on to Metformin

In this 26-week, open-label trial, 665 patients on a background of metformin ≥1500 mg per day were randomized to VICTOZA® 1.2 mg once-daily, VICTOZA® 1.8 mg once-daily or sitagliptin 100 mg once-daily, all dosed according to approved labeling. Patients were to continue their current treatment on metformin at a stable, pre-trial dose level and dosing frequency.
The mean age of participants was 56 years, and the mean duration of diabetes was 6 years. Participants were 52.9% male, 86.6% White, 7.2% Black or African American and 16.2% of Hispanic ethnicity. The mean BMI was 32.8 kg/m².

The primary endpoint was the change in HbA1c from baseline to Week 26. Treatment with VICTOZA® 1.2 mg and VICTOZA® 1.8 mg resulted in statistically significant reductions in HbA1c relative to sitagliptin 100 mg (Table 5). The percentage of patients who discontinued due to ineffective therapy was 3.1% in the VICTOZA® 1.2 mg group, 0.5% in the VICTOZA® 1.8 mg treatment group, and 4.1% in the sitagliptin 100 mg treatment group.

From a mean baseline body weight of 94 kg, there was a mean reduction of 2.7 kg for VICTOZA® 1.2 mg, 3.3 kg for VICTOZA® 1.8 mg, and 0.8 kg for sitagliptin 100 mg.

Table 5 Results of a 26-week open-label trial of VICTOZA® Compared to Sitagliptin (both in combination with metformin)

<table>
<thead>
<tr>
<th>Intent-to-Treat Population (N)</th>
<th>VICTOZA® 1.8 mg + Metformin</th>
<th>VICTOZA® 1.2 mg + Metformin</th>
<th>Sitagliptin 100 mg + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%) (Mean)</td>
<td>7.6</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.5</td>
<td>-0.5**</td>
<td>-0.5**</td>
</tr>
<tr>
<td>Difference from VICTOZA® + metformin arm (LS mean)</td>
<td>-0.5**</td>
<td>-0.5**</td>
<td>-0.5**</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(-0.7, -0.4)</td>
<td>(-0.6, -0.4)</td>
<td>(-0.6, -0.4)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c&lt;7%</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>

Fasting Plasma Glucose (mg/dL) (Mean)

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose (mg/dL) (Mean)</th>
<th>Baseline</th>
<th>Change from baseline (adjusted mean)</th>
<th>Difference from sitagliptin arm (adjusted mean)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.4</td>
<td>-1.5</td>
<td>-0.6**</td>
<td>(-0.8, -0.4)</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
<td>-1.2</td>
<td>-0.9</td>
<td>(-0.5, -0.4)</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 2 mg/day or 0 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/m².

Treatment with VICTOZA® 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA1c 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, 7.5% 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

Combination Therapy with Metformin and Insulin

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA1c 7-10%) on metformin (>1500 mg/day) alone or inadequate glycemic control (HbA1c 7-8.5%) on metformin (>1500 mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then 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. At the end of the run-in period, 496 patients (50%) achieved HbA1c<7% with VICTOZA® 1.8 mg and metformin and continued treatment in a non-randomized, 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 Adverse Reactions (6.1)). The remaining 323 patients with HbA1c≥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. During the 26 week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% 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 mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic ethnicity. The mean BMI was 34.0 kg/m².

Treatment with insulin detemir as add-on to VICTOZA® 1.8 mg + metformin resulted in a statistically significant reduction in HbA1c and FPG compared to continued, unchanged treatment with VICTOZA® 1.8 mg + metformin alone. After Week 8, the frequency of self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin detemir administered was 39 units/day. During the 26 week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with VICTOZA® 1.2 mg and metformin and 1.2% in the group randomized to add-on therapy with insulin detemir.
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 ≤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/m². Treatment with VICTOZA® as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA₁c, 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

<table>
<thead>
<tr>
<th>Intent-to-Treat Population (N)</th>
<th>VICTOZA® 1.8 mg + Metformin + Glimepiride</th>
<th>Placebo + Metformin + Glimepiride</th>
<th>Insulin glargine + Metformin + Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%) (Mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.3</td>
<td>-0.2</td>
<td>-1.1</td>
</tr>
<tr>
<td>Difference from placebo + metformin + glimepiride arm (adjusted mean)</td>
<td>-1.1**</td>
<td>1.0**</td>
<td>(-1.3, -0.9)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of patients achieving A₁c &lt;7%</td>
<td>53</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL) (Mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>165</td>
<td>170</td>
<td>164</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-28</td>
<td>10</td>
<td>-32</td>
</tr>
<tr>
<td>Difference from placebo + metformin + glimepiride arm (adjusted mean)</td>
<td>-36**</td>
<td>36**</td>
<td>(-46, -30)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg) (Mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>85.8</td>
<td>85.4</td>
<td>85.2</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.8</td>
<td>0.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Difference from placebo + metformin + glimepiride arm (adjusted mean)</td>
<td>-1.4**</td>
<td>-0.7</td>
<td>(-2.1, -0.7)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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. Maximal 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 51.5% male, 91.8% White, 5.4% Black or African American and 12.3% of Hispanic ethnicity. The mean BMI was 33.9 kg/m². Treatment with VICTOZA® 1.8 mg resulted in statistically significant reductions in HbA₁c, from baseline at Week 6 and Week 26 (Table 9). 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 9 Results of a 26-week open-label trial of VICTOZA® versus Exenatide (both in combination with metformin and/or sulfonylurea)

<table>
<thead>
<tr>
<th>Intent-to-Treat Population (N)</th>
<th>VICTOZA® 1.8 mg once daily + metformin and/or sulfonylurea</th>
<th>Exenatide 10 mcg twice daily + metformin and/or sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%) (Mean)</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.1</td>
<td>-1.1</td>
</tr>
<tr>
<td>Difference from exenatide arm (adjusted mean)</td>
<td>-0.3**</td>
<td>0.8</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of patients achieving A₁c &lt;7%</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL) (Mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>176</td>
<td>171</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-11</td>
<td>-11</td>
</tr>
<tr>
<td>Difference from exenatide arm (adjusted mean)</td>
<td>-18**</td>
<td>-11</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**p-value <0.0001

VICTOZA® (liraglutide) injection, for subcutaneous use
of the population identified as Hispanic or Latino. The mean duration of type 2 diabetes was 12.8 years, and the population was 64.3% male, 77.5% Caucasian, 10.0% Asian, and 8.3% Black. In the study, 12.1% of patients reported prior myocardial infarction, 36.2% reported prior ischemic stroke, 7.6% reported unstable angina, 24.4% had prior ischemic heart failure, 26.7% had documented coronary artery disease, 5.6% had documented peripheral artery disease, 21.7% had documented lower extremity arterial disease, 17.9% had documented retinal disease, and 21.2% had documented aortic disease. Prior to randomization, patients were treated with background antidiabetic drugs used at baseline and in the trial were metformin, sulfonylurea and/or thiazolidinedione, DPP-4 inhibitors, GLP-1 receptor agonists, and insulin. Use of DPP-4 inhibitors and other GLP-1 receptor agonists was excluded by protocol and design.

At baseline, patients treated their diabetes with; diet and exercise only (3.9%), oral antidiabetic drugs (51.5%), oral antidiabetic drugs and insulin (36.7%) or insulin only (7.9%). The most common background antidiabetic medications 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 design.

Boxed Warning and Warnings and Precautions (5.1). Adequate and well-controlled studies have not been conducted to determine whether VICTOZA® treatment results in a clinically relevant reduction in the rate of cardiovascular events and death. The longer-term potential of VICTOZA® treatment to prevent cardiovascular disease and death is unknown.

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 therapies for type 2 diabetes. The primary endpoint, MACE, was the time to first occurrence of a composite of 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 arterial 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/m². 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 m² and 41.8% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73m²), 20.7% had moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²) and 2.4% of patients had severe renal impairment (eGFR < 30 mL/min/1.73m²).

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 medications 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 design.

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 0.85 (0.74, 0.97). Refer to Figure 5 and Table 12.
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.

Never Share a VICTOZA® Pen Between Patients
Advise patients that they must never share a VICTOZA® pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of VICTOZA®. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking VICTOZA® and seek medical advice promptly if such symptoms occur [see Warnings and Precautions (5.6)].

Jaundice and Hepatitis
Inform patients that jaundice and hepatitis have been reported during postmarketing use of liraglutide. Instruct patients to contact their physician if they develop jaundice.

Instructions
Advise patients that the most common side effects of VICTOZA® are headache, nausea and diarrhea. Nausea is most common when first starting VICTOZA®, but decreases over time in the majority of patients and does not typically require discontinuation of VICTOZA®.

Inform patients not to take an extra dose of VICTOZA® to make up for a missed dose. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. If more than 3 days have elapsed since the last dose, advise the patient to reinitiate VICTOZA® at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. VICTOZA® should be titrated at the discretion of the prescribing physician [see Dosage and Administration (2)].
**Victoza® (liraglutide) injection, for subcutaneous use**

**Medication Guide**

**Victoza® (VIC-tow-za)**

(liraglutide) injection, for subcutaneous use

Read this Medication Guide before you start using Victoza® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about Victoza®?**

**Victoza® may cause serious side effects, including:**

- Possible thyroid tumors, including cancer. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, Victoza® and medicines that work like Victoza® caused thyroid tumors, including thyroid cancer. It is not known if Victoza® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use Victoza® if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

**What is Victoza®?**

Victoza® is an injectable prescription medicine for adults with type 2 diabetes mellitus that:
- along with diet and exercise may improve blood sugar (glucose).
- along with your current treatment for your cardiovascular disease may reduce the risk of major cardiovascular events such as heart attack, stroke or death.
- is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis. It is not known if Victoza® can be used with mealtime insulin. It is not known if Victoza® is safe and effective for use in children.

**Who should not use Victoza®?**

Do not use Victoza® if:
- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you are allergic to liraglutide or any of the ingredients in Victoza®. See the end of this Medication Guide for a complete list of ingredients in Victoza®.

**What should I tell my healthcare provider before using Victoza®?**

Before using Victoza®, tell your healthcare provider if you have any other medical conditions, including if you:
- have or have had problems with your pancreas, kidneys, or liver.
- have severe problems with your stomach, such as slow emptying of your stomach (gastroparesis) or problems with digesting food.
- are pregnant or plan to become pregnant. It is not known if Victoza® will harm your unborn baby. Tell your healthcare provider if you become pregnant while using Victoza®.
- are breastfeeding or plan to breastfeed. It is not known if Victoza® passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using Victoza®.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Victoza® may affect the way some medicines work and some medicines may affect the way Victoza® works.

**How should I use Victoza®?**

- Read the Instructions for Use that comes with Victoza®.
- Use Victoza® exactly as your healthcare provider tells you to.
- Your healthcare provider should show you how to use Victoza® before you use it for the first time.
- Victoza® is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. Do not inject Victoza® into a muscle (intramuscularly) or vein (intravenously).
- Use Victoza® 1 time each day, at any time of the day.
- If you miss a dose of Victoza®, take the missed dose at the next scheduled dose. Do not take 2 doses of Victoza® at the same time.
- Victoza® may be taken with or without food.
- Do not mix insulin and Victoza® together in the same injection.
- You may give an injection of Victoza® and insulin in the same body area (such as your stomach area), but not right next to each other.
- Change (rotate) your injection site with each injection. Do not use the same site for each injection.
- Do not share your Victoza® pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

**What is the most common side effects of Victoza®?**

Victoza® may cause serious side effects, including:
- See “What is the most important information I should know about Victoza®?”
- Inflammation of your pancreas (pancreatitis). Stop using Victoza® and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- Low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use Victoza® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin.

**Signs and symptoms of low blood sugar may include:**

- dizziness or light-headedness
- anxiety, irritability, or mood changes
- slurred speech
- confusion or drowsiness
- weakness
- fast heartbeat
- kidney problems (kidney failure). In people who have kidney problems, diabetes, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
- serious allergic reactions. Stop using Victoza® and get medical help right away, if you have any symptoms of a serious allergic reaction including:
  - Swelling of your face, lips, tongue or throat
  - Problems breathing or swallowing
  - Severe rash or itching
- gallbladder problems. Gallbladder problems have happened in some people who take Victoza®. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
  - pain in the right or middle upper stomach area
  - fever
  - nausea and vomiting
  - your skin or the white part of your eyes turns yellow

**The most common side effects of Victoza® may include:**

- nausea, diarrhea, vomiting, decreased appetite, indigestion and constipation.

**Tell your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of Victoza®.**

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of Victoza®.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Victoza® for a condition for which it was not prescribed. Do not give Victoza® to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Victoza® that is written for health professionals.

**What are the ingredients in Victoza®?**

**Active Ingredient:** liraglutide

**Inactive Ingredients:** disodium phosphate dihydrate, propylene glycol, phenol and water for injection

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

Victoza® is a registered trademark of Novo Nordisk A/S.

For more information, go to victoza.com or call 1-877-848-2869.


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Instructions for Use
Victoza® (liraglutide) injection

First read the Medication Guide that comes with your Victoza® pen and then read these Patient Instructions for Use for information about how to use your Victoza® pen the right way.

These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment.

Do not share your Victoza® Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Your Victoza® pen contains 3 mL of Victoza® and will deliver doses of 0.6 mg, 1.2 mg or 1.8 mg. The number of doses that you can take with a Victoza® pen depends on the dose of medicine that is prescribed for you. Your healthcare provider will tell you how much Victoza® to take.

Victoza® pen should be used with Novo Nordisk disposable needles. Talk to your healthcare provider or pharmacist for more information about needles for your Victoza® pen.

Important Information

- Do not share your Victoza® pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.
- Always use a new needle for each injection. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.
- Keep your Victoza® pen and all medicines out of the reach of children.
- If you drop your Victoza® pen, repeat “First Time Use For Each New Pen” (steps A through D).
- Be careful not to bend or damage the needle.
- Do not use the cartridge scale to measure how much Victoza® to inject.
- Be careful when handling used needles to avoid needle stick injuries.
- You can use your Victoza® pen for up to 30 days after you use it the first time.

First Time Use for Each New Pen

Step A. Check the Pen
- Take your new Victoza® pen out of the refrigerator.
- 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 B. 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 C. Dial to the Flow Check Symbol
- 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 (2ºC to 8ºC).
- 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 (30ºC), 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.