Saxenda®
liraglutide injection 3mg

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

SAXENDA® (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 Saxenda® 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).

• Saxenda® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma 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, 13.1).

——— RECENT MAJOR CHANGES ———
Indications and Usage, Limitations of Use (1). Removed 3/2020
Dosage and Administration (2). 3/2020
Warnings and Precautions (5.4). 3/2020

——— INDICATIONS AND USAGE ———
Saxenda® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:
• 30 kg/m² or greater (obesity) (1) or
• 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) (1).

Limitations of Use:
• Saxenda® is not indicated for the treatment of type 2 diabetes (1).
• Saxenda® should not be used in combination with any other GLP-1 receptor agonist (1).
• The safety and efficacy of coadministration with other products for weight loss have not been established (1).

——— DOSAGE AND ADMINISTRATION ———
Recommended dose of Saxenda® is 3 mg daily. Administer at any time of day, without regard to the timing of meals (2).
Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached (2).
Inject subcutaneously in the abdomen, thigh or upper arm (2).
The injection site and timing can be changed without dose adjustment (2).

——— DOSAGE FORMS AND STRENGTHS ———
Injection, pre-filled, multi-dose, pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg (6 mg/mL, 3 mL) (3).

——— CONTRAINDICATIONS ———
Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1).
Hypersensitivity to liraglutide or any product components (4, 5.7).
Renal impairment (5.6).

——— WARNINGS AND PRECAUTIONS ———
Thyroid C-cell Tumors: See Boxed Warning (5.1).
Acute Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.3).
Serious Hypoglycemia: Can occur when Saxenda® is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin. Consider lowering the dose of anti-diabetic drugs to reduce the risk of hypoglycemia (2, 5.4).
Heart Rate Increase: Monitor heart rate at regular intervals (5.5).
Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Saxenda® in patients with renal impairment (5.6).
Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue Saxenda® and other suspect medications and promptly seek medical advice (5.7).
Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Saxenda® if symptoms develop (5.8).

——— ADVERSE REACTIONS ———
Most common adverse reactions, reported in greater than or equal to 5%: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-844-363-4448 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

——— DRUG INTERACTIONS ———
Saxenda® delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution (7).

——— USE IN SPECIFIC POPULATIONS ———
Pediatrie Use: Safety and effectiveness not established and use not recommended (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2020

FULL PRESCRIBING INFORMATION: CONTENTS* BOXED WARNING: RISK OF THYROID C-CELL TUMORS

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3 DOSAGE FORMS AND STRENGTHS
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1 INDICATIONS AND USAGE

Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:
- 30 kg/m² or greater (obesity), or
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Saxenda® is administered by subcutaneous injection once daily. The starting dose is 3 mg. The dose may be increased in increments of 1.8 mg at weekly intervals to a maximum of 18 mg.

2.2 Dose Escalation

Table 1. Dose Escalation Schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>2</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>3</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>4</td>
<td>2.4 mg</td>
</tr>
<tr>
<td>5 and onward</td>
<td>3 mg</td>
</tr>
</tbody>
</table>

Saxenda® should be taken once daily at any time of day, without regard to the timing of meals. Saxenda® can be injected subcutaneously in the abdomen, thigh, or upper arm. The injection site and timing can be changed without dose adjustment. Saxenda® must not be administered intravenously or intramuscularly.

Table 2. BMI Conversion Chart

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Height (in)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>58</td>
<td>24.9</td>
</tr>
<tr>
<td>130</td>
<td>58</td>
<td>25.3</td>
</tr>
<tr>
<td>135</td>
<td>60</td>
<td>25.7</td>
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<tr>
<td>140</td>
<td>62</td>
<td>26.0</td>
</tr>
<tr>
<td>145</td>
<td>64</td>
<td>26.3</td>
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<tr>
<td>150</td>
<td>66</td>
<td>26.7</td>
</tr>
<tr>
<td>155</td>
<td>68</td>
<td>27.0</td>
</tr>
<tr>
<td>160</td>
<td>70</td>
<td>27.3</td>
</tr>
<tr>
<td>165</td>
<td>72</td>
<td>27.6</td>
</tr>
<tr>
<td>170</td>
<td>74</td>
<td>27.9</td>
</tr>
<tr>
<td>175</td>
<td>76</td>
<td>28.2</td>
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<tr>
<td>180</td>
<td>78</td>
<td>28.5</td>
</tr>
<tr>
<td>185</td>
<td>80</td>
<td>28.8</td>
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<tr>
<td>190</td>
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<td>29.1</td>
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<tr>
<td>195</td>
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<td>29.4</td>
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<tr>
<td>200</td>
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<td>29.7</td>
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<tr>
<td>205</td>
<td>88</td>
<td>30.0</td>
</tr>
<tr>
<td>210</td>
<td>90</td>
<td>30.3</td>
</tr>
<tr>
<td>215</td>
<td>92</td>
<td>30.6</td>
</tr>
<tr>
<td>220</td>
<td>94</td>
<td>30.9</td>
</tr>
<tr>
<td>225</td>
<td>96</td>
<td>31.2</td>
</tr>
</tbody>
</table>

3 DOSAGE FORMS AND STRENGTHS

Solution for subcutaneous injection, pre-filled, multi-dose, pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg (6 mg/mL, 3 mL).

4 CONTRAINDICATIONS

Saxenda® is contraindicated in:
- Patients with a personal or family history of medullary thyroid carcinoma (MTC) or patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see Warnings and Precautions (5.1)].
- Patients with a prior serious hypersensitivity reaction to liraglutide or to any of the product components [see Warnings and Precautions (5.2)].
- Pregnancy [see Use in Specific Populations (8.1)].

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 Saxenda® 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 liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.

Saxenda® 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 Saxenda® 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 Saxenda® [see Contraindications (4), Warnings and Precautions (5.1)].

5.2 Acute Pancreatitis

Saxenda® is contraindicated in patients with a personal or family history of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, which has been observed in patients treated with liraglutide. After initial initiation of Saxenda®, 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, Saxenda® should be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Saxenda® should not be restarted.

In Saxenda® clinical trials, acute pancreatitis was confirmed by adjudication in 6 (0.3%) of 3291 Saxenda®-treated patients and 2 (0.1%) of 1843 placebo-treated patients. In addition, there were 2 cases of acute pancreatitis in Saxenda®-treated patients who prematurely withdrew from these clinical trials, occurring 74 and 124 days after the last dose. There were 2 additional cases in Saxenda®-treated patients, 1 during an off-treatment follow-up period within 2 weeks of discontinuing Saxenda®, and 1 that occurred in a patient who completed treatment and was off-treatment for 106 days.

When initiating Saxenda® in patients taking insulin secretagogues (such as sulfonylureas) or insulin, consider reducing the dose of the insulin secretagogue (for example, by one-half) or insulin to reduce the risk for hypoglycemia, and monitor blood glucose [see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]. Conversely, if discontinuing Saxenda® in patients with type 2 diabetes, monitor for an increase in blood glucose. Evaluate the change in body weight 16 weeks after initiating Saxenda® and discontinuation should be considered if the patient has not lost at least 4% of baseline body weight, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose. If more than 3 days have elapsed since the last Saxenda® dose, patients should reintimate Saxenda® at 0.6 mg daily and follow the dose escalation schedule in Table 1, which may reduce the occurrence of gastrointestinal symptoms associated with reinitiation of treatment.

Prior to initiation of Saxenda®, patients should be trained by their healthcare professional on proper injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations. Saxenda® solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

BMI is calculated by dividing weight (in kilograms) by height (in meters) squared. A chart for determining BMI based on height and weight is provided in Table 2.

5.3 Hypoglycemia

Nonclinical trials, acute pancreatitis was confirmed by adju
The following serious adverse reactions are described below or elsewhere in this prescribing information:

**Hypoglycemia**
- Risk of Thyroid C-Cell Tumors (See Warnings and Precautions (5.2))
- Acute Gastritis (See Warnings and Precautions (5.2))
- Acute Gallbladder Disease (See Warnings and Precautions (5.3))
- Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy (See Warnings and Precautions (5.4))
- Heart Rate Increase (See Warnings and Precautions (5.5))
- Renal Impairment (See Warnings and Precautions (5.6))
- Hypersensitivity Reactions (See Warnings and Precautions (5.7))
- Suicidal Behavior and Ideation (See Warnings and Precautions (5.8))

**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 studies of another drug and may not reflect the rates observed in practice. Saxenda® was evaluated for safety in 5 double-blind, placebo-controlled trials that included 3384 patients with overweight (excess weight) or obesity treated with Saxenda® for a treatment period up to 56 weeks (3 trials), 52 weeks (1 trial), and 32 weeks (1 trial). All patients received study drug in addition to diet and exercise counseling. In these trials, patients received Saxenda® for a mean treatment duration of 46 weeks (median, 56 weeks). Baseline characteristics included a mean age of 47 years, 71% women, 85% white, 39% with hypertension, 15% with type 2 diabetes, 34% with dyslipidemia, 29% with a BMI greater than 40 kg/m², and 9% with cardiovascular disease. In one of the 56-week trials, a subset of patients with abnormal glucose measurements at randomization (Clinical Studies (14)) were enrolled for a placebo-controlled 160-week period instead, followed by a 12-week off-treatment follow-up. For those participating in this 160-week period, patients received Saxenda® for a mean treatment duration of 110 weeks (median, 159 weeks). For all trials, dosing was initiated and increased weekly to reach the 3 mg dose.

In clinical trials, 9.8% of patients treated with Saxenda® and 4.3% of patients treated with placebo prematurely discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for Saxenda® and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%). Adverse reactions reported in greater than or equal to 2% of Saxenda®-treated patients and more frequently than in placebo-treated patients are shown in Table 3.

**Table 3. Adverse Reactions Reported in Greater Than or Equal to 2% of Saxenda®-treated Patients and More Frequently Than with Placebo**

<table>
<thead>
<tr>
<th>Gastrointestinal Disorders</th>
<th>Placebo N = 1041</th>
<th>Saxenda® N = 1041</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>13.8</td>
<td>39.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.9</td>
<td>20.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.5</td>
<td>19.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.9</td>
<td>15.7</td>
</tr>
<tr>
<td>Dyspepsis</td>
<td>2.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>2.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease</td>
<td>1.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>3.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Erosion</td>
<td>2.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Psychiatric Disorders**

| Hypoglycemia in TZDM* | 6.6             | 12.6             |

**Nervous System Disorders**

| Headache                  | 12.6            | 13.6             |
| Dizziness                 | 5.0             | 6.9              |

**General Disorders and Administration Site Conditions**

| Fatigue                   | 4.6             | 7.5              |

**Injection Site Erythema** | 0.2 | 2.5 |
| Injection Site Reaction   | 0.6 | 2.9 |
| Asthenia                  | 0.8 | 2.1 |

**Infections and Infections**

| Gastroenteritis            | 3.2             | 4.7              |
| Urinary Tract Infection   | 3.1             | 4.3              |
| Viral Gastroenteritis      | 1.6             | 2.8              |

**Investigations**

| Increased Lipase        | 2.2             | 5.3              |

**Psychiatric Disorders**

| Insomnia                 | 1.7             | 2.4              |
| Anxiety                  | 1.6             | 2.0              |

*Defined as blood glucose <54 mg/dL with or without symptoms of hypoglycemia in patients with type 2 diabetes not on concomitant insulin (Study 2). See text below for further information regarding hypoglycemia in patients with and without type 2 diabetes. TZDM = type 2 diabetes mellitus **

**Adverse reactions for trials with treatment period up to 56 weeks**

**Hypoglycemia**

Patients with Type 2 Diabetes

In a clinical trial in patients with type 2 diabetes mellitus and patients without type 2 diabetes mellitus not on concomitant insulin (Study 2), patients treated with Saxenda® had lower blood glucose compared with placebo, and more frequently than in placebo-treated patients, with this occurring at two consecutive study visits in 24% (11.4% with Saxenda® and 5.7% with placebo) of patients taking a sulfonylurea, hypoglycemia defined as a plasma glucose less than 54 mg/dL with or without symptoms occurred in 31 (28.2%) of 110 Saxenda®-treated patients and 7 (12.7%) of 55 placebo-treated patients.

Other postmarketing reports of hypoglycemia under conditions of use other than those studied in clinical trials involving patients without type 2 diabetes mellitus, there was no systematic recording or reporting of hypoglycemia, as patients were not provided with blood glucose meters or hypoglycemia diaries. Spontaneously reported symptomatic episodes of hypoglycemia were reported by 46 (1.5%) of 2962 Saxenda-treated patients and 19 (1.1%) of 1729 placebo-treated patients. Fastigia plasma glucose values obtained at routine clinical visits less than 54 mg/dL, irrespective of hypoglycemic symptoms, were reported as hypoglycemia in 2 (0.1%) Saxenda-treated patients and 1 (0.1%) placebo-treated patients.

**Gastrointestinal Adverse Reactions**

In the clinical trials, approximately 68% of Saxenda®-treated patients and 39% of placebo-treated patients reported gastrointestinal disorders; the most frequently reported was nausea (39% and 14% of patients treated with Saxenda® and placebo, respectively). The percentage of patients with weight loss greater than 5% also was greater for Saxenda® than placebo, with 43% and 29% of patients not taking a sulfonylurea, blood glucose less than 54 mg/dL with or without symptoms occurred in 31 (28.2%) of 110 Saxenda®-treated patients and 7 (12.7%) of 55 placebo-treated patients. Because Saxenda® can lower blood glucose, the doses of sulfonylureas were reduced by 50% at the time of initiating Saxenda® therapy. The frequency of hypoglycemia may be higher if the dose of sulfonylurea is not reduced. Among patients not taking a sulfonylurea, blood glucose less than 54 mg/dL with or without symptoms occurred in 22 (71%) of 312 Saxenda®-treated patients and 7 (4.5%) of 157 placebo-treated patients in Saxenda® clinical trials involving patients with overweight (excess weight) or obesity with type 2 diabetes mellitus treated with basal insulin and Saxenda® in combination with a reduced-calorie diet and increased physical activity and up to 2 oral anti-diabetes medications. Symptoms of hypoglycemia were reported by 3 (1.5%) of 195 Saxenda-treated patients and 2 (1.0%) of 197 placebo-treated patients. No meaningful difference in hypoglycemia, defined as blood glucose less than 54 mg/dL with or without symptoms, was reported between groups.

**Gastrointestinal Reactions**

In Saxenda® clinical trials involving patients without type 2 diabetes mellitus, there was no systematic recording or reporting of hypoglycemia, as patients were not provided with blood glucose meters or hypoglycemia diaries. Spontaneously reported symptomatic episodes of hypoglycemia were reported by 46 (1.5%) of 2962 Saxenda-treated patients and 19 (1.1%) of 1729 placebo-treated patients. Fastigia plasma glucose values obtained at routine clinical visits less than 54 mg/dL, irrespective of hypoglycemic symptoms, were reported as hypoglycemia in 2 (0.1%) Saxenda-treated patients and 1 (0.1%) placebo-treated patients.

**Psychiatric Reactions**

In other clinical trials involving patients without type 2 diabetes mellitus, there was no systematic recording or reporting of hypoglycemia, as patients were not provided with blood glucose meters or hypoglycemia diaries. Spontaneously reported symptomatic episodes of hypoglycemia were reported by 46 (1.5%) of 2962 Saxenda-treated patients and 19 (1.1%) of 1729 placebo-treated patients. Fastigia plasma glucose values obtained at routine clinical visits less than 54 mg/dL, irrespective of hypoglycemic symptoms, were reported as hypoglycemia in 2 (0.1%) Saxenda-treated patients and 1 (0.1%) placebo-treated patients.
Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 18 (1.2%) of 1505 Saxenda®-treated patients. Presence of antibodies may be associated with a higher incidence of injection site reactions and reports of low blood glucose. In clinical trials, these events were usually classified as mild and resolved while patients continued on treatment.

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 any assay is prone to 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 Saxenda® cannot be directly compared with the incidence of antibodies to other products.

Allergic Reactions
Urticaria was reported in 0.7% of Saxenda®-treated patients and 0.5% of placebo-treated patients. Anaphylactic reactions, asthma, bronchial hyperreactivity, bronchospasm, oropharyngeal swelling, facial swelling, angioedema, pharyngeal edema, type IV hypersensitivity reactions, have been reported in patients treated with liraglutide in clinical trials. Cases of anaphylactic reactions with additional symptoms such as hypotension, palpitati, dyspnea, and edema have been reported with marketed use of liraglutide. Anaphylactic reactions may potentially be life-threatening.

Injection Site Reactions
Injection site reactions were reported in approximately 13.9% of Saxenda®-treated patients and 10.5% of placebo-treated patients. The most common reactions, each reported by 1% to 2.5% of Saxenda®-treated patients and more commonly than by placebo-treated patients, included erythema, pruritus, and rash at the site of injection. 0.6% of Saxenda®-treated patients and 0.5% of placebo-treated patients discontinued treatment due to injection site reactions.

Breast Cancer
In Saxenda® clinical trials, breast cancer confirmed by adjudication was reported in 17 (0.7%) of 2379 Saxenda®-treated women compared with 3 (0.2%) of 1520 placebo-treated women, including invasive cancer (13 Saxenda®- and 2 placebo-treated women) and ductal carcinoma in situ (4 Saxenda® and 1 placebo-treated woman). The majority of cancers were estrogen- and progesterone-receptor negative. There were two few cases to determine whether these cases were related to Saxenda®. In addition, there are insufficient data to determine whether Saxenda® has an effect on pre-existing breast neoplasms.

Papillary Thyroid Cancer
In Saxenda® clinical trials, papillary thyroid carcinoma confirmed by pathology was reported in 5 (0.2%) of 2379 Saxenda®-treated patients compared with no cases among 1843 placebo-treated patients. Four of these papillary thyroid carcinomas were less than 1 cm in greatest diameter and 4 were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings identified prior to treatment.

Colorectal Neoplasms
In Saxenda® clinical trials, benign colorectal neoplasms (mostly colon adenoma) confirmed by adjudication were reported in 20 (0.6%) of 3291 Saxenda®-treated patients compared with 7 (0.4%) of 1843 placebo-treated patients. Six positively adjudicated cases of colorectal cancer (2.9% of Saxenda®-treated patients 0.2%, mostly adenocarcinoma) and 1 in a placebo-treated patient (0.1%, neuroendocrine tumor of the rectum).

Cardiac Conduction Disorders
In Saxenda® clinical trials, 11 (0.3%) of 3384 Saxenda®-treated patients compared with none of the 1941 placebo-treated patients had cardiac conduction disorders, reported as first degree atrioventricular block, right bundle branch block, or left bundle branch block.

Hypotension
Adverse reactions related to hypotension (that is, reports of hypotension, orthostatic hypotension, circulatory collapse, and decreased blood pressure) were reported more frequently with Saxenda (80 mmHg were observed in 4 (0.1%) Saxenda®-treated patients compared with 7 (0.4%) in placebo-treated patients). In clinical trials, 232 (6.9%) of the Saxenda®-treated patients compared with 7 (0.4%) of placebo-treated patients had blood pressure readings below 80/50 mmHg. In pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 3 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. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embroyal risk
A minimum weight gain, and no weight loss, is recommended for all pregnant women, including those who already have overweight (excess weight) or obesity, due to the necessary weight gain that occurs during normal tissues during pregnancy.

Animal Data
Liraglutide has been shown to be teratogenic in rats at and over 0.8-times systemic exposures in humans with obesity resulting from the maximum recommended human dose (MRHD) of 3 mg/day based on body weight and plasma AUC comparison. Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rats at systemic exposures below exposure in humans with obesity at the MRHD based on plasma AUC comparison.

Female rats given subcutaneous doses of 0.1, 0.25 and 1 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the exposure in humans with obesity at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the highest dose 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 fur and minimally knitted ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated dams was less than the exposure in humans with obesity at the MRHD of 3 mg/day at all doses, based on plasma AUC comparison. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses and total incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), greater than or equal to 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), greater than or equal to 0.025 mg/kg/day (sternum), and 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 mg/kg/day liraglutide from gestation day 6 through day 16 inclusive, the mean body weight on postpartum day 24 was less than the exposure in humans with obesity at the MRHD of 3 mg/day at all doses, based on plasma AUC comparison. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses and total incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), greater than or equal to 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), greater than or equal to 0.025 mg/kg/day (sternum) and 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 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing (cash litters), body weight at the MRHD 2-4% and 15-20%, respectively. Allergic Reactions (6.1) General Disorders and Administration Site Conditions (6.1) Allergic reactions; rash and pruritus (see Adverse Reactions (6.1)) Immune System Disorders Angioedema and anaphylactic reactions (see Warnings and Precautions (5.2)) Hepatobiliary Disorders Elevations of liver enzymes, hyperbilirubinemia, cholestasis and hepatitis (see Adverse Reactions (6.1)) 7 DRUG INTERACTIONS 7.1 Oral Medications Saxenda® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with Saxenda®. 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Risk Summary Saxenda® is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm (see Clinical Considerations). There are no data from adequately controlled clinical trials in pregnant women. Saxenda® should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Saxenda® should be discontinued.

Animal data. In lactating rats, liraglutide was present in the milk of lactating rats (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Saxenda® and any potential adverse effects on the breastfed infant from Saxenda® or from the underlying maternal condition.

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

8.4 Pediatric Use Safety and effectiveness of Saxenda® have not been established in pediatric patients. Saxenda® is not recommended for use in pediatric patients.

8.5 Geriatric Use In the Saxenda® clinical trials, 232 (6.9%) of the Saxenda®-treated patients were 65 years of age and over, and 17 (0.5%) of the Saxenda®-treated patients were 75 years of age and over. No overall differences in safety or effectiveness were observed between these age groups.

Saxenda® (liraglutide) injection 3mg
patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
There is limited experience with Saxenda® in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure with liraglutide, which may sometimes require hemodialysis (see Warnings and Precautions (5.5) and Adverse Reactions (6.2)). Saxenda® should be given with appropriate caution in this patient population (see Clinical Pharmacology (12.3)).

8.7 Hepatic Impairment
There is limited experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Saxenda® should be used with caution in this patient population (see Clinical Pharmacology (12.3)).

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

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

11 DESCRIPTION
Saxenda® 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 asparagine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glucamic acid spacer on the remaining lysiine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C127H202N42O53S and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

Cardiac Electrophysiology (QTc) in healthy volunteers
The effect of liraglutide on cardiac repolarization was tested in a QTc study. Liraglutide at steadystate concentrations after daily doses up to 1.8 mg did not produce QTc prolongation. The maximum liraglutide plasma concentration at peak (AUCmax) and exposure (AUC0-24) was not increased with the addition of liraglutide at steadystate doses (3 mg/day) compared to doses of 0.6 mg/day and 1.8 mg/day. In addition, a therapeutic ratio of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs.

12.3 Pharmacokinetics
Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 11 hours post dosing. The mean bioavailability of liraglutide AUC was 11% following single dose administration. Liraglutide exposures were considered similar among three subcutaneous injection sites (upper arm, abdomen, and thigh). Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution - The mean apparent volume of distribution after subcutaneous administration of liraglutide 3 mg is 20-25 L (for a person weighing approximately 100 kg). The mean volume of distribution after intravenous administration of liraglutide is 0.07 L/kg. Liraglutide is extensively bound to plasma proteins (greater than 98%).

Metabolism - During 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 plasma clearance of liraglutide from the plasma of a single dose of liraglutide is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration.

Specific Populations
Elderly - No dosage adjustment is required based on age. Age had no effect on the pharmacokinetics of liraglutide based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of data from patients with overweight (excess weight) and obesity 18 to 82 years of age (see Use in Specific Populations (8.7)).

Gender - Based on the results of population pharmacokinetic analyses (women vs. men) and in all female liraglutide-treated groups with incidences of 10%, 16%, 42%, and 46%, respectively. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the maximum recommended human dose (MRHD) of 3 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 3 and 5 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not recur in control groups or 0.5 mg/kg/day. Treatment-related malignant C-cell carcinomas occurred in 5% of females in the 3 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in benign thyroid C-cell lesions was seen in female liraglutide-treated groups with incidences of 12%, 16%, 42%, and 46%, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-
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.

14 CLINICAL STUDIES

The safety and efficacy of Saxenda® for chronic weight management in conjunction with reduced caloric intake and increased physical activity were studied in three 56-week, randomized, double-blind, placebo-controlled trials. In all studies, Saxenda® was titrated to 3 mg daily during a 4-week period. All patients received instruction for a reduced calorie diet (approximately 500 kcal/day deficit) and exercise counseling (recommended increase in physical activity of minimum 150 mins/week) that began with the first dose of study medication or placebo and continued throughout the trial. Study 1 enrolled 3731 patients with obesity (BMI) greater than or equal to 30 kg/m^2^ or with overweight (BMI) 27.2-29.9 kg/m^2^ and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. Patients were randomized in a 2:1 ratio to either Saxenda® or placebo. Patients were stratified based on the presence or absence of abnormal blood glucose measurements at randomization. All patients were treated for up to 56 weeks. Those patients with abnormal glucose measurements at randomization (2254 of the 3731 patients) were treated for a total of 160 weeks. At baseline, mean age was 45 years (range 18-78), 79% were women, 85% were Caucasian, 10% were African American, and 11% were Hispanic/Latino. Mean baseline body weight was 106.3 kg and mean BMI was 38.3 kg/m^2^.

Study 2 was a 56-week trial that enrolled 635 patients with type 2 diabetes with obesity or overweight (as defined above). Patients were to have an HbA1c of 7-10% and be treated with metformin, a sulfonylurea, or a glitazone as single agent or in combination, with or without diet and exercise alone. Patients were randomized in a 2:1 ratio to receive either Saxenda® or placebo. The mean age was 55 years (range 18-82), 50% were women, 83% were Caucasian, 12% were African American, and 10% were Hispanic/Latino. Mean baseline body weight was 105.9 kg and mean BMI was 35.6 kg/m^2^.

Study 3 was a 56-week trial that enrolled 422 patients with obesity (BMI) greater than or equal to 30 kg/m^2^ or with overweight (BMI) 27.2-29.9 kg/m^2^ and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. Patients were randomized to receive either Saxenda® or placebo at week 0 and Saxenda® or placebo at weeks 12 and 24. The mean age was 46 years (range 18-73), 81% were women, 84% were Caucasian, 13% were African American, and 7% were Hispanic/Latino. Mean baseline body weight was 99.6 kg and mean BMI was 35.6 kg/m^2^.

The proportions of patients who discontinued study drug in the 56-week trials were 27% for the Saxenda®-treated group and 35% for the placebo-treated group, and in the 160-week trial the proportions of patients who discontinued were 47% and 53%, respectively. In the 56-week trials, approximately 10% of patients treated with Saxenda® and 4% of patients treated with placebo discontinued treatment due to an adverse reaction (see Adverse Reactions (6.1)). The majority of patients who discontinued Saxenda® due to adverse reactions did so during the first few months of treatment. In the 160-week trial the proportions of patients who discontinued due to an adverse reaction was 13% and 6% for Saxenda®- and placebo-treated patients, respectively.

Effect of Saxenda® on Body Weight in 56-week Trials

For Study 1 and Study 2, the primary efficacy parameters were mean percent change in body weight and the percentages of patients achieving greater than or equal to 5% and 10% weight loss from baseline to week 56. For Study 3, the primary efficacy parameters were mean percent change in body weight from randomization to week 56, the percentage of patients not gaining more than 0.5% body weight from randomization (i.e., after run-in) to week 56, and the percentage of patients achieving greater than or equal to 5% weight loss from randomization to week 56. Because losing at least 5% of fasting body weight through lifestyle intervention during the 4- to 12-week run-in was a condition for their continued participation in the randomized treatment period, the results may not reflect those expected in the general population.

Table 4 presents the results for the changes in weight observed in Studies 1, 2, and 3. After 56 weeks, treatment with Saxenda® resulted in a statistically significant reduction in weight compared with placebo. Statistically significantly greater proportions of patients treated with Saxenda® achieved 5% and 10% weight loss than those treated with placebo. In Study 3, statistically significantly more patients randomized to Saxenda® than placebo had not gained more than 0.5% of body weight from randomization to week 56.

![Figure 2. Change in body weight (%) from baseline to week 56 (Study 1 on left and Study 2 on right)](image)

**Table 4. Changes in Weight at Week 56 for Studies 1, 2, and 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>(Obesity or overweight with comorbidity)</th>
<th>(Type 2 diabetes with obesity or overweight)</th>
<th>(Obesity or overweight with comorbidity following at least 5% weight loss with diet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxenda®</td>
<td>Placebo</td>
<td>Saxenda®</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=2487</td>
<td>N=1244</td>
<td>N=423</td>
<td>N=212</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean (SD) (kg)</td>
<td>106.2 (21.2)</td>
<td>106.2 (21.7)</td>
<td>105.7 (21.9)</td>
</tr>
<tr>
<td>Percent change from baseline (LSMean)</td>
<td>-10.6*</td>
<td>-10.6*</td>
<td>-10.7*</td>
</tr>
<tr>
<td>Difference from placebo (LSMean) (95% CI)</td>
<td>-4.5* (-5.2; -3.8)</td>
<td>-4.3* (-4.7; -3.7)</td>
<td>-5.2* (-6.3; -4.1)</td>
</tr>
<tr>
<td>% of Patients losing greater than or equal to 5% body weight</td>
<td>62.3%</td>
<td>34.4%</td>
<td>49.0%</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>27.9* (23.9; 31.9)</td>
<td>32.6* (25.1; 40.1)</td>
<td>18.5* (15.2; 21.7)</td>
</tr>
<tr>
<td>% of Patients losing greater than or equal to 10% body weight</td>
<td>33.8%</td>
<td>15.4%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

**SD = Standard Deviation; CI = Confidence Interval**

*p < 0.0001 compared to placebo. Type 1 error was controlled across the three endpoints.

Includes all randomized subjects who had a baseline body weight measurement. All available body weight data during the 56 week treatment period are included in the analysis. In Studies 1 and 2 missing values for week 56 were handled using multiple imputations analysis. In Study 3 missing values for week 56 were handled using weighted regression analysis.

The cumulative frequency distributions of change in body weight from baseline to week 56 are shown in Figure 2 for Studies 1 and 2. One way to interpret this figure is to select a change in body weight of interest on the horizontal axis and note the corresponding proportions at that change in body weight. For example, note that the vertical line arising from -10% in Study 1 intersects the Saxenda® and placebo curves at approximately 34% and 15%, respectively, which correspond to the values shown in Table 4.

**Figure 2. Change in body weight (%) from baseline to week 56 (Study 1 on left and Study 2 on right)**

The time courses of weight loss with Saxenda® and placebo from baseline through week 56 are depicted in Figures 3 and 4.

**Figure 3. Change from baseline (%) in body weight (Study 1 on left and Study 2 on right)**

Observed values for patients on study drug completing each scheduled visit, and ITT with multiple imputations (ITT-MI)
Figure 4. Change from baseline (%) in body weight during Study 3

Effect of Saxenda® on Body Weight in a 160-week Trial (Study 1, Subset of Patients with Abnormal Blood Glucose at Randomization)

The numbers and percentages of patients known to have lost greater than or equal to 5% body weight at week 56 and/or week 160 in Study 1 (patients with abnormal glucose at randomization only) are summarized in Table 5 for descriptive purposes.

Table 5. Changes in Weight at Week 56 and Week 160 for Study 1 (Subset of Patients with Abnormal Blood Glucose at Randomization)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saxenda® N = 1505</th>
<th>Placebo N = 749</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean body weight (SD) (kg)</td>
<td>107.3 (21.6)</td>
<td>107.9 (21.8)</td>
<td>.59</td>
</tr>
<tr>
<td>Number (%) of patients known to lose greater than or equal to 5% body weight at week 56</td>
<td>817 (55%)</td>
<td>182 (25%)</td>
<td>.001</td>
</tr>
<tr>
<td>Number (%) of patients known to lose greater than or equal to 5% body weight at week 160</td>
<td>424 (29%)</td>
<td>102 (14%)</td>
<td>.001</td>
</tr>
<tr>
<td>Number (%) of patients known to lose greater than or equal to 5% body weight at both weeks 56 and 160</td>
<td>391 (26%)</td>
<td>74 (10%)</td>
<td>.001</td>
</tr>
<tr>
<td>Number (%) of patients with weight assessment at 160 weeks</td>
<td>747 (50%)</td>
<td>322 (43%)</td>
<td>.10</td>
</tr>
</tbody>
</table>

SD = Standard Deviation

Includes all randomized subjects who had a baseline body weight measurement. All available body weight data at 56 and 160 weeks are included in the analysis.

Effect of Saxenda® on Anthropometry and Cardiometabolic Parameters in 56-week Trials

Changes in waist circumference and cardiometabolic parameters with Saxenda® are shown in Table 6 for Study 1 (patients without diabetes mellitus) and Table 7 for Study 2 (patients with type 2 diabetes). Results from Study 3, which also enrolled patients without diabetes mellitus, were similar to Study 1.

Table 6. Mean Changes in Anthropometry and Cardiometabolic Parameters in Study 1 (Patients without Diabetes)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saxenda® N = 2487</th>
<th>Placebo N = 2444</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Circumference (cm)</td>
<td>115.0</td>
<td>114.9</td>
<td>.23</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>113.0</td>
<td>113.1</td>
<td>.23</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>78.7</td>
<td>78.9</td>
<td>.10</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>71.4</td>
<td>71.3</td>
<td>.10</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)*</td>
<td>193.8</td>
<td>194.4</td>
<td>.23</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)*</td>
<td>111.8</td>
<td>112.3</td>
<td>.23</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)*</td>
<td>51.4</td>
<td>50.9</td>
<td>.23</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)*</td>
<td>125.7</td>
<td>128.3</td>
<td>.23</td>
</tr>
</tbody>
</table>

Based on last observation carried forward method while on study drug

Table 7. Mean Changes in Anthropometry and Cardiometabolic Parameters in Study 2 (Patients with Diabetes Mellitus)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saxenda® N = 423</th>
<th>Placebo N = 212</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Circumference (cm)</td>
<td>118.1</td>
<td>117.3</td>
<td>.23</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>128.9</td>
<td>129.2</td>
<td>.23</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>79.0</td>
<td>79.3</td>
<td>.23</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>74.0</td>
<td>74.0</td>
<td>.23</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)*</td>
<td>171.0</td>
<td>169.4</td>
<td>.23</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)*</td>
<td>86.4</td>
<td>85.2</td>
<td>.23</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)*</td>
<td>45.2</td>
<td>45.4</td>
<td>.23</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)*</td>
<td>156.2</td>
<td>155.8</td>
<td>.23</td>
</tr>
</tbody>
</table>

Based on last observation carried forward method while on study drug

Cardiovascular Outcomes Trial of Liraglutide 1.8 mg in Patients with Type 2 Diabetes and Cardiovascular Disease

Liraglutide 1.8 mg (Victoza®) is used in the treatment of type 2 diabetes mellitus in adults. The efficacy of liraglutide at doses below 3 mg daily has not been established for chronic weight management. The LEADER trial (NCT01179048) randomized 9340 patients with inadequately controlled type 2 diabetes and cardiovascular disease to liraglutide 1.8 mg or placebo in addition to standard of care treatments for type 2 diabetes for a median duration of 5.5 years. Patients either were 50 years of age or older with established, stable cardiovascular, cerebrovascular, peripheral vascular disease, chronic renal failure or chronic heart failure (80% of patients), or were 50 years of age or older and had other specified risk factors of vascular disease (20% of patients). The population was 64% male, 78% Caucasian, 10% Asian and 8% Black; 12% of the population was Hispanic or Latino.

In total, 96.8% of the patients completed the trial; vital status was known at the end of the trial for 99.7%. The primary endpoint was the time from randomization to first occurrence of a major adverse cardiovascular event (MACE) defined as: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. No increased risk for MACE was observed with liraglutide 1.8 mg. The total number of primary component MACE endpoints was 1302 (60.3% with liraglutide 1.8 mg and 694 [14.9%] with placebo).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Saxenda® 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, 1.8 mg, 2.4 mg or 3 mg (6 mg/mL, 3 mL).

5 x Saxenda® pen

NDC 0169-2800-15

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

16.2 Recommended Storage

Prior to first use, Saxenda® should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 8). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Saxenda® and do not use Saxenda® if it has been frozen.

After first use of the Saxenda® pen, the can be stored for 30 days at controlled room temperature (68°F to 77°F; 20°C to 25°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Discard pen 30 days after first use. Saxenda® should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Saxenda® pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy.

Table 8. Recommended Storage Conditions for Saxenda®

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Prior to first use</th>
<th>After first use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated</td>
<td>36°F to 46°F</td>
<td>36°F to 46°F</td>
</tr>
<tr>
<td>Room Temperature</td>
<td>59°F to 86°F</td>
<td>59°F to 86°F</td>
</tr>
<tr>
<td>(2°C to 8°C)</td>
<td>(15°C to 30°C)</td>
<td>(15°C to 30°C)</td>
</tr>
</tbody>
</table>

Until expiration date 30 days
the absence of substantial or rapid weight loss. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected.

**Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-Diabetic Therapy**

Educate patients on the signs and symptoms of hypoglycemia. Advise patients with type 2 diabetes mellitus on glycemic lowering therapy to report signs and/or symptoms of hypoglycemia to their healthcare provider.

**Heart Rate Increase**

Inform patients to report symptoms of sustained periods of heart pounding or racing while at rest to their healthcare provider. Discontinue Saxenda® in patients who experience a sustained increase in resting heart rate.

**Dehydration and Renal Impairment**

Advise patients of the 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.

**Hypersensitivity Reactions**

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of Saxenda®. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking Saxenda® and seek medical advice promptly if such symptoms occur (see Warnings and Precautions [5.7]).

**Suicidal Behavior and Ideation**

Advise patients to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Inform patients that if they experience suicidal thoughts or behaviors, they should stop taking Saxenda®.

**Jaundice and Hepatitis**

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

**Never Share a Saxenda® Pen Between Patients**

Inform patients that they should never share a Saxenda® pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.
MEDICATION GUIDE
SAXENDA® (sax-end-ah) (liraglutide) injection, for subcutaneous use

Do not share your SAXENDA® pen with others 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 important information I should know about SAXENDA®?

Serious side effects may happen in people who take SAXENDA®, 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, SAXENDA® and medicines that work like SAXENDA® caused thyroid tumors, including thyroid cancer. It is not known if SAXENDA® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.

Do not use SAXENDA® 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 Saxenda®?

SAXENDA® is an injectable prescription medicine used for adults with obesity or overweight (excess weight) who also have weight related medical problems to help them lose weight and keep the weight off.

• SAXENDA® should be used with a reduced calorie meal plan and increased physical activity.
• SAXENDA® is not for the treatment of type 2 diabetes mellitus.
• SAXENDA® and VICTOZA have the same active ingredient, liraglutide, and should not be used together or with other GLP-1 receptor agonist medicines.
• It is not known if SAXENDA® is safe and effective when taken with other prescription over-the-counter medicines or herbal weight loss products.
• It is not known if SAXENDA® is safe and effective in children under 18 years of age.

Who should not use Saxenda®?

Do not use Saxenda® 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 SAXENDA®. See the end of this Medication Guide for a complete list of ingredients in SAXENDA®.
• you are pregnant or plan to become pregnant. SAXENDA® may harm your unborn baby.

Before taking SAXENDA®, tell your healthcare provider if you have any other medical conditions, including if you:

• are taking certain medicines called GLP-1 receptor agonists.
• have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
• have or have had problems with your pancreas, kidneys or liver.
• have or have had depression, suicidal thoughts, or mental health issues.
• are breastfeeding or plan to breastfeed. It is not known if SAXENDA® passes into your breast milk. You and your healthcare provider should decide if you will take SAXENDA® or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements. SAXENDA® slows stomach emptying and can affect medicines that need to pass through the stomach quickly. SAXENDA® may affect the way some medicines work and some other medicines may affect the way SAXENDA® works.

Tell your healthcare provider if you take diabetes medicines, especially insulin and sulfonylurea medicines. Talk with your healthcare provider if you are not sure if you take any of these medicines.

How should I use Saxenda®?

• Read the Instructions for Use that comes with SAXENDA®.
• Use SAXENDA® exactly as prescribed by your healthcare provider.
• Your healthcare provider should show you how to use SAXENDA® before you use it for the first time.
• Start SAXENDA® with 0.6 mg per day in your first week. In your second week, increase your daily dose to 1.2 mg. In the third week, increase your daily dose to 1.8 mg. In the fourth week, increase your daily dose to 2.4 mg and in the fifth week onwards, increase your daily dose to the full dose of 3.0 mg. After that, do not change your dose unless your healthcare provider tells you to.
• SAXENDA® is injected 1 time each day, at any time during the day.
• Inject your dose of SAXENDA® under the skin (subcutaneously) in your stomach area (abdomen), upper leg (thigh), or upper arm, as instructed by your healthcare provider. Do not inject into a vein or muscle.
• If you take too much SAXENDA®, call your healthcare provider right away. Taking too much SAXENDA® may cause severe nausea and vomiting.
• If you miss your daily dose of SAXENDA®, take the missed dose as soon as you remember. Take your next daily dose as usual on the following day. Do not take an extra dose of SAXENDA® or increase your dose on the following day to make up for your missed dose. If you miss your dose of SAXENDA® for 3 days or more, call your healthcare provider to talk about how to restart your treatment.
• You can take SAXENDA® with or without food.
• Throw away the used SAXENDA® pen after 30 days.

Your healthcare provider should start you on a reduced calorie meal plan and increased physical activity when you start taking SAXENDA®. Stay on this program while you are taking SAXENDA®.
What are the possible side effects of Saxenda®?

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

- See “What is the most important information I should know about SAXENDA®?”
- inflammation of the pancreas (pancreatitis). Stop using SAXENDA® 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 stomach area (abdomen) to your back.

- gallbladder problems. SAXENDA® may cause gallbladder problems including gallstones. Some gallbladder problems need surgery. Call your healthcare provider if you have any of the following symptoms:
  - pain in your upper stomach (abdomen)
  - fever
- increased risk of low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines to treat type 2 diabetes mellitus such as sulfonylureas or insulin. Signs and symptoms of low blood sugar may include:
  - shakiness
  - sweating
  - headache
  - drowsiness

Talk to your healthcare provider about how to recognize and treat low blood sugar. You should check your blood sugar before you start taking SAXENDA® and while you take SAXENDA®.

- increased heart rate. SAXENDA® can increase your heart rate while you are at rest. Your healthcare provider should check your heart rate while you take SAXENDA®. Tell your healthcare provider if you feel your heart racing or pounding in your chest and it lasts for several minutes.

- kidney problems (kidney failure). SAXENDA® may cause nausea, vomiting or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration. Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that does not go away, or if you cannot drink liquids by mouth.

- serious allergic reactions. Stop using SAXENDA®, 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
  - very rapid heartbeat

- depression or thoughts of suicide. You should pay attention to any mental changes, especially sudden changes, in your mood, behaviors, thoughts, or feelings. Call your healthcare provider right away if you have any mental changes that are new, worse, or worry you.

The most common side effects of SAXENDA® include:

- nausea
- diarrhea
- constipation
- vomiting
- low blood sugar (hypoglycemia)
- headache
- upset stomach (dyspepsia)
- tiredness (fatigue)
- dizziness
- stomach pain
- change in enzyme (lipase) levels in your blood

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SAXENDA®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Keep your Saxenda® pen, pen needles, and all medicines out of the reach of children.

General information about the safe and effective use of Saxenda®.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SAXENDA® for a condition for which it was not prescribed. Do not give SAXENDA® to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about SAXENDA® that is written for health professionals.

What are the ingredients in Saxenda®?

**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.

For information about SAXENDA® go to www.SAXENDA.com or contact: Novo Nordisk Inc. 800 Scudders Mill Road, Plainsboro, NJ 08536 1-844-363-4446.

SAXENDA®, VICTOZA®, NovoFine®, and NovoTwist® are registered trademarks of Novo Nordisk A/S.


This Medication Guide has been approved by the U.S. Food and Drug Administration.
Saxenda® (liraglutide) injection 3mg Instructions for Use

Instructions for Use
- Read these instructions carefully before using your Saxenda® pen.
- Do not use your pen without proper training from your healthcare provider. Make sure that you know how to give yourself an injection with the pen before you start your treatment.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Saxenda® pen.
- You can refresh your training at any time by watching the online training video at www.saxenda.com.
- Start by checking your pen to make sure that it contains Saxenda®, then look at the pictures below to get to know the different parts of your pen and needle.
- Your pen is a prefilled dial-a-dose pen. It contains 18 mg of liraglutide, and you can select doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg. Your pen is made to be used with NovoFine® or NovoTwist® disposable needles up to a length of 6 mm.

Step 1. Prepare your pen with a new needle
- Wash your hands with soap and water.
- Check the name and colored label of your pen, to make sure that it contains Saxenda®. This is especially important if you take more than 1 type of medicine.
- Pull off the pen cap.
- Check that Saxenda® in your pen is clear and colorless. Look through the pen window. If Saxenda® looks cloudy, do not use the pen.

Step 2. Check the Saxenda® flow with each new pen.
- Hold the pen with the needle pointing up. Press and hold in the dose button until the dose counter shows 0. The 0 must line up with the dose pointer.
- A drop of Saxenda® will appear at the needle tip.
- If no drop appears, repeat Step 2 above as shown in Figures G and H up to 6 times. If there is still no drop, change the needle and repeat Step 2 as shown in Figures G and H 1 more time.
- Do not use the pen if a drop of Saxenda® still does not appear.
- Contact Novo Nordisk at 1-844-363-4448.
- Always make sure that a drop appears at the needle tip before you use a new pen for the first time. This makes sure that Saxenda® flows.
- If no drop appears, you will not inject any Saxenda®, even though the dose counter may move. This may mean that there is a blocked or damaged needle.

Step 3. Select your dose
- Turn the dose selector until the dose counter shows your dose (0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg).
- Make sure you know the dose of Saxenda® you should use.
- If you select the wrong dose, you can turn the dose selector forward or backwards to the correct dose.
- Always use the dose counter and the dose pointer to see how many mg you select. You will hear a “click” every time you turn the dose selector.

Step 4. Inject your dose
- Insert the needle into your skin as your healthcare provider has shown you.
- Make sure you can see the dose counter. Do not cover it with your fingers. This could stop the injection.

Saxenda® pen and needle (example)

NovoFine®

NovoTwist®

Step 4. Inject your dose

NovoTwist®

NovoFine®
**Saxenda® (liraglutide) injection 3mg Instructions for Use**

- **Press and hold down the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer. You may then hear or feel a click.

- **Keep the needle in your skin after the dose counter has returned to 0 and count slowly to 6.**

- **If the needle is removed earlier, you may see a stream of Saxenda® coming from the needle tip. If this happens, the full dose will not be delivered.**

- **Put the pen cap on your pen after each use to protect Saxenda® from light.**

- **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area.

- **Always watch the dose counter to know how many mg you inject.** Hold the dose button down until the dose counter shows 0.

**How to identify a blocked or damaged needle?**
- If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
- If this happens you have not received any Saxenda® even though the dose counter has moved from the original dose that you have set.

**How to handle a blocked needle?**
Change the needle as described in Step 5, and repeat all steps starting with Step 1: “Prepare your pen with a new needle.” Make sure you select the full dose you need. Never touch the dose counter when you inject. This can stop the injection.

- You may see a drop of Saxenda® at the needle tip after injecting. This is normal and does not affect your dose.

**Step 5. After your injection**
- **Carefully remove the needle from the pen.** Do not put the needle caps back on the needle, to avoid needle sticks.

- **Place the needle in a sharps container right away to reduce the risk of needle sticks.**

- **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.

- **Always remove the needle from your pen.** This prevents contamination, infection, leakage of Saxenda®, and blocked needles leading to the wrong dose. If the needle is blocked, you will not inject any Saxenda®.

- **Always dispose of the needle after each injection.**
  - **Do not throw away in the household trash.** Put the needle and any empty Saxenda® pen or any pen used for 30 days still containing Saxenda® in a FDA-cleared sharps disposal container right away after use.
  - **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. 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.
  - **Safely dispose of Saxenda® that is out of date or no longer needed.**

**Important**
- **Caregivers must be very careful when handling used needles to prevent needle sticks and cross infection.**
- **Never use a syringe to withdraw Saxenda® from your pen.**
- **Always carry an extra pen and new needles with you, in case of loss or damage.**
- **Always keep your pen and needles out of reach of others, especially children.**
- **Do not share your Saxenda® pen or needles with anyone else.** You may give an infection to them or get an infection from them.
- **Always keep your pen with you.** Do not leave it in a car or other place where it can get too hot or too cold.

**Caring for your pen**
- **Do not drop your pen or knock it against hard surfaces.** If you drop it or suspect a problem, attach a new needle and check the Saxenda® flow before you inject.
- **Do not try to repair your pen or pull it apart.**
- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak, or lubricate your pen.** If necessary, clean it with mild detergent on a moistened cloth.

**How should I store my Saxenda® pen?**
- **Store your new, unused Saxenda® pens in the refrigerator at 36°F to 46°F (2°C to 8°C).**
- **Store your pen in use for 30 days at 59°F to 86°F (15°C to 30°C) or in a refrigerator at 36°F to 46°F (2°C to 8°C).**

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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