PRODUCT MONOGRAPH

SAXENDA®

liraglutide

6 mg/mL

Solution for Injection in a pre-filled pen

Human Glucagon Like Peptide-1 (GLP-1)

Weight Management

Novo Nordisk Canada Inc.
300-2680 Skymark Avenue
Mississauga, Ontario
L4W 5L6

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SAXENDA®

(liraglutide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

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 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.

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

INDICATIONS AND CLINICAL USE

SAXENDA® (liraglutide) 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/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) and who have failed a previous weight management intervention.

Limitation of Use:

1. Clinical efficacy and safety data from patients with BMI 27 to 29.9 kg/m^2 in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia) are limited (N=149).

Geriatrics (≥65 years of age): Patients ≥65 years may experience more gastrointestinal side effects when treated with SAXENDA®. Therapeutic experience in patients ≥75 years of age is very limited.
No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. (See:

WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

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

CONTRAINDICATIONS

- In patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), (see WARNINGS AND PRECAUTIONS, Malignancies).

- Patients who are hypersensitive to liraglutide or to any ingredient in the formulation. For a complete listing, (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- During pregnancy or in breast-feeding women, (see WARNINGS AND PRECAUTIONS, Special populations).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Thyroid C-cell Tumours

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice (see PART II, Toxicology Section). It is unknown whether liraglutide causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies.

SAXENDA® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. Patients should be counselled regarding the risk and symptoms of thyroid tumours **(see Contraindications, Warnings and Precautions, Adverse Drug Reactions and Toxicology).**

General

The safety and effectiveness of SAXENDA® in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs and herbal preparations, have not been established.
SAXENDA® should not be administered intravenously or intramuscularly.

Never Share a SAXENDA® pen Between Patients.
SAXENDA® pen should never be shared between patients, even if the needle if changed. Sharing poses a risk for transmission of blood-borne pathogens.

Cardiovascular
The effects of SAXENDA® on cardiovascular morbidity and mortality have not been established.

Increase in Heart Rate: In the clinical trials, mean increases in resting heart rate of 2 to 3 beats per minute (bpm) were observed with routine clinical monitoring in SAXENDA® -treated patients compared to placebo. More patients treated with SAXENDA®, compared with placebo, have changes from baseline at two consecutive visits of more than 10 bpm (34% versus 19%, respectively) and 20 bpm (5% versus 2%, respectively). At least one resting heart rate exceeding 100 bpm was recorded for 6% of SAXENDA®-treated patients compared with 4% of placebo-treated patients, with this occurring at two consecutive study visits for 0.9% and 0.3%, respectively. Tachycardia was reported as an adverse reaction in 0.6% of SAXENDA® -treated patients and in 0.1% of placebo-treated patients.

In a clinical pharmacology trial that monitored heart rate continuously for 24 hours, SAXENDA® treatment was associated with a heart rate that was 4 to 9 bpm higher than that observed with placebo. (See ADVERSE REACTIONS, QTc in healthy Volunteers).
The clinical significance of the heart rate elevation with SAXENDA® treatment is unclear, especially for patients with cardiac and cerebrovascular disease as a result of limited exposure in these patients in clinical trials.

Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should inform their healthcare professional of palpitations or feelings of a racing heartbeat while at rest during SAXENDA® treatment. For patients who experience a sustained increase in resting heart rate while taking SAXENDA®, SAXENDA® should be discontinued.

PR Interval Prolongation: A prolongation of the mean PR interval of up to 10 ms was reported with SAXENDA® treatment in a clinical trial in healthy volunteers, using lower doses than recommended for weight management (see ADVERSE REACTIONS QTc in healthy volunteers). In healthy volunteers and in patients with overweight or obesity, the incidence of first degree atrioventricular (AV) block was higher with SAXENDA® than with placebo (see ADVERSE REACTIONS, Cardiovascular disorders). The clinical significance of these changes is not fully known; however, because of limited clinical experience in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) and heart rhythm disturbances (e.g., tachyarrhythmia), caution should be observed in these patients (see DRUG INTERACTIONS).

Endocrine and Metabolism
Hypoglycemia: Severe hypoglycemia was observed in clinical trials in patients with type 2 diabetes mellitus treated with SAXENDA®. The risk of hypoglycemia may be lowered by a reduction in the dose of concomitantly administered insulin secretagogues (such as sulfonylureas). (See ADVERSE REACTIONS, Clinical Trial Adverse Drug Reaction).
SAXENDA® and insulin should not be used together. SAXENDA® has not been studied in patients taking insulin.

Hepatic/Biliary/Pancreas

Acute Pancreatitis: Based on spontaneous post-marketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide. After initiation of SAXENDA®, observe patients carefully for signs and symptoms of pancreatitis (including persistent or intermittent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, SAXENDA® should promptly be discontinued, confirmatory tests should be performed 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 9 (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 two additional cases in a SAXENDA®-treated patients. One during an off-treatment follow-up period within 2 weeks of discontinuing SAXENDA® and one that occurred in a patient who completed treatment and was off-treatment for 106 days.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using SAXENDA®, since these patients were excluded from clinical trials.

Acute Gallbladder Disease: In SAXENDA® clinical trials, 2.2% of SAXENDA®-treated patients reported adverse events of cholelithiasis versus 0.8% of placebo-treated patients. The incidence of cholecystitis was 0.8% in SAXENDA®-treated patients versus 0.4% in placebo-treated patients. The majority of SAXENDA®-treated patients with adverse events of cholelithiasis and cholecystitis required cholecystectomy. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in SAXENDA®-treated patients than in placebo-treated patients even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Immune

Hypersensitivity Reactions: There have been reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with SAXENDA® (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). If a hypersensitivity reaction occurs, the patient should discontinue SAXENDA® and other suspect medications and promptly seek medical advice.

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

Malignancies

Risk of Thyroid C-Cell Tumours: SAXENDA® causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice (see PART II, TOXICOLOGY). Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was

observed in rats receiving liraglutide at 10-times clinical exposure compared to controls. It is unknown whether SAXENDA® will cause thyroid C-cell tumours, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumours could not be determined by clinical or nonclinical studies.

Calcitonin, a biological marker of MTC, was measured throughout the SAXENDA® clinical development program. In the clinical trials, there was one reported case of thyroid C-cell hyperplasia among SAXENDA®-treated patients and no cases in placebo-treated patients. In the case of the thyroid C-cell hyperplasia, the patient had elevated blood calcitonin level at screening. There were no cases of MTC in SAXENDA®-treated patients and one case in placebo-treated patients.

Counsel patients regarding the risk for MTC and the symptoms of thyroid tumours (e.g., a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with SAXENDA®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Patients with MTC usually have calcitonin values >50 ng/L.

Breast neoplasms: In SAXENDA® clinical trials, more cases of breast cancer were observed among patients receiving SAXENDA® compared to control patients (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reaction).

Psychiatric

Suicidal Behavior and Ideation: In SAXENDA® clinical trials, 9 (0.3%) of 3384 SAXENDA®-treated patients and 2 (0.1%) of the 1941 placebo-treated patients reported suicidal ideation; one of these SAXENDA®-treated patients attempted suicide. Patients treated with SAXENDA® should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue SAXENDA® in patients who experience suicidal thoughts or behaviors. Avoid SAXENDA® in patients with a history of suicidal attempts or active suicidal ideation.

Special Populations

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

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

Renal Insufficiency: There is limited experience with SAXENDA® in patients with moderate renal insufficiency. Patients with moderate renal insufficiency may experience more fatigue and gastrointestinal adverse reactions. Gastrointestinal adverse reactions were the most common adverse reaction leading to discontinuation of treatment. There is very limited or no clinical experience in patients with severe renal insufficiency, including end-stage renal disease; use in these patients is not recommended.

Patients treated with SAXENDA® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. Renal impairment has been reported, 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 insufficiency (see ADVERSE REACTIONS).

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

Pregnant Women: SAXENDA® is contraindicated during pregnancy. Weight loss offers no benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is recommended for all pregnant women, including those who are already overweight or obese, due to the necessary weight gain that occurs in maternal tissues during pregnancy.

There have been no studies conducted in pregnant women with SAXENDA®. In SAXENDA® clinical trials, a greater proportion of reported pregnancies resulted in spontaneous abortion amongst women taking SAXENDA® (9 of 31 pregnancies) than placebo (2 of 15 pregnancies). Studies in animals have shown reproductive and developmental toxicity, including teratogenicity, at or above 0.9 times the clinical exposure (see PART II: TOXICOLOGY).

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

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

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

Geriatrics (≥65 years of age): 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. Patients ≥65 years may experience more gastrointestinal side effects when treated with SAXENDA®. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

During the main treatment period of the weight management studies, serious adverse events were both more common with SAXENDA® (6.3% vs. 4.6%), and led to withdrawal more often (1.2% vs. 0.7%), compared to placebo.

In controlled clinical trials, 9.8% of patients treated with SAXENDA® and 4.3% of patients treated with placebo prematurely discontinued treatment due to adverse reactions. The most common adverse reactions (occurring in >1% of SAXENDA® treated patients) leading to discontinuation were nausea (2.9% in SAXENDA® vs. 0.2% in placebo), vomiting (1.7% vs. <0.1%), and diarrhea (1.4% vs. 0%).

Clinical Trial Adverse Drug Reactions

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

The data below reflect exposure to SAXENDA® in four randomized, double-blind, placebo-controlled, multicenter Phase 3 clinical trials, one of 32-weeks duration and three of 56-weeks duration; and one Phase 2 supportive trial in 469 adult patients. In these trials, patients received SAXENDA® for a mean treatment duration of 45.9 weeks (median, 55.9 weeks).

In one 56-week trial, patients with abnormal glucose measurements at randomization were enrolled into a 160-week period (with a 12-week off-treatment follow-up) of the trial [see Clinical Trials, Study demographics and trial design]. For the 160-week period of the trial, patients who had abnormal glucose measurements at randomization received SAXENDA® for a mean treatment duration of 109.9 weeks (median, 159.3 weeks). In addition to the adverse reactions which have been identified in Table 1, the following adverse reactions occurred in ≥1% and more frequently in SAXENDA®-treated patients than in placebo-treated patients: gastroenteritis, urinary tract infection, gastroenteritis viral, cystitis, tonsillitis, diverticulitis, non-cardiac chest pain, musculoskeletal pain, and intervertebral disc protrusion.

Adverse reactions reported in greater than or equal to 1% of SAXENDA®-treated patients and more frequently than in the placebo group are shown in Table 1.

Table 1 Adverse Reactions Reported in Greater Than or Equal to 1% for Patients on SAXENDA® and More Frequently than in Placebo Patients.

System Organ Class Preferred Term	SAXENDA® N = 3384 n (%)	Placebo N = 1941 n (%)
	Baseline to up to Week 56 of treatment	
Gastrointestinal Disorders		
Nausea	1329 (39.3)	267 (13.8)
Diarrhea	707 (20.9)	192 (9.9)
Constipation	658 (19.4)	165 (8.5)
Vomiting	530 (15.7)	75 (3.9)
Dyspepsia	326 (9.6)	53 (2.7)
Abdominal Pain	182 (5.4)	60 (3.1)
Abdominal Pain Upper	172 (5.1)	53 (2.7)
Abdominal distension	151 (4.5)	58 (3.0)
Eructation	151 (4.5)	4 (0.2)
Flatulence	136 (4.0)	49 (2.5)
Gastroesophageal Reflux Disease	159 (4.7)	33 (1.7)
Dry Mouth	77 (2.3)	19 (1.0)
Gastritis	48 (1.4)	22 (1.1)
Metabolism and Nutrition Disorders		
Hypoglycemia*	46 (1.6)	19 (1.1)
Decreased Appetite	337 (10.0)	45 (2.3)
General Disorders and Administration Site Conditions		
Injection site erythema	86 (2.5)	4 (0.2)
Injection site reactions	86 (2.5)	11 (0.6)
Injection site pruritus	43 (1.3)	4 (0.2)
Injection site rash	36 (1.1)	2 (0.1)
Fatigue	254 (7.5)	89 (4.6)
Asthenia	70 (2.1)	15 (0.8)
Nervous System Disorders		
Dizziness	233 (6.9)	97 (5.0)
Dysgeusia	53 (1.6)	15 (0.8)
Investigations		
Increased lipase	178 (5.3)	43 (2.2)
Increased amylase	47 (1.4)	13 (0.7)
Psychiatric disorders		
Insomnia**	80 (2.4)	33 (1.7)
Hepatobiliary Disorders		
Cholelithiasis	51 (1.5)	10 (0.5)

*Hypoglycemia (based on self-reported symptoms by patients and not confirmed by blood glucose measurements) reported in patients without type 2 diabetes mellitus treated with SAXENDA® in combination with diet and exercise. Please see below for further information regarding hypoglycemia.

**Mainly seen during the first 3 months of treatment

Malignancies

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 1300 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 positive. There were too 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 neoplasia. (see WARNINGS AND PRECAUTIONS, Malignancies, Breast neoplasms)

Papillary Thyroid Cancer
In SAXENDA® clinical trials, papillary thyroid carcinoma confirmed by adjudication was reported in 8 (0.2%) of 3291 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 (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Risk of Thyroid C-Cell Tumours, Malignancies).

Colorectal Neoplasms
In SAXENDA® clinical trials, benign colorectal neoplasms (mostly colon adenomas) 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 malignant colorectal carcinoma were reported in 5 SAXENDA®-treated patients (0.2%) and 1 in a placebo-treated patients (0.1%).

Cardiovascular disorders
Heart rate increase
(See WARNINGS AND PRECAUTIONS, Cardiovascular disorders).

Tachycardia
In SAXENDA® clinical trials, tachycardia was reported in 0.6% of SAXENDA®-treated patients and in 0.1% of placebo-treated patients. The majority of events were mild or moderate. Events were isolated and majority resolved during continued treatment with SAXENDA®.

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 a cardiac conduction disorder, reported as first degree atrioventricular block, right bundle branch block, or left bundle branch block (see WARNINGS AND PRECAUTIONS, Cardiovascular disorders).

PR Interval Prolongation
(See WARNINGS AND PRECAUTIONS, Cardiovascular disorders).

Major Adverse Cardiovascular Events
Major adverse cardiovascular events (MACE) were adjudicated and defined as non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. In the clinical trials there were 8 (1.54 events per 1000 patient-years) confirmed MACE for SAXENDA®-treated patients and 10 (3.83 events per 1000 patient years) confirmed MACE for placebo-treated patients. The hazard ratio and 95% CI is 0.42 [0.17; 1.08] for SAXENDA® versus placebo. Because of the low number of MACE, interpretation should be done with caution.

Cardiac Electrophysiology (QTc) in healthy volunteers

The effect of liraglutide on cardiac repolarization was tested in a QTc study. Liraglutide at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation. The liraglutide exposure for overweight and obese subjects treated with liraglutide 3.0 mg is comparable to the exposure evaluated in the liraglutide QTc study in healthy volunteers.

Hypoglycemia in patients without type 2 diabetes mellitus
In SAXENDA® clinical trials in overweight or obese patients without type 2 diabetes mellitus, there were no events of hypoglycemia that required the assistance of another person. Hypoglycemic events (based on self-reported symptoms by patients and not confirmed by blood glucose measurements) were reported in 1.6 % of SAXENDA®-treated patients and 1.1% of placebo-treated patients. The majority of the events were mild.

Hypoglycemia in patients with type 2 diabetes mellitus
In a SAXENDA® clinical trial in overweight or obese patients with type 2 diabetes mellitus, hypoglycemia requiring the assistance of another person occurred in 3 (0.7%) SAXENDA®-treated patients and in no placebo-treated patients. Of these 3 SAXENDA®-treated patients, all were concomitantly using a sulfonylurea. In patients concomitantly using a sulfonylurea, hypoglycemia defined as blood sugar less than or equal to 3.9 mmol/L and with documented symptoms occurred in 48 (43.6%) SAXENDA®-treated patients and 15 (27.3%) placebo-treated patients. In patients not concomitantly using a sulfonylurea, hypoglycemia was reported in 49 (15.7%) SAXENDA®-patients and 12 (7.6%) placebo-treated patients.

Gastrointestinal adverse events
Gastrointestinal adverse events (AEs) were the most frequently reported AEs during treatment with SAXENDA® (67.9% vs. 39.3% with placebo) and were more often severe (4.8% vs. 1.4% with placebo) and led to withdrawal more often (6.2% vs. 0.8% with placebo).

The most frequently reported gastrointestinal AE was nausea (39% and 14% of patients treated with SAXENDA® and placebo, respectively). The percentage of patients reporting nausea declined as treatment continued. Other common adverse reactions that occurred at a higher incidence among SAXENDA®-treated patients included diarrhea, constipation, vomiting, dyspepsia, abdominal pain, dry mouth, gastritis, gastroesophageal reflux disease, flatulence, eructation and abdominal distension. Most episodes of gastrointestinal events were mild or moderate and did not lead to discontinuation of therapy. There have been reports of gastrointestinal AEs, such as nausea, vomiting, and diarrhea, associated with volume depletion and renal insufficiency (see WARNINGS AND PRECAUTIONS, Gastrointestinal Disease).

Asthenia, Fatigue, Malaise, Dysgeusia and Dizziness
Events of asthenia, fatigue, malaise, dysgeusia and dizziness were mainly reported within the first 12 weeks of treatment with SAXENDA® and often co-reported with gastrointestinal events such as nausea, vomiting and diarrhea. The majority of these events were mild to moderate, transient and did not lead to treatment discontinuation.

Hepatic/Biliary/Pancreas
Acute pancreatitis
(See WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas).

Acute Gallbladder Disease
(See WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas)

Immunogenicity
Patients treated with SAXENDA® may develop anti-liraglutide antibodies. Anti-liraglutide antibodies were detected in 42 (2.8%) of 1505 SAXENDA®-treated patients with a post-baseline assessment. 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 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 SAXENDA® cannot be directly compared with the incidence of antibodies of other products.

Allergic reactions
In SAXENDA® clinical trials, events from a composite of adverse events related to allergic reactions occurred among 2.0% of SAXENDA®-treated patients and among 2.4% of placebo-treated patients. Urticaria was reported in 0.7% of SAXENDA®-treated and 0.5% of placebo-treated patients. Few cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea, and oedema have been reported with marketed use of liraglutide. Anaphylactic reactions may potentially be life threatening.

Injection site reactions
Injection site reactions have been reported in patients treated with SAXENDA®. These reactions were usually mild and transitory and the majority disappeared during continued treatment.

Laboratory Abnormalities
Liver Enzymes
Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15%) SAXENDA®-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (0.05%) placebo-treated patient during the SAXENDA® clinical trials. Because clinical evaluation to exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to SAXENDA® is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones).

Serum Calcitonin
Calcitonin, a biological marker of MTC, was measured throughout the clinical development program (see WARNINGS AND PRECAUTIONS, Malignancies). More patients treated with SAXENDA® in the clinical trials were observed to have high calcitonin values during treatment, compared with placebo. The proportion of patients with calcitonin greater than or equal to 2

times the upper limit of normal at the end of the trial was 1.2% in SAXENDA®-treated patients and 0.6% in placebo-treated patients. Calcitonin values greater than 20 ng/L at the end of the trial occurred in 0.5% of SAXENDA®-treated patients and 0.2% of placebo-treated patients; among the patients with pre-treatment serum calcitonin less than 20 ng/L, none had calcitonin elevations to greater than 50 ng/L at the end of the trial.

Lipase and Amylase
Serum lipase and amylase were measured in the clinical trials. 2.1% of SAXENDA®-treated patients had a lipase value at any time in the trial of greater than or equal to 3 UNR versus 1.0% of placebo-treated patients.

0.1% of SAXENDA®-treated patients had an amylase value at any time in the trial of greater than or equal to 3 UNR versus 0.1% of placebo-treated patients.

In the clinical trial program elevations of serum lipase and amylase were not predictive of pancreatitis. The clinical significance of elevated lipase and amylase values is unknown.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

- Cardiac disorders: Tachycardia
- Gastrointestinal disorders: Pancreatitis
- General disorders and administration site conditions: Malaise
- Hepatobiliary disorders: Cholecystitis
- Immune system disorders: Anaphylactic reaction
- Metabolism and nutrition disorders: Dehydration
- Renal and urinary disorders: Renal failure acute, Renal impairment
- Skin and subcutaneous tissue disorders: Urticaria

Post-Market Adverse Drug Reactions
Market use of SAXENDA® has not identified additional adverse reactions to those stated in the Clinical Trial Adverse Drug Reactions above.

DRUG INTERACTIONS
No clinically significant drug interaction has been demonstrated with SAXENDA®.

Drug-Drug Interactions
In vitro assessment of drug−drug interactions
Liraglutide has very low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug−drug interactions
The drug-drug interaction studies were performed at steady state with liraglutide 1.8 mg/day. The effect on rate of gastric emptying (acetaminophen $AUC_{0\text{-}5h}$) was equivalent between liraglutide 1.8 mg and 3.0 mg. Administration of the interacting drugs was timed so that C_{max} of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Oral Medications: Liraglutide causes a delay of gastric emptying, and thereby has the potential to

impact the absorption of concomitantly administered oral medications and caution should be exercised when oral medications are concomitantly administered with SAXENDA®.

Oral Contraceptives: A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide at steady state. Liraglutide lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively. There was no effect of liraglutide on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the levonorgestrel $AUC_{0-\infty}$ by 18%. Liraglutide delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

Digoxin: A single dose of digoxin 1 mg was administered 7 hours after the dose of liraglutide at steady state. The concomitant administration with liraglutide resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril: A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide at steady state. The co-administration with liraglutide resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with liraglutide.

Atorvastatin: Liraglutide did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of liraglutide at steady state. Atorvastatin C_{max} was decreased by 38% and median T_{max} was delayed from 1 h to 3 h with liraglutide.

Acetaminophen: Liraglutide did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of liraglutide at steady state. Acetaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.

Griseofulvin: Liraglutide did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with liraglutide at steady state. Griseofulvin C_{max} increased by 37% while median T_{max} did not change.

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

Insulin:
No pharmacokinetic interaction was observed between liraglutide and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Units/kg (single-dose) and liraglutide 1.8 mg (steady state) were administered in patients with type 2 diabetes.

Drugs that Increase Heart Rate:

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

Drugs that Cause PR Interval Prolongation:
SAXENDA® causes an increase in the PR interval. The impact on the PR interval of co-administration of SAXENDA® with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digitalis glycosides, and HIV protease inhibitors) has not been evaluated in drug-drug interaction studies. As a result, co-administration of SAXENDA® with these drugs should be undertaken with caution.

Drug-Food Interactions
There are no known interactions with food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
There are no known laboratory interactions.

Drug-Lifestyle Interactions
There are no known lifestyle interactions.

DOSAGE AND ADMINISTRATION

Determine the patient's BMI. BMI is calculated by dividing weight in (kilograms) by height (in meters) squared.

Dosing Considerations
SAXENDA® and Victoza® contain the same active ingredient (liraglutide) and therefore should not be used together. SAXENDA® and Victoza® are not a substitute for each other.

SAXENDA® and insulin should not be used together. SAXENDA® has not been studied in patients taking insulin.

For Patients with Type 2 Diabetes Mellitus:
SAXENDA® should not be used in combination with another GLP-1 receptor agonist.

When initiating SAXENDA®, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and ADVERSE REACTIONS).

SAXENDA® is not a substitute for insulin.

Discontinuation of SAXENDA® in patients with type 2 diabetes may result in an increase in blood glucose.

Recommended Dose and Dosage Adjustment
In adults with an initial BMI of 27 kg/m^2 or greater, the recommended daily maintenance dose is 3.0 mg/day. Daily doses higher than 3.0 mg are not recommended.

For all patients, the dose escalation schedule in Table 2 should be used to reduce the likelihood of gastrointestinal symptoms. If patients do not tolerate an increased dose during dose escalation, the dose escalation can be changed with a total delay of up to 7 days.

Table 2. Dose escalation schedule

	Dose	Weeks
Dose escalation 4 weeks	0.6 mg	1
	1.2 mg	1
	1.8 mg	1
	2.4 mg	1
Maintenance dose	3.0 mg	

The 0.6, 1.2, 1.8, and 2.4 mg doses are intended to reduce gastrointestinal symptoms during initial dose escalation.

Treatment with SAXENDA® should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight (see SCIENTIFIC INFORMATION, Clinical Trials).

Missed Dose
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.

Based on the elimination half-life, patients should be advised to reinitiate SAXENDA® at 0.6 mg if more than 3 days have elapsed since the last SAXENDA® dose. This approach will mitigate any gastrointestinal symptoms associated with re-initiation of treatment.

Administration
SAXENDA® should be taken once daily at any time of day, independent 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.

SAXENDA® solution should be inspected prior to each injection, and the solution should be used only if it is clear, colourless, and contains no particles.

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 overdosage, appropriate

supportive treatment should be initiated according to the patient's clinical signs and symptoms.

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

ACTION AND CLINICAL PHARMACOLOGY

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). Liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase activation through the stimulatory G-protein, Gs.

GLP-1 is a physiological regulator of appetite and food intake and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.

Pharmacodynamics

Effects on appetite sensations, food intake and energy expenditure, food emptying, and fasting and postprandial glycemia in obese, non-diabetic patients

A five week clinical pharmacology trial was conducted in 49 obese (BMI 30-40 kg/m^2) non-diabetic patients to investigate the pharmacodynamic effects of liraglutide.

Appetite sensations, food intake, and energy expenditure

The weight loss effect of liraglutide is considered to be mediated by decreased appetite and food intake. Appetite sensations were assessed before and up to five hours after a standardized breakfast meal, and ad libitum food intake during the subsequent lunch meal. SAXENDA® increased post-prandial satiety and fullness ratings, reduced hunger and prospective food consumption ratings and decreased ad libitum food intake, compared to placebo. No treatment-related increase in 24-hour energy expenditure was observed as assessed in a respiratory chamber.

Gastric emptying

SAXENDA® caused a minor delay of gastric emptying during the first hour after the meal (acetaminophen $AUC_{0\text{-}1h}$ was 23% smaller than with placebo), thereby reducing the rate at which postprandial glucose appeared in the circulation.

Fasting and postprandial glucose, insulin, and glucagon

Compared to placebo, SAXENDA® reduced fasting glucose and postprandial glucose increments for the first hour after the meal and reduced the incremental glucose $AUC_{0\text{-}300min}$. In addition, SAXENDA® decreased postprandial increments in glucagon ($iAUC_{0\text{-}300min}$) and postprandial increments of insulin ($iAUC_{0\text{-}60min}$) after the meal compared with placebo.

Fasting and incremental glucose and insulin concentrations in overweight and obese patients

Fasting and incremental glucose and insulin concentrations were also assessed during a 75-g oral glucose tolerance test (OGTT) before and after 56 weeks of treatment in Study 1 (see CLINICAL TRIALS). Compared to placebo, SAXENDA® reduced fasting and incremental glucose concentrations.

Pharmacokinetics

Absorption: The absorption of liraglutide following subcutaneous administration was slow, reaching maximum concentration approximately 11 hours post dosing. The average liraglutide steady state concentration ($AUC_{\tau/24}$) reached approximately 31 nmol/L in obese (BMI 30-40 kg/m^2) subjects following administration of SAXENDA®. Liraglutide exposure increased proportionally with dose in the dose range of 0.6 mg to 3.0 mg. The absolute bioavailability of a subcutaneous single dose of liraglutide 5 µg/kg in healthy subjects is approximately 55%.

Distribution: The mean apparent volume of distribution after subcutaneous administration of liraglutide 3.0 mg is 20-25 L (for a person weighing approximately 100 kg). Liraglutide is extensively bound to plasma protein (>98%).

Metabolism: During the initial 24 hours following administration of a single [^{3}H]-liraglutide dose (0.75 mg) to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤9% and ≤5% of total plasma radioactivity exposure). Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Excretion: Following a [^{3}H]-liraglutide dose (0.75 mg), 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 liraglutide 3.0 mg is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours.

Special Populations and Conditions

Pediatrics: SAXENDA® has not been studied in pediatric patients (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Geriatrics: Age had no effect on the pharmacokinetics of liraglutide based on a pharmacokinetic study (1 mg) in healthy elderly subjects (65 to 83 years). A population pharmacokinetic analysis (liraglutide 3.0 mg) of data from overweight and obese patients 18 to 82 years of age could not detect an effect due to age. (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Gender: Based on the current population pharmacokinetic analyses (liraglutide 3.0 mg) of data from overweight and obese patients, females would appear to have 24% lower weight adjusted clearance of SAXENDA® compared to males. Based on the current analysis of the exposure response data, no dose adjustment is necessary based on gender.

Race: A population pharmacokinetics analysis could not detect any effect of race and ethnicity on the pharmacokinetics of liraglutide 3.0 mg in a population that included overweight and obese patients of Caucasian, Black, Asian and Hispanic/Non-Hispanic groups.

Body Weight: The exposure of liraglutide decreases with an increase in baseline body weight. However, the 3.0 mg daily dose of liraglutide provided adequate systemic exposures over the

body weight range of 60 – 234 kg evaluated for exposure response in the clinical trials. Liraglutide exposure was not studied in patients with body weight >234 kg.

Hepatic Insufficiency: Subjects with varying degrees of hepatic insufficiency displayed a reduced exposure to liraglutide. After a single-dose (0.75 mg), the AUC in mild (Child Pugh score 5-6), moderate, and severe (Child Pugh score > 9) compared to healthy subjects was lower on average by 23%, 13% and 44% respectively.

Renal Insufficiency: Subjects with varying degrees of renal insufficiency displayed a reduced exposure to liraglutide. After a single-dose (0.75 mg), the AUC in mild (CrCL 50-80 mL/min), moderate (CrCL 30-50 mL/min), severe (CrCL < 30 mL/min) and end-stage renal disease requiring dialysis compared to healthy subjects was lower on average by 33%, 14%, 27% and 26%, respectively.

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

SAXENDA® is a 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 3.0 mg (6 mg/mL, 3 mL). SAXENDA® is available in the following package sizes containing disposable, pre-filled, multi-dose pens.

3 x SAXENDA®
5 x SAXENDA®

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

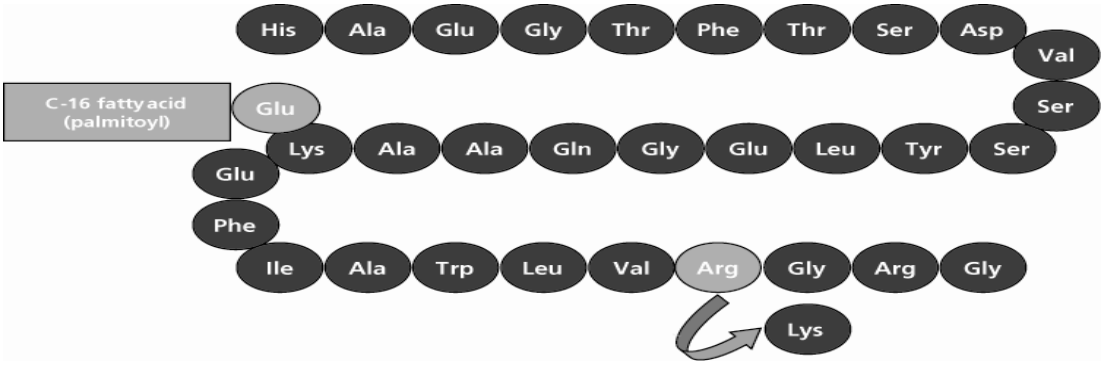
Drug Substance

Proper name: SAXENDA®

Chemical name: liraglutide

Molecular formula and molecular mass: liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and 3751.2 Daltons

Structural formula:



Physicochemical properties: Each 1 mL of SAXENDA® solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 mL solution of SAXENDA® equivalent to 18 mg liraglutide (free-base, anhydrous) and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injections.

Product Characteristics
SAXENDA® (liraglutide) is a clear, colourless solution.

CLINICAL TRIALS
Study demographics and trial design

The safety and efficacy of SAXENDA® for chronic weight management in conjunction with reduced food intake and increased physical activity were studied in three 56-week randomized, double-blind, placebo-controlled trials (Table 4). 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 minutes/week) that began with the first dose of study medication or placebo and continued throughout the trial.

Table 4 – Summary of patient demographics for SAXENDA® clinical trials

Trial #	Trial Design	Dosage, Route of Administration and duration	Trial subjects (n = number)	Mean Age (Range)	Gender	Race
1	Multicenter, randomized, double-blind, placebo-controlled trial	SAXENDA® 3.0 mg once daily or placebo SAXENDA® was administered subcutaneously once daily for 56 weeks or 160-weeks	3731 160 Weeks 2254	45 years (18-78) <u>160 Weeks</u> 48 years (18-78)	78% Female 22% Male <u>160 Weeks</u> 76% Female and 24% Male	85% Caucasian 10% African American 5% Other <u>160 Weeks</u> 85% Caucasian 10% African American 9% Other
2	Multicenter, randomized, double-blind, placebo-controlled trial	SAXENDA® 3.0 mg once daily or placebo as an add-on to their background diabetes treatment SAXENDA® was administered subcutaneously once daily for 56 weeks	635	55 years (18-82)	50% Female 50% Male	83% Caucasian 12% African American 5% Other
3	Multicenter, randomized, double-blind, placebo-controlled trial	SAXENDA® 3.0 mg once daily or placebo SAXENDA® was administered subcutaneously once daily for 56 weeks	422	46 years (18-73)	81% Female 19% Male	84% Caucasian 13% African American 3% Other

Study 1 enrolled 3731 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension. Patients with type 2 diabetes were excluded from participating. Patients were randomized in a 2:1 ratio to either SAXENDA® or placebo for either 56 or 160 weeks (with a 12-week off-treatment follow-up) based on abnormal glucose measurements (e.g., impaired glucose tolerance or impaired fasting glucose) at screening.
For the 56-week period of the trial, mean baseline body weight was 106.3 kg and mean BMI was 38.3 kg/m^2. For the 160-week period, mean baseline body weight was 107.6 kg and mean BMI was 38.8 kg/m^2. Most subjects were obese (97%) and 47% had treated or untreated dyslipidemia and/or hypertension. For the 56-week period of the trial, approximately 11% were of Hispanic or Latino ethnicity and in the 160-week period approximately 9% were Hispanic or Latino ethnicity.

Study 2 enrolled patients with type 2 diabetes and with either overweight or obesity (as defined above). Patients were to have an HbA_{1c} of 7-10% and be treated with metformin, a sulfonylurea, a glitazone as single agent or in any combination. Patients were randomized in a 2:1 manner to receive either SAXENDA® or placebo as an add-on to their background diabetes treatment. Most subjects were obese (86%) and 86% had treated or untreated dyslipidemia and/or hypertension. Approximately 10% were of Hispanic or Latino ethnicity.

Study 3 enrolled patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 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. All patients were first treated with a low calorie diet (total energy intake 1200-1400 kcal/day) in a run-in period lasting up to 12 weeks. Patients who lost at least 5% of their screening body weight after 4 to 12 weeks during the run-in were randomized in a 1:1 manner to receive either SAXENDA® or placebo for 56 weeks. Most subjects were obese (98%) and 45% had treated or untreated dyslipidemia and/or hypertension. Approximately 7% were of Hispanic or Latino ethnicity.

Study results

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 5 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.

Table 5. Changes in Weight at Week 56 for Studies 1, 2, and 3

	Study 1 (Obesity or overweight with comorbidity)		**Study 2 (Type 2 diabetes with obesity or overweight)**		**Study 3 (Obesity or overweight with comorbidity following at least 5% weight loss with diet)**	
	SAXENDA® N=2437	**Placebo N=1225**	**SAXENDA® N=412**	**Placebo N=211**	**SAXENDA® N=207**	**Placebo N=206**
Weight						
Baseline mean (kg) (SD)	106.3 (21.2)	106.3 (21.7)	105.6 (21.9)	106.7 (21.2)	100.7 (20.8)	98.9 (21.2)
Percent change from baseline (LSMean)	-8.0	-2.6	-5.9	-2.0	-6.3	-0.2
Difference from placebo (LSMean) (95% CI)	-5.4* (-5.8;-5.0)		-4.0* (-4.8;-3.1)		-6.1* (-7.5;-4.6)	
% of Patients losing greater than or equal to 5% body weight	63.5%	26.6%	49.8%	13.5%	50.7%	21.3%
Odds ratio vs placebo (LSMean) (95% CI)	4.8* (4.1;5.6)		6.4* (4.1;10.0)		3.8* (2.4;6.0)	
% of Patients losing greater than 10% body weight	32.8%	10.1%	22.9%	4.2%	27.4%	6.8%
Odds ratio vs placebo	4.3*		6.8*		5.1	

	Study 1 (Obesity or overweight with comorbidity)		Study 2 (Type 2 diabetes with obesity or overweight)		Study 3 (Obesity or overweight with comorbidity following at least 5% weight loss with diet)	
	SAXENDA® N=2437	**Placebo N=1225**	**SAXENDA® N=412**	**Placebo N=211**	**SAXENDA® N=207**	**Placebo N=206**
(LSMean) (95% CI)	(3.5;5.3)		(3.4;13.8)		(2.7;9.7)†	
% of Patients maintaining run-in weight loss (LSMean)‡					81.4%	48.9%
Odds ratio vs placebo (LSMean) for maintaining run-in weight loss					4.8 (3.0;7.7)*	

SD = Standard Deviation; CI = Confidence Interval
* $p < 0.0001$ compared to placebo. Type 1 error was controlled across the three endpoints.
† This endpoint does not claim statistical significance, because it was not part of confirmatory testing.
‡ The endpoint was defined as weight regain ≤0.5% from start of Saxenda® treatment. The number (proportion) of patients with missing data at Week 56 with SAXENDA®/placebo and who contributed to the analyses with LOCF values were 624 (26%)/401 (33%) in Study 1, 93 (23%)/94 (45%) in Study 2 and 51 (25%)/62 (30%) in Study 3. 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. Missing data were imputed using the last observation carried forward; other imputation methods have yielded similar and smaller estimated treatment effects.

In Study 1, 2254 patients who had abnormal glucose measurement at randomization were randomized to the 160 week period. Among them, 50% (1126/2254) of patients discontinued the study: 47% in the SAXENDA® group vs. 55% in the placebo group. The proportions of patients who discontinued due to an adverse reaction were 13% and 6% for SAXENDA- and placebo-treated patients, respectively. Table 6 presents changes in weight at week 160 in a subset of patients with abnormal glucose at randomization.

Table 6. Changes in Weight at Week 160 for Study 1 (Subset of Patients with Abnormal Blood Glucose at Randomization)

	SAXENDA® **N=1472**	**Placebo N=738**
Weight		
Baseline mean (SD) (kg)	107.6 (21.6)	108.0 (21.8)
Percent change from baseline (LSMean)	-6.2	-1.8
Difference from placebo (LSMean)	-4.3	
Number (%) of patients known to lose greater than or equal to 5% body weight	424 (28.8%)	102 (13.8%)
Number (%) of patients known to lose greater than 10% body weight	234 (15.9%)	49 (6.6%)
Number (%) of patients with weight assessment at 160 weeks	747 (50%)	322 (43%)

SD = Standard Deviation;
Includes all randomized subjects who had a baseline body weight measurement. All available body weight data during the 160 week treatment period are included in the analysis. Missing data were imputed using the last observation carried forward when calculating percent change from baseline. When deriving number (%) of patients known to lose greater than or equal to 5% or greater than 10% body weight, patients with missing data at week 160 were assumed non-responders.

The cumulative frequency distributions of change in body weight from baseline to week 56 are shown in Figure 1 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 of patients (vertical axis) in each treatment group who achieved at least that degree of weight loss. For example, note that the vertical line arising from -10% in Study 1 intersects the SAXENDA® and placebo curves at approximately 33% and 10%, respectively, which correspond to the values shown in Table 5.

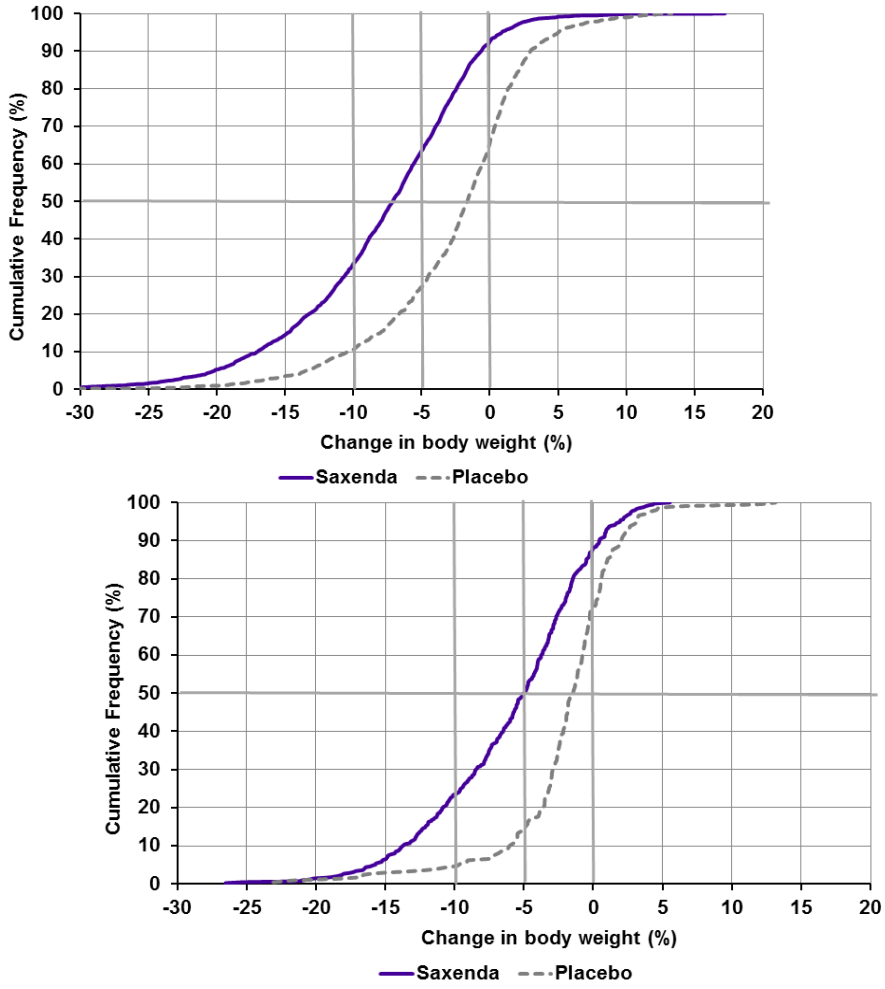


Figure 1. Change in body weight (%) from baseline to week 56 (Study 1 on top and Study 2 below)

The time courses of weight loss with SAXENDA® and placebo from baseline through week 56 are depicted in Figures 2 and 3.

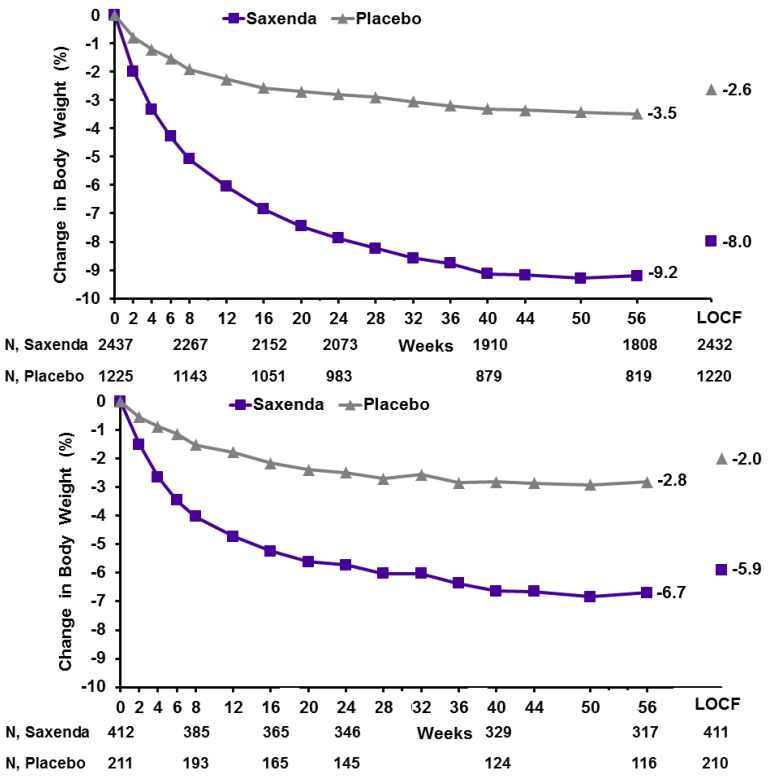


Figure 2. Change from baseline (%) in body weight (Study 1 on top and Study 2 below)

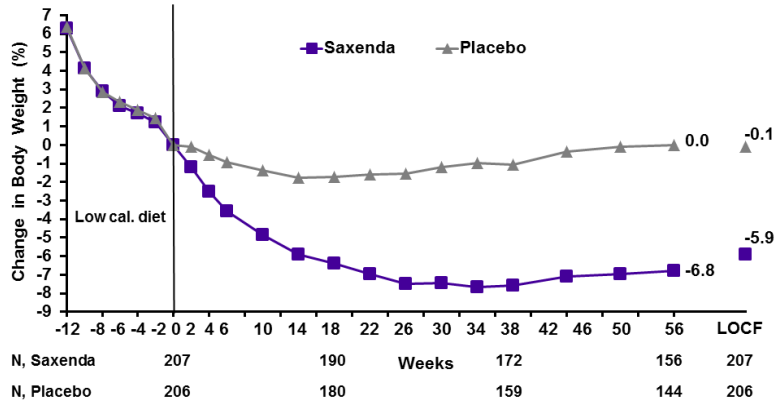


Figure 3. Change from baseline (%) in body weight during Study 3

Weight loss response of 5% after 12 weeks on SAXENDA® (3.0 mg)
Across studies 1 and 2, 65% of the patients achieved ≥5% weight loss after 12 weeks on SAXENDA® (3.0 mg). A retrospective analysis indicates that after 1 year of treatment, the mean weight loss was found to be meaningful for these patients. For the 35% of patients who achieved a weight loss of <5% after 12 weeks on SAXENDA® (3.0 mg), the weight loss at 1 year was not considered clinically meaningful (<5%).

Effect of SAXENDA® on Glycemic Control, Anthropometry and Cardiometabolic Parameters
Change in glycemic control, waist circumference and cardiometabolic parameters with SAXENDA® are shown in Tables 7-8 for Study 1 (patients without diabetes mellitus) and Table 9 for Study 2 (patients with type 2 diabetes). Results from Study 3, which only enrolled patients without diabetes mellitus, were similar to Study 1.

Table 7 Mean Changes in Glycemic Control, Anthropometry and Cardiometabolic Parameters in Study 1 (Patients without Diabetes)

	SAXENDA® N = 2437		**Placebo N = 1225**		
	Baseline	**Change from Baseline (LSMean[1])**	**Baseline**	**Change from Baseline (LSMean[1])**	**SAXENDA® minus Placebo (LSMean)**
HbA_{1c} (%)	5.6	-0.3	5.6	-0.1	-0.2
Fasting plasma glucose (mmol/L)	5.3	-0.4	5.3	-0.0	-0.4
Waist Circumference (cm)	115.0	-8.2	114.5	-4.0	-4.2
Systolic blood pressure (mm Hg)	123.0	-4.3	123.3	-1.5	-2.8
Diastolic blood pressure (mm Hg)	78.7	-2.7	78.9	-1.8	-0.9
Heart Rate (bpm)	71.4	2.6	71.3	0.1	2.5
	Baseline	**% change from Baseline (LSMean[1])**	**Baseline**	**% change from Baseline (LSMean[1])**	**Relative Difference of SAXENDA® to Placebo (LSMean)**
Total Cholesterol (mmol/L)*	5.0	-3.2	5.0	-0.9	-2.3
LDL Cholesterol (mmol/L)*	2.9	-3.1	2.9	-0.7	-2.4
HDL Cholesterol (mmol/L)*	1.3	2.3	1.3	0.5	1.9
Triglycerides (mmol/L)*	1.4	-13.6	1.5	-4.8	-9.3

Based on last observation carried forward method while on study drug.
[1] Least squares mean adjusted for treatment, country, sex, pre-diabetes status at screening, baseline BMI stratum and an interaction between pre-diabetes status at screening and BMI stratum as fixed factors, and the baseline value as covariate.
* Baseline value is the geometric mean.

Table 8. Mean Changes at Week 160 in Anthropometry and Cardiometabolic Parameters in Study 1 (Subset of Patients with Abnormal Blood Glucose at Randomization)

	Saxenda N = 1505		Placebo N = 749		
	Baseline	**Change from Baseline (LSMean[1])**	**Baseline**	**Change from Baseline (LSMean[1])**	**Saxenda minus Placebo (LSMean)**
HbA1c, %	5.8	-0.4	5.7	-0.1	-0.21
Fasting plasma glucose (mmol/L)	5.5	-0.4	5.5	0.04	-0.4
Waist Circumference (cm)	116.6	-6.9	116.7	-3.4	-3.5
Systolic Blood Pressure (mmHg)	124.8	-3.2	125.0	-0.4	-2.8
Diastolic Blood Pressure (mmHg)	79.4	-2.4	79.8	-1.7	-0.6

Based on last observation carried forward method while on study drug
[1] Least squares mean adjusted for treatment, country, sex, baseline BMI stratum as fixed factors, and the baseline value as covariate.

Table 9 Mean Changes in Anthropometry and Cardiometabolic Parameters in Study 2 (Patients with Diabetes Mellitus)

	SAXENDA® N = 412		Placebo N - 211		
	Baseline	**Change from Baseline (LSMean[1])**	**Baseline**	**Change from Baseline (LSMean[1])**	**SAXENDA® minus Placebo (LSMean)**
HbA_{1c} (%)	7.9	-1.3	7.9	-0.4	-0.9
Fasting plasma glucose (mmol/L)	8.8	-1.9	8.6	-0.1	-1.8
Waist Circumference (cm)	118.1	-6.0	117.3	-2.8	-3.2
Systolic Blood Pressure (mm Hg)	128.9	-3.0	129.2	-0.4	-2.6
Diastolic Blood Pressure (mm Hg)	79.0	-1.0	79.3	-0.6	-0.4
Heart Rate (bpm)	74.0	2.0	74.0	-1.5	3.4
	Baseline	**% change from Baseline (LSMean[1])**	**Baseline**	**% change from Baseline (LSMean[1])**	**Relative Difference of SAXENDA® to Placebo (LSMean)**
Total Cholesterol (mmol/L)*	4.4	-1.4	4.4	2.3	-3.6
LDL Cholesterol (mmol/L)*	2.2	0.8	2.2	3.1	-2.2
HDL Cholesterol (mmol/L)*	1.2	4.8	1.2	2.0	2.8
Triglycerides (mmol/L)*	1.8	-14.6	1.8	1.1	-13.7

Based on last observation carried forward method while on study drug
[1] Least squares mean adjusted for treatment, country, sex, background treatment, baseline HbA_{1c} stratum and an interaction between background treatment and HbA_{1c} stratum as fixed factors, and the baseline value as covariate.
* Baseline value is the geometric mean

TOXICOLOGY

Single dose toxicity

Single dose studies were performed in mice and rats in standard design studies and in monkeys in a maximum tolerated dose (MTD) study. A single dose of 10 mg/kg was generally well tolerated by mice and rats without mortality. In monkeys, a single SC administration of 5 mg/kg was well tolerated without mortality. The observed reductions in body weight and food consumption can be regarded as pharmacologically mediated.

Repeat dose toxicity

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

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

Study ID	**NN980183**	**NN980189**	**NN200239**
Species Strain	Rats/Sprague Dawley	Rats/Sprague Dawley	Rats/Sprague Dawley
Drug	Liraglutide	Liraglutide	Liraglutide
Dose Route	SC	SC	SC
Animals/Sex/Group	Main study: 4 groups: 10 males, 10 females/group Satellite study: 3 groups: 10 males, 10 females/group.	Main study: 4 groups: 10 males, 10 females/group Satellite study: 4 groups: 10 males, 10 females/group. Recovery study: 2 groups: 5 males, 5 females/group	4 groups: 15 males, 15 females/group
Dose Groups (mg/kg/day)	0, 0.1 , 0.25, 1.0	0, 0.1 , 0.25, 1.0	0, 0.1 , 0.25, 1.0
Duration	4 weeks	13 weeks treatment + 4 weeks recovery	26 weeks
NOEL/ NOAEL (mg/kg/day)	NOEL <0.1 mg/kg. NOAEL 1.0 mg/kg	NOEL <0.1 mg/kg NOAEL 1.0 mg/kg	NOEL <0.1 mg/kg NOAEL 1.0 mg/kg
Study ID	**NN980184**	**NN990191**	**NN200241**
Species/strain	Cynomolgus Monkeys	Cynomolgus Monkeys	Cynomolgus Monkeys
Drug	Liraglutide	Liraglutide	Liraglutide
Dose Route	SC	SC	SC

Study ID	NN980183	NN980189	NN200239
Animals/sex/group	4 groups: 3 males, 3 females/group	Main study: 4 groups: 4 males, 4 females/group. Recovery study: 2 groups: 2 males, 2 females/group	Main study: 4 groups: 4 males, 4 females/group. Recovery study: 2 groups: 2 males, 2 females/group
Dose groups (mg/kg/day)	0, 0.05, 0.5, 5.0	0, 0.05, 0.5, 5.0	0, 0.05, 0.5, 5.0
Duration	4 weeks	13 weeks treatment + 2 weeks recovery	52 weeks treatment + 4 weeks recovery
NOEL/ NOAEL (mg/kg/day)	NOEL < 0.05mg/kg NOAEL 5mg/kg	NOEL < 0.05mg/kg NOAEL 5mg/kg	NOEL 0.05mg/kg NOAEL 5mg/kg

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

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

Carcinogenicity

A 104-week carcinogenicity study was conducted in male and female 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 0.3-, 2.0-, 10- and 43-times the obese human exposure, respectively, at the maximum recommended human dose (MRHD) of 3.0 mg/day based on plasma AUC 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 carcinomas 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 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 concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 7-times the human exposure, respectively, resulting from 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 C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

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

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

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

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

In a rabbit developmental study, pregnant females were administered liraglutide subcutaneously at doses of 0.01, 0.025 and 0.05 mg/kg/day from gestation day 6 through day 18 inclusive. The estimated systemic exposures were less than the human exposure at all doses, based on plasma AUC. Fetal weight was decreased and the incidence of total major fetal abnormalities was increased at all dose levels tested. Single cases of microphthalmia were noted at all dose levels. Since microphthalmia is a very rare malformation, and was not observed in the control group, or in any of the historical control groups, this finding is considered to be related to treatment. In addition, there was an increase in the fetal incidence of connected parietals in the high dose group, and a single case of split sternum in the 0.025 and 0.05 mg/kg/day groups which could not

be ruled out as unrelated to treatment. Minor abnormalities considered to be treatment related were an increase in the incidence of jugal(s) connected/fused to maxilla at all dose levels and an increase in the incidence of bilobed/bifurcated gallbladder at 0.025 and 0.50 mg/kg/day. The noted findings exceeded the incidence noted in the concurrent and historical controls. Based on these data, a NOEL/NOAEL for embryo/fetal toxicity could not be determined. Liraglutide is considered to be a possible teratogen in rabbits due to the increased incidence of major abnormalities noted at all dose levels tested.

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

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

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

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

SAXENDA®
(liraglutide)

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Possible Risk of thyroid tumours, including cancer

As part of drug testing, liraglutide, the active ingredient in SAXENDA® was given to rats and mice in long term studies. In these studies, liraglutide caused both rats and mice to develop medullary thyroid tumours, some of which were cancer. It is not known if liraglutide will cause thyroid tumours or a rare type of thyroid cancer called medullary thyroid cancer in people. If medullary thyroid cancer occurs, it may lead to death if it is not found early and treated. If you develop a tumour of the thyroid, it may have to be surgically removed.

While taking SAXENDA®, tell your doctor if you get a lump or swelling in your neck, hoarseness, trouble swallowing or shortness of breath. These may be symptoms of thyroid cancer. You should discuss any safety concerns you have about the use of SAXENDA® with your doctor.

What is SAXENDA® used for?

SAXENDA® (liraglutide) is used for weight loss in adults aged 18 and above who have either:

- BMI* of 30 or greater (obese - very overweight), or
- BMI* of 27-30 (overweight) in the presence of at least one weight-related comorbidity and who have failed a previous weight management intervention.

**BMI (Body Mass Index) is a simple measure of your weight in relation to your height. See your doctor to have your BMI measured.*

How does SAXENDA® work?

SAXENDA® helps obese adults or overweight adults who also have weight related medical problems lose weight and keep the weight off. SAXENDA® should be used with a reduced calorie diet and increased physical activity.

What are the ingredients in SAXENDA®?

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

SAXENDA® belongs to a class of medicines called GLP-1 analogue.

SAXENDA® comes in the following dosage forms:
SAXENDA® is provided in a disposable, prefilled, multi-dose pen. Each pen can deliver a dose of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg. Each pen contains 3 mL of SAXENDA® at a concentration of 6 mg/mL.

Pens are available in packages of three and five.

Do not use SAXENDA® if:
- You or any of your family members have a history of medullary thyroid cancer.
- You have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumours in more than one gland in their body.
- You are allergic to liraglutide or any of the ingredients in SAXENDA®. (See "*What are the ingredients in SAXENDA®*?" for a complete list of ingredients).
- You are pregnant or planning to become pregnant. SAXENDA® may harm your unborn baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SAXENDA®. Talk about any health conditions or problems you may have, including if you:

- have palpitations (you feel aware of your heart beat) or if you have feelings of a racing heart beat while at rest during SAXENDA® treatment.
- lose substantial weight you are at risk of gallstones and thereby inflamed gallbladder. Stop taking SAXENDA® and contact a doctor immediately if you experience severe pain in your upper abdomen, usually worse on the right side under the ribs. The pain may be felt through to your back or right shoulder (see '*What are the possible side effects of SAXENDA®*?')
- have or have had depression or suicidal thoughts.
- have severe heart failure. There is little to no experience with this medicine in patients with heart failure.
- have ever had a heart attack (myocardial infarction). There is little or no experience with this medicine in patients who have ever had a heart attack.
- have unstable angina, a type of chest pain that happens when there is not enough blood to the heart and that is also either new or different from before. There is little or no experience with this medicine in patients with unstable angina.
- have a problem with your heart beating too fast (tachyarrhythmia) or with the normal electric impulses of your heart (conduction disorder, for example atrioventricular block). There is little or no experience with this medicine in patients with conduction disorders and arrhythmias.
- have diabetes, do not use SAXENDA® instead of insulin and do not use SAXENDA® with insulin.
- have the symptoms of inflammation of the pancreas (pancreatitis), such as severe stomach pain which does not go away, talk to your doctor immediately. Pancreatitis can be severe and lead to death. You may be more likely to get pancreatitis if you have had pancreatitis before,

or if you have had stones in your gallbladder, alcoholism or high levels of triglycerides in your blood.
- have ever had an allergic reaction to liraglutide or any of the other ingredients in SAXENDA®.
- have kidney problems.
- have liver problems.
- have severe stomach problems, such as slowed emptying of your stomach (gastroparesis) or problems digesting your food.
- are pregnant or plan to have a baby. SAXENDA® may harm your unborn baby. Tell your doctor if you become pregnant while taking SAXENDA®. If you are pregnant, stop using SAXENDA®.
- are breastfeeding or plan to breastfeed. It is not known if SAXENDA® passes into your breast milk. You and your doctor should decide if you will take SAXENDA® or breastfeed.
- have severe vomiting and/or diarrhea and/or dehydration.

When starting SAXENDA® treatment, you might have side effects like throwing up (vomiting), feeling sick (nauseated) and getting diarrhea. Throwing up and diarrhea can cause dehydration (loss of fluids). It is important to avoid dehydration by drinking plenty of fluids. Call your doctor if you have any questions. Dehydration can cause kidney problems that sometimes require hemodialysis.

SAXENDA® is not recommended for use in babies, children or teenagers under 18 years of age.

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

The following may interact with SAXENDA®:
Don't take SAXENDA® if you take insulin. Tell your doctor, Diabetes Nurse Educator or pharmacist if you are taking diabetes medicines called 'sulphonylurea' (such as glimepiride or glibenclamide). Using these medicines with SAXENDA® can make your blood sugar go too low (hypoglycemia). Your doctor may adjust the dose of your diabetes medicine to prevent you from getting low blood sugar.

How to take SAXENDA®:
Use SAXENDA® exactly as prescribed by your healthcare professional. (See *'Instructions for Use*').

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

Usual dose:
When you first start using SAXENDA®, the starting dose is 0.6 mg once a day. Your dose should be increased after using SAXENDA® for one week until you reach the 3.0 mg dose. After that, do not change your dose unless your healthcare professional tells you to.

- SAXENDA® is injected 1 time each day, at any time during the day.
- You can take SAXENDA® with or without food.
- Your doctor should start you on a diet and exercise program when you start taking SAXENDA®. Stay on this program while you are taking SAXENDA®.

Administering SAXENDA®:
SAXENDA® is an injection which is given under the skin (subcutaneously). Do not inject it into a vein or muscle.

Before you use the pen for the first time, your doctor or Diabetes Nurse Educator will show you how to use it. The best places to give yourself the injection are the front of your thighs, the front of your waist (abdomen) or your upper arm. You can give yourself the injection at any time of the day. See '*Instructions for Use'*.

Overdose:

If you think you have taken too much SAXENDA®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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

Missed Dose:
If you miss your daily dose of SAXENDA®, use SAXENDA® as soon as you remember. Then 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 professional to talk about how to restart your treatment.

What are the possible side effects from using SAXENDA®?
These are not all the possible side effects you may feel when taking SAXENDA®. If you experience any side effects not listed here, contact your healthcare professional. (Please also see '*Warnings and Precautions'*.)

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

Some severe allergic reactions (anaphylaxis) have been reported rarely in patients using SAXENDA®. You should see your doctor straight away if you get symptoms such as breathing problems, swelling of face and throat and fast heart beat.

Cases of inflammation of the pancreas (pancreatitis**)** have been reported uncommonly in patients using SAXENDA®. Pancreatitis can be a serious, potentially life-threatening medical condition**.** Talk to your doctor straight away if you get severe stomach pain which does not go away.

Very common: may affect more than 1 in 10 people
- feeling sick (nausea), being sick (vomiting), diarrhea, constipation - these usually go away after a few days or weeks
- lower appetite

Common: may affect up to 1 in 10 people
- problems affecting the stomach and intestines such as: indigestion (dyspepsia), inflamed lining of the stomach (gastritis), stomach discomfort, upper stomach pain, heart burn, feeling bloating, wind (flatulence), belching, dry mouth
- feeling weak or tired
- changed sense of taste
- dizziness
- gallstones
- injection site reactions (such as bruising, pain, irritation, itching and rash)
- low blood sugar (hypoglycemia) - the warning signs of low blood sugar may come on suddenly and can include: cold sweat, cool pale skin, headache, fast heart beat, feeling sick, feeling very hungry, changes in vision, feeling sleepy, feeling weak, nervous, anxious, confused, difficulty concentrating, shaking (tremor). Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs.
- Difficulty sleeping (insomnia). This usually occurs during the first 3 months of treatment
- Increase of pancreatic enzymes, such as lipase and amylase

Uncommon: may affect up to 1 in 100 people
- loss of fluids (dehydration) - this is more likely at the start of treatment and may be due to being sick (vomiting), feeling sick (nausea) and diarrhea
- inflamed gallbladder
- allergic reactions including skin rash
- feeling generally unwell
- faster pulse
- inflammation of the pancreas (pancreatitis)

Rare: may affect up to 1 in 1,000 people
- reduced kidney function
- acute kidney failure - signs include metallic taste in mouth and easily bruising
- severe allergic reactions (anaphylaxis)

If any of the side effects do not go away or get worse, or if you notice any side effects not listed in the leaflet, please tell your doctor, Diabetes Nurse Educator or pharmacist.

Serious side effects and what to do about them				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Increases in Heart Rate. If you experience, while at rest, a racing or pounding feeling in your chest lasting several minutes when taking SAXENDA®, notify your doctor.		√	
Rare	Severe form of allergic reaction (anaphylactic reaction) with symptoms of breathing problems, swelling of throat and face, and fast heart beat. You should seek immediate medical attention.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);.

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

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

- **Before you start to use** SAXENDA®, store it in a refrigerator (2˚C to 8˚C) away from the freezer compartment. Do not freeze it.
- **When** SAXENDA® is being used, you can keep it for 1 month either at room temperature (not above 30˚C) or in a refrigerator (2˚C to 8˚C).

- Do not use SAXENDA® if it has been frozen.
- Do not use SAXENDA® if it is not clear and colourless.
- Always remove the injection needle after each injection and store your SAXENDA® pen without an injection needle attached. The dosing is accurate.
- When you are not using the pen, keep the cap on. This will protect the medicine from light.
- Protect SAXENDA® from high temperatures and sunlight.
- Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of reach and sight of children.

If you want more information about SAXENDA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; or by contacting the sponsor, Novo Nordisk Canada Inc., at 1-800-465-4334, www.novonordisk.ca.

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PrSaxenda® Instructions for use

Instructions on how to use Saxenda® 6 mg/mL solution for injection in prefilled pen

Please read these instructions carefully before using your Saxenda® prefilled pen.

Do not use the pen without proper training from your doctor or Diabetes Nurse Educator.

Start by checking your pen to **make sure that it contains Saxenda® 6 mg/mL,** then look at the illustrations below to get to know the different parts of your pen and needle.

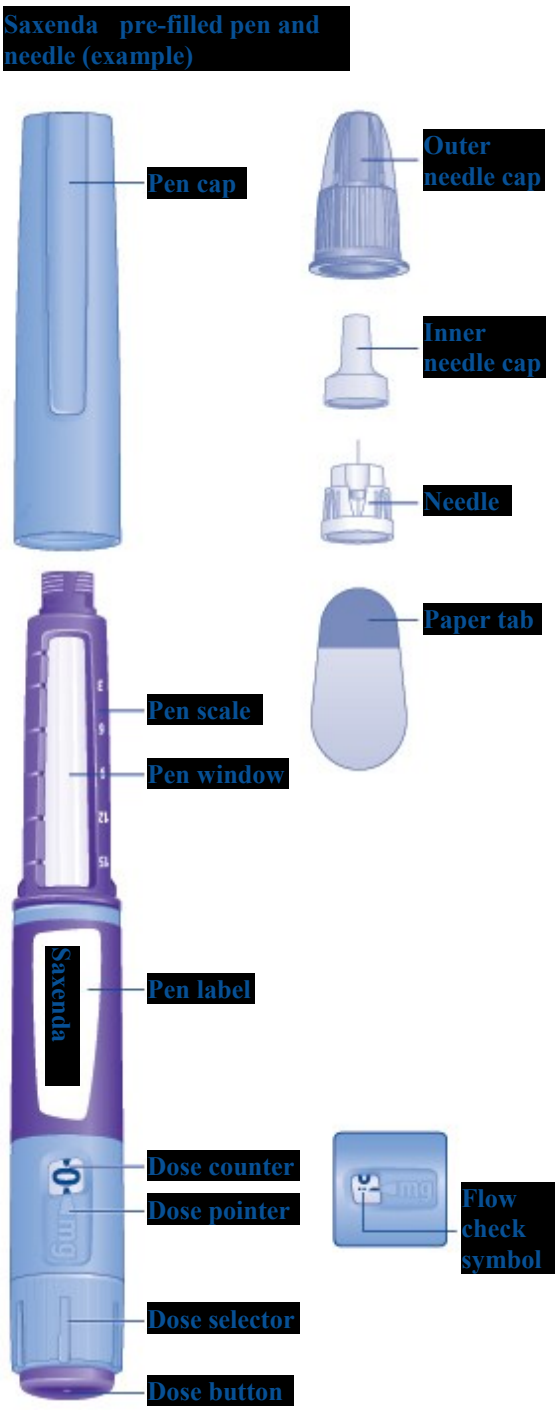
If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Saxenda® prefilled pen.

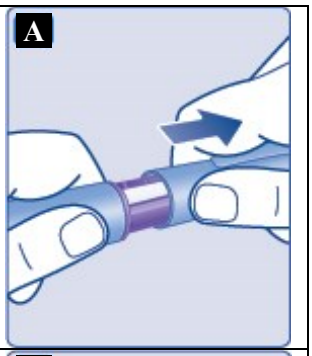
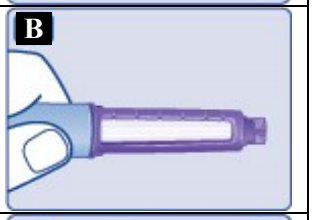
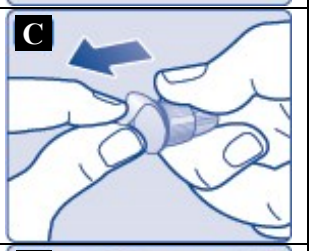
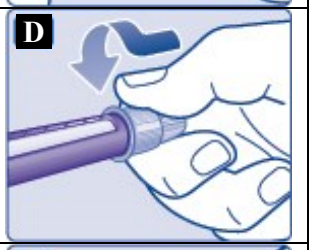
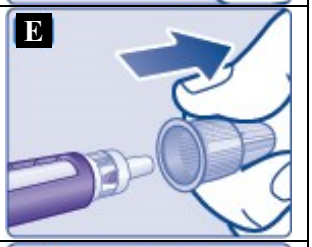
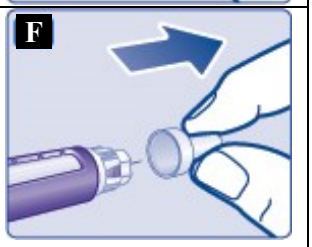
Your pen is a prefilled dial-a-dose pen. It contains 18 mg of liraglutide, and delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg. Your pen is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm.

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

Needles are not included in the pack.

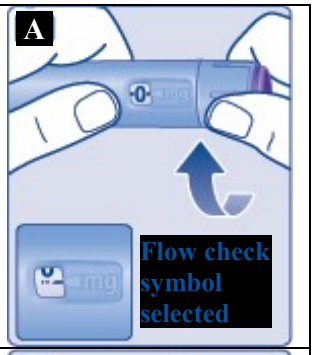
⚠ **Important information**
Pay special attention to these notes as they are important for safe use of the pen.


Saxenda pre-filled pen and needle (example)
Pen cap
Outer needle cap
Inner needle cap
Needle
Paper tab
Pen scale
Pen window
Saxenda
Pen label
Dose counter
Dose pointer
Flow check symbol
Dose selector
Dose button

1 Prepare your pen with a new needle • **Check the name and coloured label** of your pen, to make sure that it contains Saxenda®. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could be harmful to your health. • **Pull off the pen cap.**	
• **Check that Saxenda® in your pen is clear** and colourless. Look through the pen window. If Saxenda® looks cloudy, do not use the pen.	
• **Take a new needle,** and tear off the paper tab.	
• **Push the needle straight onto the pen. Turn until it is on tight.**	
• **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.	
• **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally stick yourself with the needle. A drop of Saxenda® may appear at the needle tip. This is normal, but you must still check the flow, if you use a new pen for the first time. **Do not attach a new needle** to your pen until you are ready to take your injection. ⚠ **Always use a new needle for each injection.** This may prevent blocked needles, contamination, infection and inaccurate dosing. Do not reuse or share needles with another person. ⚠ **Never use a bent or damaged needle.**	

2 Check the flow

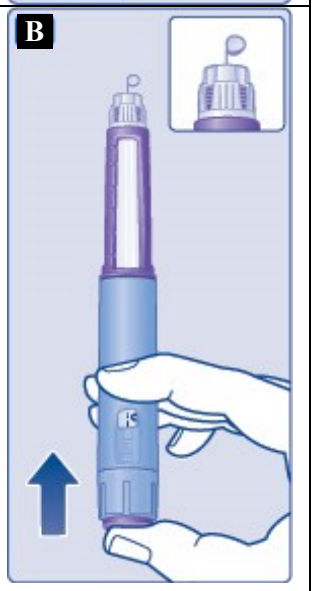
- **Before your first injection with each new pen, check the flow.** If your Saxenda® pen is already in use, go to 3 '*Select your dose'*.
- Turn the dose selector **until the dose counter shows the flow check symbol** (▪▪—).



- Hold the pen with the needle pointing up.
  Press and hold in the dose button until the dose counter returns to 0.
  The 0 must line up with the dose pointer.
  A drop of Saxenda® should appear at the needle tip.

  A small drop may remain at the needle tip, but it will not be injected.
  If no drop appears, repeat steps 2 '*Check the flow'* up to 6 times. If there is still no drop, change the needle and repeat steps 2'*Check the flow*' once more.
  If a drop of Saxenda® still does not appear, dispose of the pen and use a new one.
  Only check the Saxenda® flow, before your first injection with each new pen.

⚠ **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 indicate a blocked or damaged needle.**
If you do not check the flow before your first injection with each new pen, you may not get the prescribed dose and the intended effect of Saxenda®.

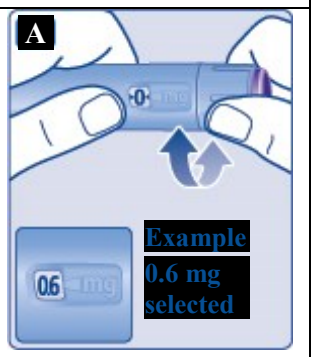


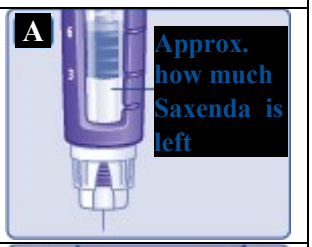
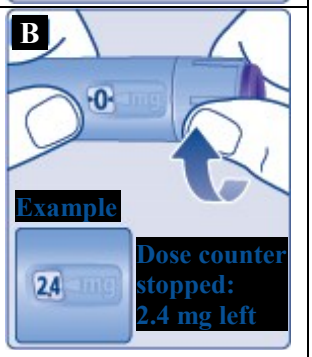
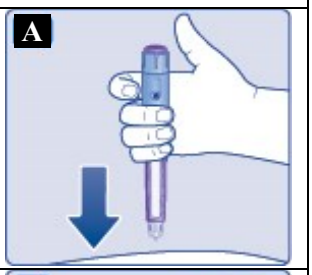
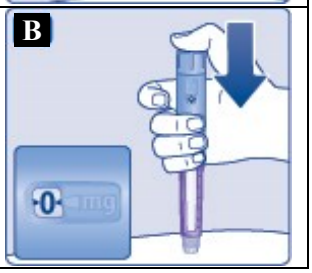
3 Select your dose

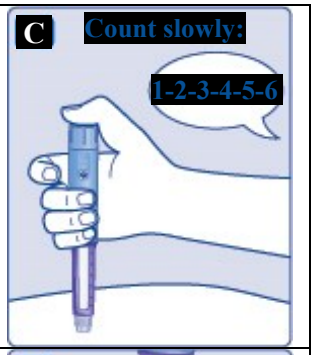
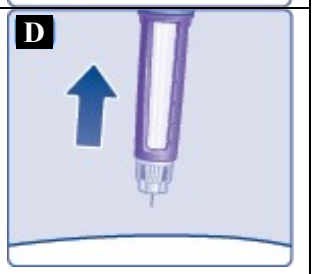
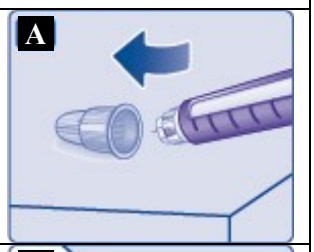
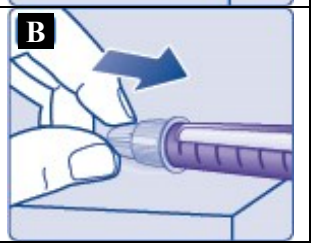
- **Turn the dose selector until the dose counter shows your dose (0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg).**
  If you select the wrong dose, you can turn the dose selector forward or backwards to the correct dose.
  The pen can dial up to a maximum of 3.0 mg.

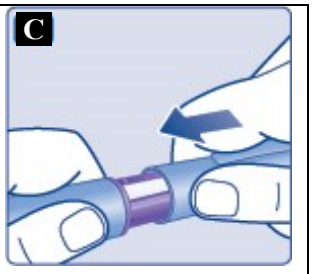
  The dose selector changes the dose. Only the dose counter and dose pointer will show how many mg you select per dose.
  You can select up to 3.0 mg per dose. When your pen contains less than 3.0 mg the dose counter stops before 3.0 is shown.
  The dose selector clicks differently when turned forward, backwards or past the number of mg left. Do not count the pen clicks.

⚠ **Always use the dose counter and the dose pointer to see how many mg you have selected before injecting Saxenda®.**
Do not count the pen clicks.



Do not use the pen scale. It only shows approximately how much Saxenda® is left in your pen. **Only doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg can be selected with the dose selector.** The selected dose must line up precisely with the dose pointer to ensure that you get a correct dose.	
How much Saxenda® is left? • The **pen scale** shows you **approximately** how much Saxenda® is left in your pen.	
• **To see precisely how much Saxenda® is left,** use the dose counter: Turn the dose selector until the **dose counter stops.** If it shows 3.0, **at least 3.0 mg** are left in your pen. If the **dose counter stops before 3.0 mg,** there is not enough Saxenda® left for a full dose of 3.0 mg. **If you need more Saxenda® than what is left in your pen** Only if trained or advised by your doctor or Diabetes Nurse Educator, you may split your dose between your current pen and a new pen. Use a calculator to plan the doses as instructed by your doctor or Diabetes Nurse Educator. ⚠ **Be very careful to calculate correctly.** If you are not sure how to split your dose using two pens, then select and inject the dose you need with a new pen.	
4 Inject your dose • **Insert the needle into your skin** as your doctor or Diabetes Nurse Educator has shown you. • **Make sure you can see the dose counter.** Do not cover it with your fingers. This could interrupt the injection.	
• **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 so, the full dose will not be delivered.	
• **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area. You may see a drop of Saxenda® at the needle tip after injecting. This is normal and does not affect your dose. ⚠ **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. • In this case - 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 section 5 '*After your injection'*, and repeat all steps starting with section 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 interrupt the injection.	
5 After your injection • **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.	
• Once the needle is covered, **carefully push the outer needle cap completely on.** • **Unscrew the needle** and dispose of it carefully.	

• **Put the pen cap on** your pen after each use to protect Saxenda® from light. **Always dispose of the needle after each injection** to ensure convenient injections and prevent blocked needles. If the needle is blocked, you will **not** inject any Saxenda®. When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities. ⚠ **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 after each injection.** This may prevent blocked needles, contamination, infection, leakage of Saxenda® and inaccurate dosing.	
⚠ **Further important information** • Always keep your pen and needles **out of sight and reach of others,** especially children. • **Never share** your pen or your needles with other people. • Caregivers must **be very careful when handling used needles** - to prevent needle injury and cross-infection.	
Caring for your pen • **Do not leave the pen in a car** or other place where it can get too hot or too cold. • **Do not inject Saxenda® which has been frozen.** If you do that, you may not get the intended effect of Saxenda®. • **Do not expose your pen to dust, dirt or liquid.** • **Do not wash, soak or lubricate your pen.** If necessary, clean it with a mild detergent on a moistened cloth. • **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 refill your pen.** Once empty, it must be disposed of. • **Do not try to repair your pen** or pull it apart.	