Saxenda®
liraglutide injection 3 mg

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

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

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

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

——— RECENT MAJOR CHANGES ———

Indications and Usage, Limitations of Use (1) 12/2020
Dosage and Administration (2.1, 2.2, 2.3) 12/2020
Warnings and Precautions (5.2, 5.4, 5.5, 5.8) 12/2020

——— INDICATIONS AND USAGE ———

SAXENDA® is a glucagon like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:

Adult patients with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia) (1).

Pediatric patients aged 12 years and older with:

- body weight above 60 kg and
- an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cut-offs (1).

Limitations of Use:

- SAXENDA® contains liraglutide and should not be coadministered with other liraglutide-containing products or with any other GLP-1 receptor agonist(1).
- The safety and effectiveness of SAXENDA® in pediatric patients with type 2 diabetes have not been established (1).
- The safety and efficacy of SAXENDA® in combination with other products intended for weight loss have not been established (1).

——— DOSAGE AND ADMINISTRATION ———

- Inject SAXENDA® subcutaneously in the abdomen, thigh, or upper arm once daily at any time of day, without regard to the timing of meals (2.2).
- The recommended dose of SAXENDA® is 3 mg daily (2.3).
- Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached (2.3).
- If pediatric patients do not tolerate an increased dose during dose escalation, the dose may also be lowered to the previous level. Dose escalation for pediatric patients may take up to 8 weeks (2.3).
- Pediatric patients who do not tolerate 3 mg daily may have their dose reduced to 2.4 mg daily (2.3).
- Adult patients with type 2 diabetes should monitor blood glucose prior to starting SAXENDA® and during SAXENDA® treatment (2.3).

——— DOSAGE FORMS AND STRENGTHS ———

- Injection: 6 mg/mL solution in a 3 mL pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg (3).

——— CONTRAINDICATIONS ———

- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1).
- Hypersensitivity to liraglutide or any excipients in SAXENDA® (4, 5.7).
- Pregnancy (4, 8.1).

——— WARNINGS AND PRECAUTIONS ———

- Thyroid C-cell Tumors: See Boxed Warning (5.1).
- Acute Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.3).
- Hypoglycemia: Can occur in adults when SAXENDA® is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin. The risk may be lowered by a reduction in the dose of concomitantly administered insulin secretagogues or insulin. In the pediatric clinical trial, patients did not have type 2 diabetes. Hypoglycemia occurred in SAXENDA®-treated pediatric patients. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia (2, 5.4).
- Heart Rate Increase: Monitor heart rate at regular intervals (5.5).
- Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of SAXENDA® in patients with renal impairment (5.6).
- Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue SAXENDA® and other suspect medications and promptly seek medical advice (5.7).
- Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue SAXENDA® if symptoms develop (5.8).

——— ADVERSE REACTIONS ———

- Most common adverse reactions, reported in greater than or equal to 5% are: nausea, diarrhea, constipation, vomiting, injection site reactions, headache, hypoglycemia, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase, upper abdominal pain, pyrexia, and gastroenteritis (6.1).

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

——— DRUG INTERACTIONS ———

- SAXENDA® delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2021

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

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

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

1 INDICATIONS AND USAGE

SAXENDA® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:

- Adult patients with an initial body mass index (BMI) of *[see Dosage and Administration (2.1)]*:
  - 30 kg/m^2 or greater (obese), or
  - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)
- Pediatric patients aged 12 years and older with:
  - body weight above 60 kg and
  - an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs (Cole Criteria, Table 2) *[see Dosage and Administration (2.1)]*

Limitations of Use

- SAXENDA® contains liraglutide and should not be coadministered with other liraglutide-containing products or with any other GLP-1 receptor agonist.
- The safety and effectiveness of SAXENDA® in pediatric patients with type 2 diabetes have not been established.
- 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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for SAXENDA® treatment as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management based on the BMI values provided in Tables 1 and 2.

Adult and Pediatric Patients

BMI is calculated by dividing weight in (kilograms) by height (in meters) squared. A chart for determining BMI based on height and weight is provided in Table 1.

Table 1. BMI Conversion Chart

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7	100.0	102.3
Height																						
(in)	(cm)																					
58	147.3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149.9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152.4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154.9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157.5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160.0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162.6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165.1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167.6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170.2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172.7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175.3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177.8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180.3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182.9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185.4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188.0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190.5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193.0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

Pediatric Patients Aged 12 Years and Older

BMI cut-offs for obesity in pediatric patients aged 12 years and older are presented in Table 2.

Table 2: International Obesity Task Force BMI Cut-offs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older (Cole Criteria)

	Body mass index 30 kg/m^2	
Age (years)	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84

2.2 Important Administration Instructions

- Prior to initiation of SAXENDA®, train patients on proper injection technique. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Inspect SAXENDA® visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Inject SAXENDA® subcutaneously once daily at any time of day, without regard to the timing of meals.
- Inject SAXENDA® subcutaneously in the abdomen, thigh, or upper arm. No dose adjustment is needed if changing the injection site and/or timing.
- If a dose is missed, resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose.
- If more than 3 days have elapsed since the last SAXENDA® dose, reinitiate SAXENDA® at 0.6 mg daily and follow the dose escalation schedule in Table 3, to reduce the occurrence of gastrointestinal adverse reactions associated with reinitiation of treatment.

2.3 Dosage in Adults and Pediatric Patients Aged 12 Years and Older

- Initiate SAXENDA® with a dose of 0.6 mg daily for one week. Then follow the dose escalation schedule in Table 3 to minimize gastrointestinal adverse reactions *[see Adverse Reactions (6.1)]*.

Table 3. Dose Escalation Schedule

Week	Daily Dose
1	0.6 mg
2	1.2 mg
3	1.8 mg
4	2.4 mg
5 and onward	3 mg

Adult Patients

- For adults, the recommended dosage of SAXENDA® is 3 mg daily, lower doses are for titration only.
- Discontinue SAXENDA® if the patient cannot tolerate the 3 mg dose.
- If patients do not tolerate an increased dose during dose escalation, consider delaying dose escalation for approximately one additional week.
- Evaluate the change in body weight 16 weeks after initiating SAXENDA® and discontinue SAXENDA® if the patient has not lost at least 4% of baseline body weight, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
- In adult patients with type 2 diabetes, monitor blood glucose prior to starting SAXENDA® and during SAXENDA® treatment.

Pediatric Patients

- For pediatric patients, the recommended maintenance dosage of SAXENDA® is 3 mg daily. Pediatric patients who do not tolerate 3 mg daily may have their maintenance dose reduced to 2.4 mg daily. Discontinue SAXENDA® if the patient cannot tolerate the 2.4 mg dose.
- If pediatric patients do not tolerate an increased dose during dose escalation, the dose may also be lowered to the previous level. Dose escalation for pediatric patients may take up to 8 weeks.
- Evaluate the change in BMI after 12 weeks on the maintenance dose and discontinue SAXENDA® if the patient has not had a reduction in BMI of at least 1% from baseline, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

3 DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/mL clear, colorless solution in a 3 mL pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg.

4 CONTRAINDICATIONS

SAXENDA® is contraindicated in:

- Patients with a personal or family history of medullary thyroid carcinoma (MTC) or patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions (5.1)]*.
- Patients with a prior serious hypersensitivity reaction to liraglutide or to any of the excipients in SAXENDA® *[see Warnings and Precautions (5.7)]*.
- Pregnancy *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

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

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

SAXENDA® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of SAXENDA® and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with SAXENDA®. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC, and patients with MTC usually have calcitonin values greater than 50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Acute Pancreatitis

Based on spontaneous postmarketing 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 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 and appropriate management should be initiated. If pancreatitis is confirmed, SAXENDA® should not be restarted.

In SAXENDA® clinical trials in adults, 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 2 additional cases in SAXENDA®-treated patients, 1 during an off-treatment follow-up period within 2 weeks of discontinuing SAXENDA®, and 1 that occurred in a patient who completed treatment and was off-treatment for 106 days.

In a SAXENDA® pediatric clinical trial, pancreatitis was not independently adjudicated. Pancreatitis was reported in 1 (0.8%) SAXENDA®-treated patient and resulted in treatment discontinuation.

Liraglutide has been studied in a limited number of adult patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on SAXENDA®.

5.3 Acute Gallbladder Disease

In SAXENDA® clinical trials in adults, 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.

5.4 Hypoglycemia

Adult patients with type 2 diabetes mellitus on an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia with use of SAXENDA®, including severe hypoglycemia. In patients with type 2 diabetes, monitor blood glucose prior to starting SAXENDA® and during SAXENDA® treatment *[see Dosage and Administration (2) and Adverse Reactions (6.1)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

In the pediatric clinical trial, patients did not have type 2 diabetes but were provided with blood glucose meters. Clinically significant hypoglycemia, defined as blood glucose <54 mg/dL, occurred in 1.6% of the SAXENDA®- treated patients compared to 0.8% of placebo-treated patients *[see Adverse Reactions (6.1)]*. Inform all pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.5 Heart Rate Increase

Mean increases in resting heart rate of 2 to 3 beats per minute (bpm) were observed with routine clinical monitoring in SAXENDA®-treated adult patients compared to placebo in clinical trials. More patients treated with SAXENDA®, compared with placebo, had 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.

In a pediatric clinical trial, mean increases from baseline in resting heart rate of 3 to 7 bpm were observed with SAXENDA® treatment.

Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should inform health care providers 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.

5.6 Renal Impairment

In patients treated with GLP-1 receptor agonists, including SAXENDA®, there have been reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis *[see Adverse Reactions (6.2)]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Use caution when initiating or escalating doses of SAXENDA® in patients with renal impairment *[see Use in Specific Populations (8.6)]*.

5.7 Hypersensitivity Reactions

There have been reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide *[see Contraindications (4) and Adverse Reactions (6.1, 6.2)]*. If a hypersensitivity reaction occurs, the patient should discontinue SAXENDA® and other suspect medications and promptly seek medical advice.

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

5.8 Suicidal Behavior and Ideation

In SAXENDA® adult 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.

In a SAXENDA® pediatric clinical trial, 1 (0.8%) of the 125 SAXENDA®-treated patients died by suicide. There was insufficient information to establish a causal relationship to SAXENDA®.

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.

6 ADVERSE REACTIONS

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

- Risk of Thyroid C-Cell Tumors *[see Warnings and Precautions (5.1)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.3)]*
- Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy *[see Warnings and Precautions (5.4)]*
- Heart Rate Increase *[see Warnings and Precautions (5.5)]*
- Renal Impairment *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

SAXENDA® was evaluated for safety in 5 double-blind, placebo controlled trials that included 3384 overweight or obese adult patients treated with SAXENDA® for a treatment period up to 56 weeks (3 trials), 52 weeks (1 trial), and 32 weeks (1 trial) and one trial of 56 weeks in 125 pediatric patients with obesity aged 12 years and older *[see Clinical Studies (14.1, 14.2)]*. All patients received study drug in addition to a reduced-calorie diet and increased physical activity counseling. In the adult trials, patients received SAXENDA® for a mean treatment duration of 46 weeks (median, 56 weeks). Baseline characteristics included a mean age of 47 years, 71% women, 85% white, 39% with hypertension, 15% with type 2 diabetes, 34% with dyslipidemia, 29% with a BMI greater than 40 kg/m^2, and 9% with cardiovascular disease. In one of the 56-week trials, a subset of patients (with abnormal glucose measurements at randomization) *[see Clinical Studies (14.1)]* were enrolled for a placebo-controlled 160-week period instead, followed by a 12-week off-treatment follow-up. For those participating in this 160-week period, patients received SAXENDA® for a mean treatment duration of 110 weeks (median, 159 weeks). For all trials, dosing was initiated and increased weekly to reach the 3 mg dose.

In adult clinical trials, 9.8% of patients treated with SAXENDA® and 4.3% of patients treated with placebo prematurely discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for SAXENDA® and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%).

Adverse reactions reported in greater than or equal to 2% of SAXENDA®-treated adult patients and more frequently than in placebo-treated patients are shown in Table 4. Adverse reactions reported in greater than or equal to 3% of SAXENDA®-treated pediatric patients and more frequently than in placebo-treated patients are shown in Table 5.

Table 4. Adverse Reactions Occurring in ≥2% of SAXENDA®-treated Adult Patients and More Frequently than Placebo

	Placebo N = 1941 %	SAXENDA® N = 3384 %
Nausea	13.8	39.3
Diarrhea	9.9	20.9
Constipation	8.5	19.4
Vomiting	3.9	15.7
Injection Site Reaction[1]	10.5	13.9
Headache	12.6	13.6
Hypoglycemia in T2DM[2]	6.6	12.6
Dyspepsia	2.7	9.6
Fatigue	4.6	7.5
Dizziness	5.0	6.9
Abdominal Pain	3.1	5.4
Increased Lipase	2.2	5.3
Upper Abdominal Pain	2.7	5.1
Gastroenteritis	3.2	4.7
Gastroesophageal Reflux Disease	1.7	4.7
Abdominal Distension	3.0	4.5
Eructation	0.2	4.5
Urinary Tract Infection	3.1	4.3
Flatulence	2.5	4.0
Viral Gastroenteritis	1.6	2.8
Insomnia	1.7	2.4
Dry Mouth	1.0	2.3
Asthenia	0.8	2.1
Anxiety	1.6	2.0

[1] The most common reactions, each reported by 1% to 2.5% of SAXENDA®-treated patients and more commonly than by placebo-treated patients, included erythema, pruritus, and rash at the injection site.

[2] Defined as blood glucose <54 mg/dL with or without symptoms of hypoglycemia in patients with type 2 diabetes not on concomitant insulin (Study 2, SAXENDA® N=423, Placebo N=212). See text below for further information regarding hypoglycemia in patients with and without type 2 diabetes. T2DM = type 2 diabetes mellitus

Table 5. Adverse Reactions Occurring in ≥3% of SAXENDA®-treated Pediatric Patients and More Frequently than Placebo in a 56 Week Clinical Trial

	Placebo N = 126 %	SAXENDA® N = 125 %
Nausea	14.3	42.4
Vomiting	4.0	34.4
Diarrhea	14.3	22.4
Hypoglycemia[1]	4.0	15.2
Gastroenteritis	4.8	12.8
Dizziness	3.2	10.4
Pyrexia	7.1	8.0
Abdominal discomfort	0.8	4.8
Constipation	2.4	4.8
Dyslipidemia	3.2	4.8
Fatigue	3.2	4.8
Cough	3.2	4.0
Depression	2.4	4.0
Dyspepsia	2.4	4.0
Pain in extremity	2.4	4.0
Injection site pain	3.2	3.2
Flatulence	0	3.2
Increased Blood Creatine Kinase	2.4	3.2
Increased Lipase	0.8	3.2
Rash	0	3.2

[1] Defined as blood glucose <70 mg/dL with symptoms of hypoglycemia. Pediatric patients did not have type 2 diabetes mellitus. See text below for more detailed hypoglycemia information.

Hypoglycemia

Adult Patients with Type 2 Diabetes

In a clinical trial in adult patients with type 2 diabetes mellitus and overweight (excess weight) or obesity, severe hypoglycemia (defined as requiring the assistance of another person) occurred in 3 (0.7%) of 422 SAXENDA®-treated patients (all taking a sulfonylurea) and in none of the 212 placebo-treated patients. In this trial, among patients taking a sulfonylurea, hypoglycemia defined as a plasma glucose less than 54 mg/dL with or without symptoms occurred in 31 (28.2%) of 110 SAXENDA®-treated patients and 7 (12.7%) of 55 placebo-treated patients. The doses of sulfonylureas were reduced by 50% at the beginning of the trial per protocol. Among patients not taking a sulfonylurea, blood glucose less than 54 mg/dL with or without symptoms occurred in 22 (7.1%) of 312 SAXENDA®-treated patients and 7 (4.5%) of 157 placebo-treated patients.

In a SAXENDA® clinical trial in adult patients with overweight (excess weight) or obesity with type 2 diabetes mellitus treated with basal insulin and SAXENDA® in combination with a reduced-calorie diet and increased physical activity and up to 2 oral anti-diabetes medications, severe hypoglycemia was reported by 3 (1.5%) of 195 SAXENDA®-treated patients and 2 (1.0%) of 197 placebo-treated patients. No meaningful difference in hypoglycemia, defined as blood glucose less than 54 mg/dL with or without symptoms, was reported between groups.

Adult Patients without Type 2 Diabetes

In SAXENDA® clinical trials in adult patients without type 2 diabetes mellitus, there was no systematic capturing or reporting of hypoglycemia; patients were not provided with blood glucose meters or hypoglycemia diaries. Spontaneously reported symptomatic episodes of unconfirmed hypoglycemia were reported by 46 (1.6%) of 2962 SAXENDA®-treated patients and 19 (1.1%) of 1729 placebo-treated patients. Fasting plasma glucose values obtained at routine clinic visits less than 54 mg/dL, irrespective of hypoglycemic symptoms, occurred in 2 (0.1%) SAXENDA®-treated patients and 1 (0.1%) placebo-treated patients.

Pediatric Patients without Type 2 Diabetes

In a 56-week placebo-controlled clinical trial of pediatric patients without type 2 diabetes mellitus in which blood glucose meters were provided, 19 (15.2%) of SAXENDA®-treated patients had hypoglycemia with a blood glucose less than 70 mg/dL with symptoms as compared to 5 (4.0%) of placebo-treated patients. Four (4) events of hypoglycemia defined as a plasma glucose less than 54 mg/dL occurred in 2 (1.6%) of 125 SAXENDA®-treated patients and 1 event occurred in 1 (0.8%) of 126 placebo-treated patients. No severe hypoglycemic episodes, defined as requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, occurred in the SAXENDA® treatment group.

Gastrointestinal Adverse Reactions

In the adult clinical trials, approximately 68% of SAXENDA®-treated patients and 39% of placebo-treated patients reported gastrointestinal disorders; the most frequently reported was nausea (39% and 14% of patients treated with SAXENDA® and placebo, respectively). The percentage of patients 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 (6.2% with SAXENDA® versus 0.8% with placebo discontinued treatment as a result of gastrointestinal adverse reactions). There have been reports of gastrointestinal adverse reactions, such as nausea, vomiting, and diarrhea, associated with volume depletion and renal impairment.

In a pediatric clinical trial, 8.0% of patients treated with SAXENDA® versus no patients who received placebo discontinued treatment as a result of gastrointestinal adverse reactions. Most adverse reactions leading to discontinuation were due to vomiting and nausea (4.8% and 3.2% of SAXENDA®-treated patients, respectively).

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 were often co-reported with gastrointestinal events such as nausea, vomiting, and diarrhea.

Immunogenicity

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.

Patients treated with SAXENDA® may develop anti-liraglutide antibodies. Anti-liraglutide antibodies were detected in 42 (2.8%) of 1505 SAXENDA®-treated adult 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.

In a pediatric clinical trial, anti-liraglutide antibodies were detected in 14 (12%) of 117 SAXENDA®-treated patients with a post-baseline assessment; 5 (4.3%) had persistent antibodies as defined by more than 2 antibody visits at least 16 weeks apart. Two patients (1.7%) remained positive throughout the follow-up period; 1 (0.9%) had antibodies cross reactive to native GLP-1. No patients had neutralizing antibodies.

Allergic Reactions

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

Breast Cancer

In SAXENDA® clinical trials in adults, 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.

Papillary Thyroid Cancer

In SAXENDA® clinical trials in adults, 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.

Colorectal Neoplasms

In SAXENDA® clinical trials in adults, 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 neoplasms were reported in 5 SAXENDA®-treated patients (0.2%, mostly adenocarcinomas) and 1 in a placebo-treated patient (0.1%, neuroendocrine tumor of the rectum).

Cardiac Conduction Disorders

In SAXENDA® clinical trials in adults, 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.

Hypotension

Adverse reactions related to hypotension (hypotension, orthostatic hypotension, circulatory collapse, and decreased blood pressure) were reported more frequently with SAXENDA® (1.1%) compared with placebo (0.5%) in SAXENDA® clinical trials in adults. Systolic blood pressure decreases to less than 80 mmHg were observed in 4 (0.1%) SAXENDA®-treated patients compared with no placebo-treated patients. One of the SAXENDA®-treated patients had hypotension associated with gastrointestinal adverse reactions and renal failure *[see Warnings and Precautions (5.6)]*.

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 (5.1)]*. 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 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.

Serum Lipase and Amylase

Serum lipase and amylase were routinely measured in the SAXENDA® clinical trials. Among SAXENDA®-treated patients, 2.1% had a lipase value at anytime during treatment of greater than or equal to 3 times the upper limit of normal compared with 1.0% of placebo-treated patients. 0.1% of SAXENDA®-treated patients had an amylase value at anytime in the trial of greater than or equal to 3 times the upper limit of normal versus 0.1% of placebo-treated patients. The clinical significance of elevations in lipase or amylase with SAXENDA® is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions (5.2)]*.

6.2 Post-Marketing Experience

The following adverse reactions have been reported during post-approval use of liraglutide, the active ingredient of SAXENDA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neoplasms

Medullary thyroid carcinoma

Gastrointestinal Disorders

Acute pancreatitis, hemorrhagic and necrotizing pancreatitis, sometimes resulting in death

Metabolism and Nutrition Disorders

Dehydration resulting from nausea, vomiting and diarrhea

Renal and Urinary Disorders

Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis

General Disorders and Administration Site Conditions

Allergic reactions: rash and pruritus

Immune System Disorders
Angioedema and anaphylactic reactions

Hepatobiliary Disorders
Hyperbilirubinemia, elevations of liver enzymes, cholestasis and hepatitis

7 DRUG INTERACTIONS

7.1 Oral Medications

SAXENDA® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with SAXENDA®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SAXENDA® is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm *[see Clinical Considerations].* There are no available data with liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage. SAXENDA® should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with SAXENDA® should be discontinued.

Animal reproduction studies identified increased adverse embryo-fetal developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 3 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Animal Data].*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

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.

Animal Data

Liraglutide has been shown to be teratogenic in rats at or above 0.8-times systemic exposures in obese humans resulting from the maximum recommended human dose (MRHD) of 3 mg/day based on plasma area under the time-concentration curve (AUC) comparison. Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below exposure in obese humans at the MRHD based on plasma AUC comparison.

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

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the exposure in obese humans at the MRHD of 3 mg/day at all doses, based on plasma AUC comparison. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), greater than or equal to 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), greater than or equal to 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1 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 exposure in obese humans at the MRHD of 3 mg/day, based on plasma AUC comparison. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F_2 generation rats descended from liraglutide-treated rats compared to F_2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

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

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

Data

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

8.4 Pediatric Use

The safety and effectiveness of SAXENDA® as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management have been established in pediatric patients aged 12 years and older with body weight above 60 kg and an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs (see Table 2). Use of SAXENDA® for this indication is supported by a 56-week double-blind, placebo-controlled clinical trial in 251 pediatric patients aged 12 to 17 years, a pharmacokinetic study in pediatric patients, and studies in adults with obesity *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1,14.2)]*.

In the pediatric clinical trial, there was one death due to suicide in a SAXENDA®-treated patient *[see Warnings and Precautions (5.8)];* one SAXENDA®-treated patient had an event of pancreatitis *[see Warnings and Precautions (5.2)];* more episodes of hypoglycemia confirmed by self blood glucose monitoring occurred in SAXENDA®-treated patients compared to placebo *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)];* and mean increases in resting heart rate of 3 to 7 bpm from baseline were observed with SAXENDA®-treated patients *[see Warnings and Precautions (5.5)].*

The safety and effectiveness of SAXENDA® have not been established in patients less than 12 years of age.

8.5 Geriatric Use

In the SAXENDA® clinical trials, 232 (6.9%) of the SAXENDA®-treated patients were 65 years of age and over, and 17 (0.5%) of the SAXENDA®-treated patients were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

There is limited experience with SAXENDA® in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure with liraglutide, which may sometimes require hemodialysis *[see Warnings and Precautions (5.6) and Adverse Reactions (6.2)].* SAXENDA® should be used with caution in this patient population *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate, or severe hepatic impairment. Therefore, SAXENDA® should be used with caution in this patient population *[see Clinical Pharmacology (12.3)]*.

8.8 Gastroparesis

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

10 OVERDOSAGE

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

11 DESCRIPTION

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

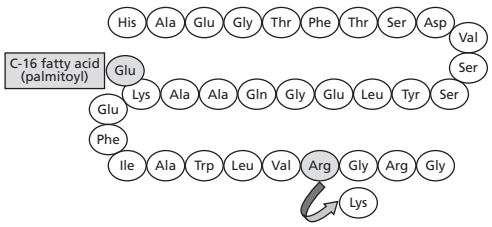

Figure 1. Structural Formula of liraglutide

SAXENDA® injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of SAXENDA® solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. SAXENDA® has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of SAXENDA® equivalent to 18 mg liraglutide (free-base, anhydrous).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). Like endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase activation through the stimulatory G-protein, Gs. Endogenous GLP-1 has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once-daily administration, is a result of self-association that delays absorption, plasma protein binding, and stability against metabolic degradation by DPP-4 and NEP.

GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. In animal studies, peripheral administration of liraglutide resulted in the presence of liraglutide in specific brain regions regulating appetite, including the hypothalamus. Although liraglutide activated neurons in brain regions known to regulate appetite, specific brain regions mediating the effects of liraglutide on appetite were not identified in rats.

12.2 Pharmacodynamics

Liraglutide lowers body weight through decreased calorie intake. Liraglutide does not increase 24-hour energy expenditure.

As with other GLP-1 receptor agonists, liraglutide stimulates insulin secretion and reduces glucagon secretion in a glucose-dependent manner. These effects can lead to a reduction of blood glucose.

Cardiac Electrophysiology (QTc) in healthy volunteers

The effect of liraglutide on cardiac repolarization was tested in a QTc study. Liraglutide at steady-state concentrations after daily doses up to 1.8 mg did not produce QTc prolongation. The maximum liraglutide plasma concentration (C_{max}) in overweight and obese subjects treated with liraglutide 3 mg is similar to the C_{max} observed in the liraglutide QTc study in healthy volunteers.

12.3 Pharmacokinetics

Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 11 hours post dosing. The average liraglutide steady state concentration (AUCτ/24) reached approximately 116 ng/mL in obese (BMI 30-40 kg/m^2) subjects following administration of SAXENDA®. Liraglutide exposure increased proportionally in the dose range of 0.6 mg to 3 mg. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration. Liraglutide exposures were considered similar among three subcutaneous injection sites (upper arm, abdomen, and thigh). Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

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

Metabolism - During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major

component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination - Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration.

Specific Populations

Elderly - Age had no effect on the pharmacokinetics of liraglutide based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of data from overweight and obese patients 18 to 82 years of age *[see Use in Specific Populations (8.5)]*.

Gender - Based on the results of population pharmacokinetic analyses, females have 24% lower weight adjusted clearance of SAXENDA® compared to males.

Race and Ethnicity - Race and ethnicity had no effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analyses that included overweight and obese patients of Caucasian, Black, Asian and Hispanic/Non-Hispanic groups.

Body Weight - Body weight significantly affects the pharmacokinetics of liraglutide based on results of population pharmacokinetic analyses conducted in patients with body weight range of 60-234 kg. The exposure of liraglutide decreases as baseline body weight increases.

Pediatric - A population pharmacokinetic analysis was conducted for SAXENDA® using data from 134 pediatric patients (12 to 17 years of age) with obesity. The liraglutide exposure in the pediatric patients was similar to that in adults with obesity *[see Use in Specific Populations (8.4)]*.

Renal Impairment - The single-dose pharmacokinetics of liraglutide were evaluated in patients with varying degrees of renal impairment. Patients with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance less than 30 mL/min) renal impairment and patients with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment - The single-dose pharmacokinetics of liraglutide were evaluated in patients with varying degrees of hepatic impairment. Patients with mild (Child Pugh score 5-6) to severe (Child Pugh score greater than 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro assessment of drug–drug interactions

Liraglutide has 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 was equivalent between liraglutide 1.8 mg and 3 mg (acetaminophen $AUC_{0\text{-}300min}$). 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 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 $AUC_{0\text{-}\infty}$ 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.

Insulin Detemir

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1, and 3 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 43-times the exposure in obese humans, respectively, at the maximum recommended human dose (MRHD) of 3 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1 and the 3 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 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 exposure in obese humans, 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 liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the RE arranged during Transfection (RET) proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1 mg/kg/day, a high dose yielding an estimated systemic exposure 11-times the exposure in obese humans at the MRHD, based on plasma AUC comparison. In female rats, an increase in early embryonic deaths occurred at 1 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1 mg/kg/day dose.

14 CLINICAL STUDIES

14.1 Weight Management Trials in Adults with Overweight or Obesity

The safety and efficacy of SAXENDA® for chronic weight management in conjunction with reduced caloric intake and increased physical activity were studied in three 56-week, randomized, double-blind, placebo-controlled trials. In all studies, SAXENDA® was titrated to 3 mg daily during a 4-week period. All patients received instruction for a reduced-calorie diet (approximately 500 kcal/day deficit) and physical activity counseling (recommended increase in physical activity of minimum 150 mins/week) that began with the first dose of study medication or placebo and continued throughout the trial.

Study 1 enrolled 3731 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. Patients were randomized in a 2:1 ratio to either SAXENDA® or placebo. Patients were stratified based on the presence or absence of abnormal blood glucose measurements at randomization. All patients were treated for up to 56 weeks. Those patients with abnormal glucose measurements at randomization (2254 of the 3731 patients) were treated for a total of 160 weeks. At baseline, mean age was 45 years (range 18-78), 79% were women, 85% were Caucasian, 10% were African American, and 11% were Hispanic/Latino. Mean baseline body weight was 106.3 kg and mean BMI was 38.3 kg/m^2.

Study 2 was a 56-week trial that enrolled 635 patients with type 2 diabetes 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, or a glitazone as single agent or in any combination, or with a reduced-calorie diet and physical activity alone. Patients were randomized in a 2:1 ratio to receive either SAXENDA® or placebo. The mean age was 55 years (range 18-82), 50% were women, 83% were Caucasian, 12% were African American, and 10% were Hispanic/Latino. Mean baseline body weight was 105.9 kg and mean BMI was 37.1 kg/m^2.

Study 3 was a 56-week trial that enrolled 422 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 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 then randomized, with equal allocation, to receive either SAXENDA® or placebo for 56 weeks. The mean age was 46 years (range 18-73), 81% were women, 84% were Caucasian, 13% were African American, and 7% were Hispanic/Latino. Mean baseline body weight was 99.6 kg and mean BMI was 35.6 kg/m^2.

The proportions of patients who discontinued study drug in the 56-week trials were 27% for the SAXENDA®-treated group and 35% for the placebo-treated group, and in the 160-week trial the proportions of patients who discontinued were 47% and 55%, respectively. In the 56-week trials, approximately 10% of patients treated with SAXENDA® and 4% of patients treated with placebo discontinued treatment due to an adverse reaction *[see Adverse Reactions (6.1)]*. The majority of patients who discontinued SAXENDA® due to adverse reactions did so during the first few months of treatment. In the 160-week trial the proportions of patients who discontinued due to an adverse reaction was 13% and 6% for SAXENDA®- and placebo-treated patients, respectively.

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

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

Table 6 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.