SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Saxenda 6 mg/ml solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 6 mg of liraglutide*. One pre-filled pen contains 18 mg liraglutide in 3 ml.

*human glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless or almost colourless, isotonic solution; pH=8.15.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of

- ≥30 kg/m² (obeseity), or
- ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

Adolescents (≥12 years)

Saxenda can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:

- obesity (BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points)* and
- body weight above 60 kg.

Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*IOTF BMI cut-off points for obesity by sex between 12–18 years (see table 1):

Table 1 IOTF BMI cut-off points for obesity by sex between 12–18 years

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	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
18	30.00	30.00

4.2 Posology and method of administration

Posology

Adults

The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg with at least one week intervals to improve gastro-intestinal tolerability (see table 1). If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment. Daily doses higher than 3.0 mg are not recommended.

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**	

Adolescents (≥12 years)

For adolescents from the age of 12 to below 18 years old a similar dose escalation schedule as for adults should be applied (see table 2). The dose should be increased until 3.0 mg (maintenance dose) or maximum tolerated dose has been reached. Daily doses higher than 3.0 mg are not recommended.

Missed doses

If a dose is missed within 12 hours from when it is usually taken, the patient should take the dose as soon as possible. If there is less than 12 hours to the next dose, the patient should not take the missed dose and resume the once-daily regimen with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose.

Patients with type 2 diabetes mellitus

Saxenda should not be used in combination with another GLP-1 receptor agonist.

When initiating Saxenda, it should be considered to reduce the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of insulin or insulin-secretagogues (see section 4.4).

Special populations

Elderly (≥65 years old)
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited and use in these patients is not recommended (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance ≥30 ml/min). Saxenda is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Saxenda is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
No dose adjustment is required for adolescents from the age of 12 years and above.
The safety and efficacy of Saxenda in children below 12 years of age has not been established (see section 5.1).

Method of administration

Saxenda is for subcutaneous use only. It must not be administered intravenously or intramuscularly.

Saxenda is administered once daily at any time, independent of meals. It should be injected in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Saxenda is injected around the same time of the day, when the most convenient time of the day has been chosen.

For further instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to liraglutide or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients with heart failure

There is no clinical experience in patients with congestive heart failure New York Heart Association (NYHA) class IV, and liraglutide is therefore not recommended for use in these patients.

Special populations

The safety and efficacy of liraglutide for weight management have not been established in patients:

– aged 75 years or more,
– treated with other products for weight management,
– with obesity secondary to endocrinological or eating disorders or to treatment with medicinal products that may cause weight gain,
– with severe renal impairment,
– with severe hepatic impairment.

Use in these patients is not recommended (see section 4.2).
As liraglutide for weight management was not investigated in subjects with mild or moderate hepatic impairment, it should be used with caution in these patients (see sections 4.2 and 5.2).

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis. Use of liraglutide is not recommended in these patients since it is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted.

Cholelithiasis and cholecystitis

In clinical trials for weight management, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with liraglutide than in patients on placebo. The fact that substantial weight loss can increase the risk of cholelithiasis and thereby cholecystitis only partially explained the higher rate with liraglutide. Cholelithiasis and cholecystitis may lead to hospitalisation and cholecystectomy. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis.

Thyroid disease

In clinical trials in type 2 diabetes, thyroid adverse events, such as goitre, have been reported in particular in patients with pre-existing thyroid disease. Liraglutide should therefore be used with caution in patients with thyroid disease.

Heart rate

An increase in heart rate was observed with liraglutide in clinical trials (see section 5.1). Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should be informed of the symptoms of increased heart rate (palpitations or feelings of a racing heartbeat while at rest). For patients who experience a clinically relevant sustained increase in resting heart rate, treatment with liraglutide should be discontinued.

Dehydration

Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with GLP-1 receptor agonists. Patients treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Hypoglycaemia in patients with type 2 diabetes mellitus

Patients with type 2 diabetes mellitus receiving liraglutide in combination with insulin and/or sulfonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of insulin and/or sulfonylurea.

Paediatric population

Episodes of clinically significant hypoglycaemia have been reported in adolescents (≥12 years) treated with liraglutide. Patients should be informed about the characteristic symptoms of hypoglycaemia and the appropriate actions.

Hyperglycaemia in insulin treated patients with diabetes mellitus

In patients with diabetes mellitus Saxenda must not be used as a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Excipients

Saxenda contains less than 1 mmol sodium (23 mg) per dose, therefore the medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption and therefore no dose adjustment is required.

Interaction studies have been performed with 1.8 mg liraglutide. The effect on rate of gastric emptying was equivalent between liraglutide 1.8 mg and 3.0 mg, (paracetamol $AUC_{0\text{-}300\ min}$). Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Warfarin and other coumarin derivatives

No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or 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 International Normalised Ratio (INR) is recommended.

Paracetamol (Acetaminophen)

Liraglutide did not change the overall exposure of paracetamol following a single dose of 1,000 mg. Paracetamol C_{max} was decreased by 31% and median t_{max} was delayed up to 15 min. No dose adjustment for concomitant use of paracetamol is required.

Atorvastatin

Liraglutide did not change the overall exposure of atorvastatin following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin

Liraglutide did not change the overall exposure of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin C_{max} increased by 37% while median t_{max} did not change. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

Digoxin

A single dose administration of digoxin 1 mg with liraglutide resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median t_{max} was delayed from 1 h to 1.5 h. No dose adjustment of digoxin is required based on these results.

Lisinopril

A single dose administration of lisinopril 20 mg 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. No dose adjustment of lisinopril is required based on these results.

Oral contraceptives

Liraglutide lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product. t_{max} was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of liraglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Liraglutide should not be used during pregnancy. If a patient wishes to become pregnant or pregnancy occurs, treatment with liraglutide should be discontinued.

Breast-feeding

It is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk is low. Non-clinical studies have shown a treatment-related reduction of neonatal growth in suckling rat pups (see section 5.3). Because of lack of experience, Saxenda should not be used during breast-feeding.

Fertility

Apart from a slight decrease in the number of live implants, animal studies did not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Saxenda has no or negligible influence on the ability to drive and use machines. However, dizziness can be experienced mainly during the first 3 months of treatment with Saxenda. Driving or use of machines should be exercised with caution if dizziness occurs.

4.8 Undesirable effects

Summary of the safety profile:

Saxenda was evaluated for safety in 5 double-blind, placebo controlled trials that enrolled 5,813 adult patients with overweight or obesity with at least one weight-related comorbidity. Overall,

gastrointestinal reactions were the most frequently reported adverse reactions during treatment (67.9%) (see section 'Description of selected adverse reactions').

Tabulated list of adverse reactions

Table 3 lists adverse reactions reported in adults. Adverse reactions are listed by system organ class and frequency. Frequency categories are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions reported in adults

MedDRA system organ classes	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders		Hypoglycaemia*	Dehydration	
Psychiatric disorders		Insomnia**		
Nervous system disorders	Headache	Dizziness Dysgeusia		
Cardiac disorders			Tachycardia	
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Constipation	Dry mouth Dyspepsia Gastritis Gastro-oesophageal reflux disease Abdominal pain upper Flatulence Eructation Abdominal distension	Pancreatitis*** Delayed gastric emptying****	
Hepatobiliary disorders		Cholelithiasis***	Cholecystitis***	
Skin and subcutaneous tissue disorders			Urticaria	
Renal and urinary disorders				Acute renal failure Renal impairment
General disorders and administration site conditions		Injection site reactions Asthenia Fatigue	Malaise	
Investigations		Increased lipase Increased amylase		

*Hypoglycaemia (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 section 'Description of selected adverse reactions' for further information.
**Insomnia was mainly seen during the first 3 months of treatment.
***See section 4.4.
****From controlled phase 2, 3a and 3b clinical trials.

Description of selected adverse reactions:

Hypoglycaemia in patients without type 2 diabetes mellitus

In clinical trials in overweight or obese patients without type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise, no severe hypoglycaemic events (requiring third party assistance) were reported. Symptoms of hypoglycaemic events were reported by 1.6 % of patients treated with Saxenda and 1.1% of patients treated with placebo; however, these events were not confirmed by blood glucose measurements. The majority of events were mild.

Hypoglycaemia in patients with type 2 diabetes mellitus

In a clinical trial in overweight or obese patients with type 2 diabetes mellitus treated with Saxenda in combination with diet and exercise, severe hypoglycaemia (requiring third party assistance) was reported by 0.7% of patients treated with Saxenda and only in patients concomitantly treated with sulfonylurea. Also, in these patients documented symptomatic hypoglycaemia was reported by 43.6% of patients treated with Saxenda and in 27.3% of patients treated with placebo. Among patients not concomitantly treated with sulfonylurea, 15.7% of patients treated with Saxenda and 7.6% of patients treated with placebo reported documented symptomatic hypoglycaemic events (defined as plasma glucose ≤3.9 mmol/L accompanied by symptoms).

Hypoglycaemia in patients with type 2 diabetes mellitus treated with insulin

In a clinical trial in overweight or obese patients with type 2 diabetes mellitus treated with insulin and liraglutide 3.0 mg/day in combination with diet and exercise and up to 2 OADs, severe hypoglycaemia (requiring third party assistance) was reported by 1.5% of patients treated with liraglutide 3.0 mg/day. In this trial, documented symptomatic hypoglycaemia (defined as plasma glucose ≤3.9 mmol/L accompanied by symptoms) was reported by 47.2% of patients treated with liraglutide 3.0 mg/day and by 51.8% of patients treated with placebo. Among patients concomitantly treated with sulfonylurea, 60.9% of patients treated with liraglutide 3.0 mg/day and 60.0% of patients treated with placebo reported documented symptomatic hypoglycaemic events.

Gastrointestinal adverse reactions

Most episodes of gastrointestinal events were mild to moderate, transient and the majority did not lead to discontinuation of therapy. The reactions usually occurred during the first weeks of treatment and diminished within a few days or weeks on continued treatment.

Patients ≥65 years of age may experience more gastrointestinal effects when treated with Saxenda.

Patients with mild or moderate renal impairment (creatinine clearance ≥30 ml/min) may experience more gastrointestinal effects when treated with Saxenda.

Acute renal failure

In patients treated with GLP-1 receptor agonists, there have been reports of acute renal failure. A majority of the reported events occurred in patients who had experienced nausea, vomiting or diarrhoea leading to volume depletion (see section 4.4).

Allergic reactions

Few cases of anaphylactic reactions with symptoms such as hypotension, palpitations, dyspnoea and oedema have been reported with marketed use of liraglutide. Anaphylactic reactions may potentially be life threatening. If an anaphylactic reaction is suspected, liraglutide should be discontinued and treatment should not be restarted (see section 4.3).

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.

Tachycardia

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

Paediatric population

In a clinical trial conducted in adolescents of 12 years to less than 18 years with obesity, 125 patients were exposed to Saxenda for 56 weeks.
Overall, the frequency, type and severity of adverse reactions in the adolescents with obesity were comparable to that observed in the adult population. Vomiting occurred with a 2-fold higher frequency in adolescents compared to adults.
The percentage of patients reporting at least one episode of clinically significant hypoglycaemia was higher with liraglutide (1.6%) compared to placebo (0.8%). No severe hypoglycaemic episodes occurred in the trial.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

Great Britain:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

From clinical trials and post-marketing use of liraglutide overdoses have been reported up to 72 mg (24 times the recommended dose for weight management). Events reported included severe nausea, severe vomiting and severe hypoglycaemia.

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues.
ATC code: A10BJ02

Mechanism of action

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid sequence homology to endogenous human GLP-1. Liraglutide binds to and activates the GLP-1 receptor (GLP-1R).

GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear. In animal studies, peripheral administration of liraglutide led to uptake in specific

brain regions involved in regulation of appetite, where liraglutide, via specific activation of the GLP-1R, increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

Pharmacodynamic effects

Liraglutide lowers body weight in humans mainly through loss of fat mass with relative reductions in visceral fat being greater than for subcutaneous fat loss. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption, thereby leading to reduced food intake. Liraglutide does not increase energy expenditure compared to placebo.

Liraglutide stimulates insulin secretion and lowers glucagon secretion in a glucose-dependent manner which results in a lowering of fasting and post-prandial glucose. The glucose-lowering effect is more pronounced in patients with pre-diabetes and diabetes compared to patients with normoglycaemia. Clinical trials suggest that liraglutide improves and sustains beta-cell function, according to HOMA-B and the proinsulin-to-insulin ratio.

Clinical efficacy and safety

The efficacy and safety of liraglutide for weight management in conjunction with reduced calorie intake and increased physical activity were studied in four phase 3 randomised, double-blind, placebo-controlled trials which included a total of 5,358 adult patients.

- **Trial 1 (SCALE Obesity & Pre-Diabetes - 1839):** A total of 3,731 patients with obesity (BMI ≥30 kg/m²) or with overweight (BMI ≥27 kg/m²) with dyslipidaemia and/or hypertension were stratified according to prediabetes status at screening and BMI at baseline (≥30 kg/m² or <30 kg/m²). All 3,731 patients were randomised to 56 weeks of treatment and the 2,254 patients with prediabetes at screening were randomised to 160 weeks of treatment. Both treatment periods were followed by a 12-week off drug/placebo observational follow-up period. Lifestyle intervention in the form of an energy-restricted diet and exercise counselling was background therapy for all patients.
  The 56-week part of trial 1 assessed body weight loss in all the 3,731 randomised patients (2,590 completers).
  The 160-week part of trial 1 assessed time to onset of type 2 diabetes in the 2,254 randomised patients with prediabetes (1,128 completers).
- **Trial 2 (SCALE Diabetes - 1922):** A 56-week trial assessing body weight loss in 846 randomised (628 completers) obese and overweight patients with insufficiently controlled type 2 diabetes mellitus (HbA_{1c} range 7–10%). The background treatment at trial start was either diet and exercise alone, metformin, a sulfonylurea, a glitazone as single agents or any combination hereof.
- **Trial 3 (SCALE Sleep Apnoea - 3970):** A 32-week trial assessing sleep apnoea severity and body weight loss in 359 randomised (276 completers) obese patients with moderate or severe obstructive sleep apnoea.
- **Trial 4 (SCALE Maintenance - 1923):** A 56-week trial assessing body weight maintenance and weight loss in 422 randomised (305 completers) obese and overweight patients with hypertension or dyslipidaemia after a preceding weight loss of ≥5% induced by a low-calorie diet.

Body weight

Superior weight loss was achieved with liraglutide compared to placebo in obese/overweight patients in all groups studied. Across the trial populations, greater proportions of the patients achieved ≥5%

and >10% weight loss with liraglutide than with placebo (tables 4–6). In the 160-weeks part of trial 1, the weight loss occurred mainly in the first year and was sustained throughout 160 weeks. In trial 4, more patients maintained the weight loss achieved prior to treatment initiation with liraglutide than with placebo (81.4% and 48.9%, respectively). Specific data on weight loss, responders, time course and cumulative distribution of weight change (%) for trials 1–4 are presented in tables 4–8 and figures 1, 2 and 3.

Weight loss response after 12 weeks with liraglutide (3.0 mg) treatment

Early responders were defined as patients who achieved ≥5% weight loss after 12 weeks on treatment dose of liraglutide (4 weeks of dose escalation and 12 weeks on treatment dose). In the 56-week part of trial 1, 67.5% achieved ≥5% weight loss after 12 weeks. In trial 2, 50.4% achieved ≥5% weight loss after 12 weeks. With continued treatment with liraglutide, 86.2% of these early responders are predicted to achieve a weight loss of ≥5% and 51% are predicted to achieve a weight loss of ≥10% after 1 year of treatment. The predicted mean weight loss in early responders who complete 1 year of treatment is 11.2% of their baseline body weight (9.7% for males and 11.6% for females). For patients who have achieved a weight loss of <5% after 12 weeks on treatment dose of liraglutide, the proportion of patients not reaching a weight loss of ≥10% after 1 year is 93.4%.

Glycaemic control

Treatment with liraglutide significantly improved glycaemic parameters across sub-populations with normoglycaemia, prediabetes and type 2 diabetes mellitus. In the 56-week part of trial 1, fewer patients treated with liraglutide had developed type 2 diabetes mellitus compared to patients treated with placebo (0.2% vs. 1.1%). More patients with prediabetes at baseline had reversed their prediabetes compared to patients treated with placebo (69.2% vs. 32.7%). In the 160-week part of trial 1, the primary efficacy endpoint was the proportion of patients with onset of type 2 diabetes mellitus evaluated as time to onset. At week 160, while on treatment, 3% treated with Saxenda and 11% treated with placebo were diagnosed with type 2 diabetes mellitus. The estimated time to onset of type 2 diabetes mellitus for patients treated with liraglutide 3.0 mg was 2.7 times longer (with a 95% confidence interval of [1.9, 3.9]), and the hazard ratio for risk of developing type 2 diabetes mellitus was 0.2 for liraglutide versus placebo.

Cardiometabolic risk factors

Treatment with liraglutide significantly improved systolic blood pressure and waist circumference compared with placebo (tables 4, 5 and 6).

Apnoea-Hypopnoea Index (AHI)

Treatment with liraglutide significantly reduced the severity of obstructive sleep apnoea as assessed by change from baseline in the AHI compared with placebo (table 6).

Table 4 Trial 1: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 56

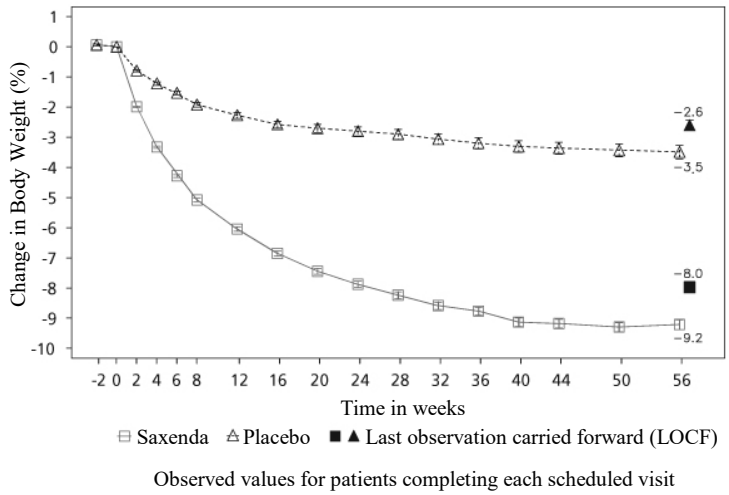
	Saxenda (N=2437)		Placebo (N=1225)		Saxenda vs. placebo
Body weight					
Baseline, kg (SD)	106.3 (21.2)		106.3 (21.7)		-
Mean change at week 56, % (95% CI)	-8.0		-2.6		-5.4** (-5.8; -5.0)
Mean change at week 56, kg (95% CI)	-8.4		-2.8		-5.6** (-6.0; -5.1)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	63.5		26.6		4.8** (4.1; 5.6)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	32.8		10.1		4.3** (3.5; 5.3)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA_{1c}, %	5.6	-0.3	5.6	-0.1	-0.23** (-0.25; -0.21)
FPG, mmol/L	5.3	-0.4	5.3	-0.01	-0.38** (-0.42; -0.35)
Systolic blood pressure, mmHg	123.0	-4.3	123.3	-1.5	-2.8** (-3.6; -2.1)
Diastolic blood pressure, mmHg	78.7	-2.7	78.9	-1.8	-0.9* (-1.4; -0.4)
Waist circumference, cm	115.0	-8.2	114.5	-4.0	-4.2** (-4.7; -3.7)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward.
* p<0.05. ** p<0.0001. CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.

Table 5 Trial 1: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 160

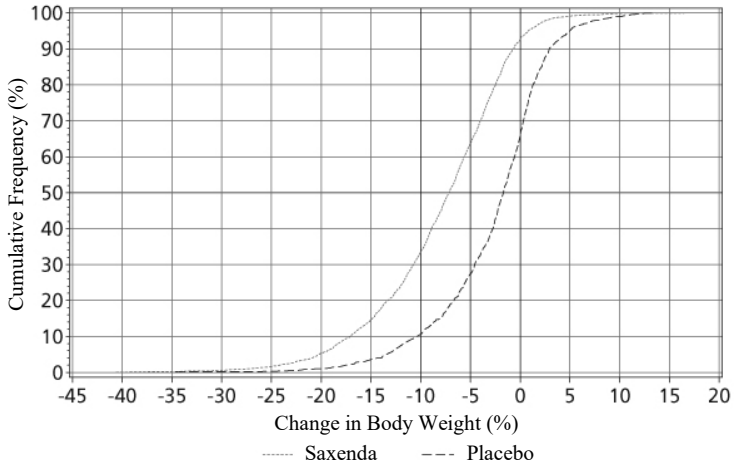
	Saxenda (N=1472)		Placebo (N=738)		Saxenda vs. placebo
Body weight					
Baseline, kg (SD)	107.6 (21.6)		108.0 (21.8)		
Mean change at week 160, % (95% CI)	-6.2		-1.8		-4.3** (-4.9; -3.7)
Mean change at week 160, kg (95% CI)	-6.5		-2.0		-4.6** (-5.3; -3.9)
Proportion of patients losing ≥5% body weight at week 160, % (95% CI)	49.6		23.4		3.2** (2.6; 3.9)
Proportion of patients losing >10% body weight at week 160, % (95% CI)	24.4		9.5		3.1** (2.3; 4.1)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA_{1c}, %	5.8	-0.4	5.7	-0.1	-0.21** (-0.24; -0.18)
FPG, mmol/L	5.5	-0.4	5.5	0.04	-0.4** (-0.5; -0.4)
Systolic blood pressure, mmHg	124.8	-3.2	125.0	-0.4	-2.8** (-3.8; -1.8)
Diastolic blood pressure, mmHg	79.4	-2.4	79.8	-1.7	-0.6 (-1.3; 0.1)
Waist circumference, cm	116.6	-6.9	116.7	-3.4	-3.5** (-4.2; -2.8)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 160 are estimated means (least-squares) and treatment contrasts at week 160 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward.
** p<0.0001. CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.



Observed values for patients completing each scheduled visit

Figure 1 Change from baseline in body weight (%) by time in trial 1 (0–56 weeks)



Last observation carried forward.

Figure 2 Cumulative distribution of weight change (%) after 56 weeks of treatment in trial 1

Table 6 Trial 2: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 56

	Saxenda (N=412)		**Placebo (N=211)**		**Saxenda vs. placebo**
Body weight					
Baseline, kg (SD)	105.6 (21.9)		106.7 (21.2)		-
Mean change at week 56, % (95% CI)	-5.9		-2.0		-4.0** (-4.8; -3.1)
Mean change at week 56, kg (95% CI)	-6.2		-2.2		-4.1** (-5.0; -3.1)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	49.8		13.5		6.4** (4.1; 10.0)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	22.9		4.2		6.8** (3.4; 13.8)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA_{1c}, %	7.9	-1.3	7.9	-0.4	-0.9** (-1.1; -0.8)
FPG, mmol/L	8.8	-1.9	8.6	-0.1	-1.8** (-2.1; -1.4)
Systolic blood pressure, mmHg	128.9	-3.0	129.2	-0.4	-2.6* (-4.6; -0.6)
Diastolic blood pressure, mmHg	79.0	-1.0	79.3	-0.6	-0.4 (-1.7; 1.0)
Waist circumference, cm	118.1	-6.0	117.3	-2.8	-3.2** (-4.2; -2.2)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward.
* p<0.05. ** p<0.0001. CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.

Table 7 Trial 3: Changes from baseline in body weight and Apnoea-Hypopnoea Index at week 32

	Saxenda (N=180)		**Placebo (N=179)**		**Saxenda vs. placebo**
Body weight					
Baseline, kg (SD)	116.5 (23.0)		118.7 (25.4)		-
Mean change at week 32, % (95% CI)	-5.7		-1.6		-4.2** (-5.2; -3.1)
Mean change at week 32, kg (95% CI)	-6.8		-1.8		-4.9** (-6.2; -3.7)
Proportion of patients losing ≥5% body weight at week 32, % (95% CI)	46.4		18.1		3.9** (2.4; 6.4)
Proportion of patients losing >10% body weight at week 32 % (95% CI)	22.4		1.5		19.0** (5.7; 63.1)
	Baseline	Change	Baseline	Change	
Apnoea-Hypopnoea Index, events/hour	49.0	-12.2	49.3	-6.1	-6.1* (-11.0; -1.2)

Full Analysis Set. Baseline values are means, changes from baseline at week 32 are estimated means (least-squares) and treatment contrasts at week 32 are estimated treatment differences (95% CI). For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward. * p<0.05. ** p<0.0001. CI=confidence interval. SD=standard deviation.

Table 8 Trial 4: Changes from baseline in body weight at week 56

	Saxenda (N=207)	**Placebo (N=206)**	**Saxenda vs. placebo**
Baseline, kg (SD)	100.7 (20.8)	98.9 (21.2)	-
Mean change at week 56, % (95% CI)	-6.3	-0.2	-6.1** (-7.5; -4.6)
Mean change at week 56, kg (95% CI)	-6.0	-0.2	-5.9** (-7.3; -4.4)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	50.7	21.3	3.8** (2.4; 6.0)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	27.4	6.8	5.1** (2.7; 9.7)

Full Analysis Set. Baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. Missing post-baseline values were imputed using the last observation carried forward. ** p<0.0001. CI=confidence interval. SD=standard deviation.

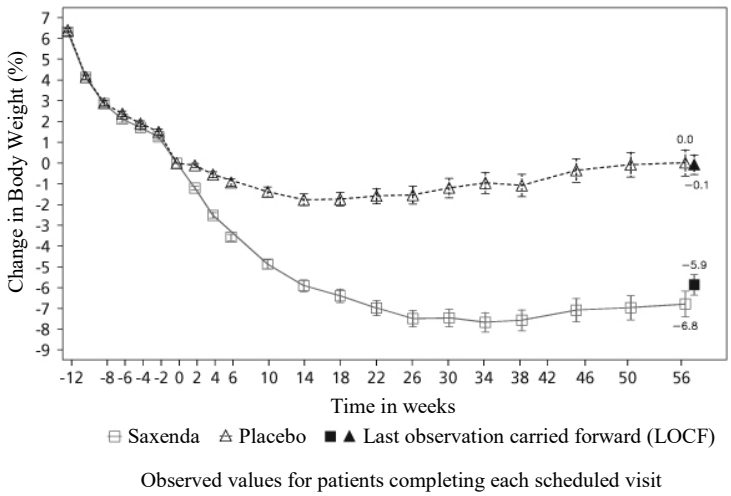


Figure 3 Change from randomisation (week 0) in body weight (%) by time in trial 4

Before week 0 patients were only treated with low-calorie diet and exercise. At week 0 patients were randomised to receive either Saxenda or placebo.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-liraglutide antibodies following treatment with liraglutide. In clinical trials, 2.5% of patients treated with liraglutide developed anti-liraglutide antibodies. Antibody formation has not been associated with reduced efficacy of liraglutide.

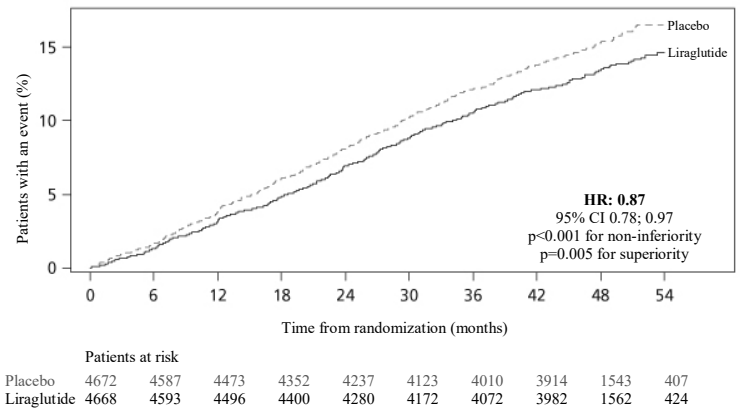
Cardiovascular evaluation

Major adverse cardiovascular events (MACE) were adjudicated by an external independent group of experts and defined as non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. In all the long-term clinical trials with Saxenda, there were 6 MACE for patients treated with liraglutide and 10 MACE for placebo-treated patients. The hazard ratio and 95% CI is 0.33 [0.12; 0.90] for liraglutide versus placebo. A mean increase in heart rate from baseline of 2.5 beats per minute (ranging across trials from 1.6 to 3.6 beats per minute) has been observed with liraglutide in clinical phase 3 trials. The heart rate peaked after approximately 6 weeks. The long-term clinical impact of this mean increase in heart rate has not been established. The change in heart rate was reversible upon discontinuation of liraglutide (see section 4.4).

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcomes Results (LEADER) trial included 9,340 patients with insufficiently controlled type 2 diabetes. The vast majority of these had established cardiovascular disease. Patients were randomly allocated to either liraglutide on a daily dose of up to 1.8 mg (4,668) or placebo (4,672), both on a background of standard of care.

The duration of exposure was between 3.5 and 5 years. The mean age was 64 years and the mean BMI was 32.5 kg/m². Mean baseline HbA_{1c} was 8.7 and had improved after 3 years by 1.2 % in patients assigned to liraglutide and by 0.8 % in patients assigned to placebo. The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Liraglutide significantly reduced the rate of major adverse cardiovascular events (primary endpoint events, MACE) vs. placebo (3.41 vs. 3.90 per 100 patient years of observation in the liraglutide and placebo groups, respectively) with a risk reduction of 13%, HR 0.87, [0.78, 0.97] [95% CI]) (p=0.005) (see figure 4).



FAS: full analysis set.

Figure 4 Kaplan Meier plot of time to first MACE – FAS population

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Saxenda in one or more subsets of the paediatric population in the treatment of obesity (see section 4.2 for information on paediatric use).

In a double-blind trial comparing the efficacy and safety of Saxenda versus placebo on weight loss in adolescent patients aged 12 years and above with obesity, Saxenda was superior to placebo in weight reduction (evaluated as BMI Standard Deviation Score) after 56 weeks of treatment (table 9).
A greater proportion of the patients achieved ≥5% and ≥10% reductions in BMI with liraglutide than with placebo, as well as greater reductions in mean BMI and body weight (table 9). After 26 weeks of off-trial product follow-up period, weight regain was observed with liraglutide vs placebo (table 9).

Table 9 Trial 4180: Changes from baseline in body weight and BMI at week 56 and change in BMI SDS from week 56 to week 82

	Saxenda (N=125)	**Placebo (N=126)**	**Saxenda vs. placebo**
BMI SDS			
Baseline, BMI SDS (SD)	3.14 (0.65)	3.20 (0.77)	
Mean change at week 56 (95% CI)	-0.23	-0.00	-0.22* (-0.37; -0.08)
Week 56, BMI SDS (SD)	2.88 (0.94)	3.14 (0.98)	
Mean change from week 56 to week 82, BMI SDS (95% CI)	0.22	0.07	0.15** (0.07; 0.23)
Body weight			
Baseline, kg (SD)	99.3 (19.7)	102.2 (21.6)	-
Mean change at week 56, % (95% CI)	-2.65	2.37	-5.01** (-7.63; -2.39)
Mean change at week 56, kg (95% CI)	-2.26	2.25	-4.50** (-7.17; -1.84)
BMI			
Baseline, kg/m^2 (SD)	35.3 (5.1)	35.8 (5.7)	-
Mean change at week 56, kg/m^2 (95% CI)	-1.39	0.19	-1.58** (-2.47; -0.69)

Proportion of patients with ≥5% reduction in baseline BMI at week 56, % (95% CI)	43.25	18.73	3.31** (1.78; 6.16)
Proportion of patients with ≥10% reduction in baseline BMI at week 56, % (95% CI)	26.08	8.11	4.00** (1.81; 8.83)

Full Analysis Set. For BMI SDS, body weight and BMI, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For BMI SDS, value at week 56 are means, changes from week 56 to week 82 are estimated means (least-squares) and treatment contrasts at week 82 are estimated treatment differences. For the proportions of patients losing ≥5%/≥10% baseline BMI, estimated odds ratios are presented. Missing observations were imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach.
*p<0.01, **p<0.001. CI=confidence interval. SD=standard deviation.

Based on tolerability, 103 patients (82.4%) escalated and remained on dose of 3.0 mg, 11 patients (8.8%) escalated and remained on dose of 2.4 mg, 4 patients (3.2%) escalated and remained on dose of 1.8 mg, 4 patients (3.2%) escalated and remained on dose of 1.2 mg and 3 patients (2.4%) remained on dose of 0.6 mg.
No effects on growth or pubertal development were found after 56 weeks of treatment.

A 16-week double-blind, 36 week open-label study was conducted to evaluate the efficacy and safety of Saxenda in paediatric patients with Prader-Willi Syndrome and obesity. The study included 32 patients between 12 to <18 years of age (part A) and 24 patients between 6 to <12 years of age (part B). Patients were randomized 2:1 to receive Saxenda or placebo. Patients with a body weight less than 45 kg started dose escalation at a lower dose; 0.3 mg instead of 0.6 mg and were escalated to a maximum dose of 2.4 mg.
The estimated treatment difference in mean BMI SDS at 16 weeks (part A: -0.20 vs -0.13, part B: -0.50 vs -0.44) and 52 weeks (part A: -0.31 vs -0.17, part B: -0.73 vs -0.67) were similar with Saxenda and placebo.
No additional safety concerns were seen in the trial.

5.2 Pharmacokinetic properties

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) patients following administration of 3 mg liraglutide. Liraglutide exposure increased proportionally with dose. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution

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

Biotransformation

During 24 hours following administration of a single [^{3}H]-liraglutide dose 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).

Elimination

Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination. Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). The urine and faeces radioactivity was mainly excreted during the first 6–8 days and corresponded to three minor metabolites, respectively.

The mean clearance following subcutaneous administration of liraglutide is approximately 0.9–1.4 L/h with an elimination half-life of approximately 13 hours.

Special populations

Elderly

Age had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results from a population pharmacokinetic analysis of data from overweight and obese patients (18 to 82 years). No dosage adjustment is required based on age.

Gender

Based on the results of population pharmacokinetic analysis, females have 24% lower weight adjusted clearance of liraglutide compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Ethnic origin

Ethnic origin had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis which included overweight and obese patients of White, Black, Asian and Hispanic/non-Hispanic groups.

Body weight

The exposure of liraglutide decreases with an increase in baseline body weight. 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 impairment

The pharmacokinetics of liraglutide was evaluated in patients with varying degree of hepatic impairment in a single-dose trial (0.75 mg). Liraglutide exposure was decreased by 13–23% in patients with mild to moderate hepatic impairment compared to healthy subjects. Exposure was significantly lower (44%) in patients with severe hepatic impairment (Child Pugh score >9).

Renal impairment

Liraglutide exposure was reduced in patients with renal impairment compared to individuals with normal renal function in a single-dose trial (0.75 mg). Liraglutide exposure was lowered by 33%, 14%, 27% and 26%, respectively, in patients with mild (creatinine clearance, CrCl 50–80 ml/min), moderate (CrCl 30–50 ml/min) and severe (CrCl <30 ml/min) renal impairment and in end-stage renal disease requiring dialysis.

Paediatric population

Pharmacokinetic properties for liraglutide 3.0 mg were assessed in clinical pharmacology studies for adolescent patients with obesity aged 12 to less than 18 years (134 patients, body weight 62-178 kg). The liraglutide exposure in adolescents (age 12 to less than 18 years) was similar to that in adults with obesity.

Pharmacokinetic properties were also assessed in a clinical pharmacology study in the paediatric population with obesity aged 7-11 years (13 patients, body weight 54-87 kg) respectively. Exposure associated with 3.0 mg liraglutide was found to be comparable between the children aged 7 to 11, adolescents and adults with obesity, after correction for body weight.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours were seen in two-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. No other treatment-related tumours have been found.

Animal studies did not indicate direct harmful effects with respect to fertility but slightly increased early embryonic deaths at the highest dose. Dosing with liraglutide during mid-gestation caused a reduction in maternal weight and foetal growth with equivocal effects on ribs in rats and skeletal variation in the rabbit. Neonatal growth was reduced in rats while exposed to liraglutide and persisted in the post-weaning period in the high dose group. It is unknown whether the reduced pup growth is caused by reduced pup milk intake due to a direct GLP-1 effect or reduced maternal milk production due to decreased caloric intake.

In juvenile rats, liraglutide caused delayed sexual maturation in both males and females at clinical relevant exposures. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate
Propylene glycol
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to Saxenda may cause degradation of liraglutide. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months

After first use: 1 month

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).
Do not freeze.
Store away from the freezer compartment.

After first use: Store below 30°C or store in a refrigerator (2°C–8°C).
Keep the cap on the pen in order to protect from light.

6.5 Nature and contents of container

Cartridge (type 1 glass) with a plunger (bromobutyl) and a laminate rubber sheet (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene.

Each pen contains 3 ml solution and is able to deliver doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg.

Pack sizes of 1, 3 or 5 pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should not be used if it does not appear clear and colourless or almost colourless.

Saxenda should not be used if it has been frozen.

The pen is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm and as thin as 32G.

Needles are not included.

The patient should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. This prevents contamination, infection and leakage. It also ensures that the dosing is accurate.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

PLGB 04668/0409

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2015
Date of latest renewal: 09 December 2019

10. DATE OF REVISION OF THE TEXT

29 July 2022