PROFESSIONAL INFORMATION

S4 Saxenda®

6 mg/ml, Liraglutide, Solution for Injection

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Saxenda®, solution for injection in pre-filled pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 6 mg of liraglutide (produced by recombinant DNA technology in *Saccharomyces cerevisiae*) and phenol 0,55 % m/v as the preservative.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, 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 medically supervised chronic weight

management programme in adult patients with an initial Body Mass Index (BMI) of:

- ≥ 30 kg/m^2 (obese),

  or

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

Adolescents

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

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

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

Age (years)	**Body mass index 30 kg/m^2**	
	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

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 1 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**	

Treatment with Saxenda® should be discontinued after 12 weeks on the 3,0 mg/day dose if a patient has not lost at least 5 % of the initial body weight.

Patients with type 2 diabetes mellitus

Saxenda® should not be used in combination with another GLP-1 receptor agonist. When initiating Saxenda®, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia.

Blood glucose self-monitoring may be necessary to adjust the dose of insulin or insulin-secretagogues.

Special populations

Elderly patients (≥ 65 years old)

No dose adjustment is required based on age. Due to limited experience in patients ≥ 75 years of age, Saxenda® should be used with caution in these patients.

Patients with renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 ml/min). There is limited experience in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Saxenda® is currently not recommended for use in patients with severe renal impairment including patients with end-stage renal disease (*see section* Special population under 5.2 Pharmacokinetic properties).

Patients with 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 section* Special population under 5.2 Pharmacokinetic properties).

Paediatric population

Saxenda® is not recommended for use in children below 12 years of age or in adolescents with a body weight below or equal to 60 kg due to lack of data.

For adolescents from the age of 12 to below 18 years old, similar dose escalation schedule as for adults should be applied. 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.

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 instructions for handling and how to administer Saxenda®* solution for injection in pre-filled pen refer to user instructions at the end of the professional information.

Missed dose

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.

4.3 Contraindications

- Hypersensitivity to liraglutide or to any of the excipients listed under Composition.
- Pregnancy and lactation (*see* 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Saxenda® must not be used as a substitute for insulin in

patients with diabetes mellitus.

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

The safety and efficacy of Saxenda® have not been established in patients:

- 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.

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis. Use of Saxenda® 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, Saxenda® should be discontinued; if acute pancreatitis is confirmed, Saxenda® should not be restarted.

In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Cholelithiasis and cholecystitis

In clinical trials, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with Saxenda® than in patients on placebo. 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. Saxenda® should therefore be used with caution in patients with thyroid disease.

Heart rate

An increase in heart rate was observed in clinical trials.
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 Saxenda® 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 such as Saxenda®. Patients treated with Saxenda® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Hypoglycaemia in overweight or obese patients with type 2 diabetes mellitus

Patients with type 2 diabetes receiving Saxenda® in combination with insulin and/or sulphonylurea have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of insulin and/or sulphonylurea. Blood glucose levels should be carefully monitored during treatment with Saxenda® in patients with type 2 diabetes.

4.5 Interaction with other medicines and other forms of interaction

In vitro assessment of interaction

Saxenda® has shown very low potential to be involved in pharmacokinetic interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of interaction

The delay of gastric emptying with Saxenda® may influence absorption of concomitantly administered oral medicines. 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 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 medicines.

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 Saxenda® treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR (International Normalised Ratio) is recommended.

Paracetamol (Acetaminophen)

Saxenda® 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

Saxenda® 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 Saxenda®. Atorvastatin C_{max} was decreased by 38 % and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin

Saxenda® 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 Saxenda®.

4.6 Fertility, pregnancy and lactation

The safety of Saxenda® in pregnancy and lactation has not been established.

Saxenda® should not be used during pregnancy and lactation (*see* 4.3 Contraindications).

If a patient wishes to become pregnant, or pregnancy occurs, treatment with Saxenda® should be discontinued.

4.7 Effects on ability to drive and use machines

Dizziness may impair the ability to drive and use machines.

4.8 Undesirable effects

Saxenda® was evaluated for safety in 5 trials that enrolled 5813 adult patients with overweight or obesity with at least one weight-related co-morbidity.

Overall, gastrointestinal reactions were the most frequently reported adverse reactions during treatment with Saxenda® (see section 'Description of selected side effects' below).

Table 2 lists adverse reactions reported in long term phase 3 and phase 2 controlled trials in adults and post-marketing reports. Adverse reactions associated with Saxenda® are listed by body system and frequency. The frequencies of the adverse reactions are based on a pool of phase 2 and 3 clinical trials. 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).

Table 2: Adverse reactions reported in phase 2 and phase 3 controlled trials and post-marketing reports

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	Pancreatitis	

		reflux disease Abdominal pain upper Flatulence Eructation Abdominal distension		
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 side effects' for further information.

Description of selected side effects

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. In these patients, documented symptomatic hypoglycaemia (defined as plasma glucose ≤ 3,9 mmol/l accompanied by symptoms) 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.

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 Saxenda® 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 Saxenda®. 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 Saxenda® and by 51,8 % of patients treated with placebo. Among patients concomitantly treated with sulfonylurea, 60,9% of patients treated with Saxenda® and 60,0 % of patients treated with placebo reported documented symptomatic hypoglycaemic events.

Gastrointestinal adverse reactions

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®.

Allergic reactions

Cases of anaphylactic reactions with symptoms such as hypotension, palpitations, dyspnoea, or oedema have been reported with marketed use of liraglutide. Anaphylactic reactions may potentially be life threatening.

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 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.
No effects on growth or pubertal development were found.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

With overdose, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. Severe hypoglycaemia has also been observed.

In the event of overdosage, 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 a human Glucagon-Like Peptide-1 (GLP-1) analogue with 97 % homology to human GLP-1 that binds to and activates the GLP-1 receptor.

The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans, suitable for once daily administration.

Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, and binding to albumin and enzymatic stability towards the dipeptidyl peptidase-4 (DPP-IV) and neutral endopeptidase (NEP) enzymes resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cAMP. Liraglutide stimulates insulin secretion in a glucose-dependent manner and improves beta-cell function. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptor (GLP-1R) is present in several areas of the brain involved in appetite regulation. In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions including the hypothalamus, where liraglutide, via specific activation of the GLP-1R, increased satiety and decreased hunger signals, thereby leading to lower body weight. Liraglutide reduces body weight and body fat mass. Body weight is lowered through decreased food intake. Liraglutide does not increase 24-hour energy expenditure.

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.

Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption.

Pharmacodynamic effects

Liraglutide has 24-hour duration of action and improves glycaemic control by lowering fasting and postprandial blood glucose.

Fasting and postprandial glucose, insulin and glucagon concentrations were assessed before and up to five hours after a standardised meal. Compared to placebo, liraglutide reduced fasting glucose and postprandial glucose ($AUC_{0\text{-}60\ min}$) in the first hour after the meal, and also reduced 5-hour glucose AUC and incremental glucose ($AUC_{0\text{-}300\ min}$). In addition, liraglutide decreased postprandial glucagon ($AUC_{0\text{-}300\ min}$), postprandial insulin ($AUC_{0\text{-}60\ min}$) and incremental insulin ($iAUC_{0\text{-}60\ min}$) after the meal compared with placebo.

Fasting and incremental glucose and insulin concentrations were also assessed during a 75 g oral glucose tolerance test (OGTT) before and after one year of treatment in 3 731 overweight and obese patients with and without pre-diabetes. Compared to placebo, liraglutide reduced fasting and incremental glucose concentrations. The effect was more pronounced in patients with pre-diabetes. In addition, liraglutide reduced fasting insulin and increased incremental insulin concentrations compared to placebo.

Effects on fasting and postprandial glucose increment in overweight and obese patients with type 2 diabetes mellitus

Liraglutide reduced fasting glucose and mean postprandial glucose increment (90 minutes after the meal, average over 3 daily meals), compared to placebo.

Fasting and incremental glucose and insulin concentrations were also assessed during a 75 g oral glucose tolerance test (OGTT) before and after 56 weeks treatment in 3 731 overweight and obese patients with and without prediabetes.

Compared to placebo, liraglutide reduced fasting and incremental glucose concentrations. The effect was more pronounced in patients with pre-diabetes. In addition, liraglutide reduced fasting insulin and increased incremental insulin concentrations compared to placebo. Compared to baseline levels, the week 160 post-challenge plasma glucose AUC was reduced with liraglutide 3,0 mg, while on treatment, but remained unchanged with placebo.

Additionally, post-challenge insulin AUC remained relatively stable with liraglutide 3,0 mg during the 160 weeks treatment period, while declining in the placebo group.

The estimated treatment effects were all statistically significant in favour of liraglutide 3,0 mg.

5.2 Pharmacokinetic properties

Liraglutide is stable against metabolic degradation 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 dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP).

Absorption

The absorption of liraglutide following subcutaneous administration was slow, reaching maximum concentration approximately 11 hours post dosing. The average liraglutide steady state concentration ($AUC_{\tau/24}$) reached approximately 31 nmol/l in obese (BMI 30 - 40 kg/m^2) subjects following administration of liraglutide 3,0 mg. Liraglutide exposure increased proportionally with dose in the dose range of 0,6 mg to 3,0 mg.

Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55 %.

Distribution

The mean apparent volume of distribution after subcutaneous administration of liraglutide 3,0 mg is 20 - 25 l (for a person weighing approximately 100 kg). Liraglutide is extensively bound to plasma protein (> 98 %).

Metabolism/biotransformation

During 24 hours following administration of a single [3H]-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 [3H]-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 apparent clearance following *s.c.* administration of liraglutide 3,0 mg is approximately 0,9 – 1,4 l/h with an elimination half-life of approximately 13 hours.

Special populations

Elderly

No dosage adjustment is required based on age. Age had no clinically relevant effect on the pharmacokinetics of liraglutide 3,0 mg based on a population pharmacokinetic analysis that included overweight and obese patients (18 to 82 years).

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 trial. Liraglutide exposure was not studied in subjects with body weight > 234 kg.

Hepatic impairment

The pharmacokinetics of liraglutide was evaluated in patients with varying degrees of hepatic impairment in a single-dose trial (0,75 mg). Liraglutide exposure was decreased by 23 % and 13 % in patients with mild and moderate hepatic impairment, respectively, 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 %, 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, respectively.

Paediatric population

Pharmacokinetic properties for liraglutide 3,0 mg were assessed in clinical 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 - 11 and adult patients, after correction for body weight.

Trial 1 (SCALE Obesity & Pre-Diabetes - 1839): A total of 3 731 patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥27 kg/m^2) with dyslipidaemia and/or hypertension were stratified according to pre-diabetes status at screening and BMI at baseline (≥ 30 kg/m^2 or < 30 kg/m^2). All 3 731 patients were randomised to 56 weeks of treatment and the 2 254 patients with pre-diabetes at screening were randomised to 160 weeks of treatment 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 pre-diabetes (1 128 completers).

Body Weight

In trial 1, patients treated with liraglutide achieved a greater weight loss, as compared to placebo. The weight loss occurred mainly in the first year and was sustained throughout the 160 weeks.

In trial 1 the mean percent change in body weight and the proportions of patients achieving greater than or equal to 5 % and greater than 10 % weight loss from baseline to week 160 were also significant compared to placebo see Table 3. Weight loss response after 12 weeks with liraglutide 3,0 mg treatment.

Glycaemic control

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 pre-diabetes at baseline had reversed their pre-diabetes 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

liraglutide 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. More patients in the liraglutide 3,0 mg group (65,9 %) than the placebo group (36,3 %) had regressed their pre-diabetes to normoglycaemia by week 160 (odds ratio 3,6 [95 % CI, 3,0 to 4,4], P <0,001).

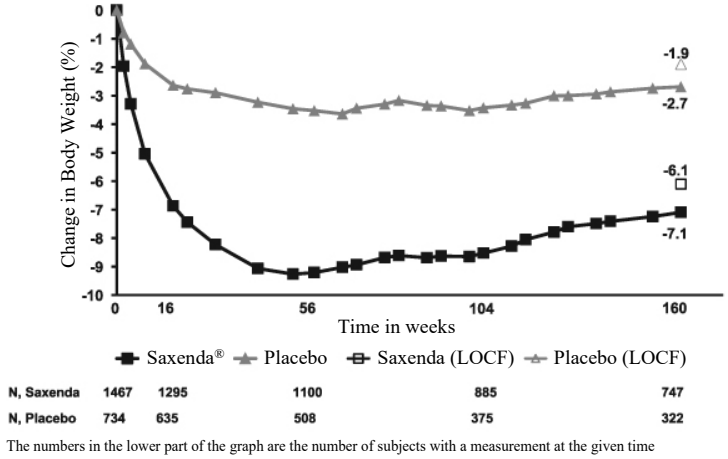


Figure 1 Change from baseline in body weight (%) by time in trial 1 (0 - 160 weeks)

Table 3 Trial 1: Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 160

	Liraglutide (N = 1472)	**Placebo (N = 738)**	**Liraglutide 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)
Lipids					
Total cholesterol, mmol/L	5,0	- 2,9 %	5,1	- 1,2 %	- 1,8* (- 3,3; - 0,2)

LDL cholesterol, mmol/L	2,9	- 4,6 %	3,0	- 2,6 %	- 2,0 (- 4,3; 0,4)
HDL cholesterol, mmol/L	1,3	4,9 %	1,3	3,9 %	1,0 (- 0,6; 2,7)
Triglycerides, mmol/L	1,5	- 11,7 %	1,5	- 5,91 %	- 6,2** (- 9,4; - 2,9)

Full Analysis Set. For body weight, HbA1c, 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. For lipids, baseline values are geometric means, changes from baseline at week 160 are relative changes, and treatment contrasts at week 160 are relative treatment differences. 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.*

Trial 1 included a 56 week part and a 160 week part. The trial enrolled 3 731 patients with obesity (BMI greater than or equal to 30 kg/m^2) or who were overweight (BMI 27-29,9 kg/m^2) and had at least one comorbid condition such as treated or untreated dyslipidemia or hypertension. Patients were randomized in a 2:1 ratio to either liraglutide or placebo. Patients were stratified based on prediabetes status (yes or no) at randomization. Pre-diabetes was defined as fasting plasma glucose of 5,6 - 6,9 mmol/l (100 - 125 mg/dl), 2-hour post challenge (OGTT) glucose of 7,8 - 11,0

mmol/l (140 - 199 mg/dl), or HbA_{1c} 5,7 - 6,4 % both inclusive. Patients with pre-diabetes at randomization were enrolled in the 160 week part of the trial (2 254 of the 3 731 patients). For the 56 week part the mean age was 45 (range 18 - 78), 79 % were women. 85 % were White and 10 % Black or African American. 11 % were Hispanic/Latino. Mean baseline body weight was 106,2 kg and mean BMI was 38,3 kg/m^2. For the 160-week part the mean age was 48 years (range 18 - 78), 76 % were women, 84 % were Caucasian, 10 % were African American and 9 % were Hispanic/Latino. Mean baseline body weight was 107,6 kg and mean BMI was 38,8 kg/m^2.

Trial 2 was a 56 week trial that enrolled 846 patients with obesity (BMI greater than or equal to 30 kg/m^2) or who were overweight (BMI 27 - 29,9 kg/m^2) with type 2 diabetes. Patients were to have an HbA_{1c} of 7 - 10 % and be treated with metformin, a sulfonylurea, a glitazone as single agent or in any combination. Patients were randomized in a 2:1 manner to receive either liraglutide or placebo as an add-on to their background diabetes treatment. The mean age was 55 (range 18 - 82); 50 % were women. 83 % were White and 12 % Black or African American. 10 % were Hispanic/Latino. Mean baseline body weight was 105,9 kg and mean BMI was 37,1 kg/m^2.

Trial 3 was a 32 week trial that enrolled 359 patients with obesity (BMI greater than or equal to 30 kg/m^2) with moderate or severe obstructive sleep apnoea and unable or unwilling to use continuous positive airway pressure treatment. Patients were

randomized in a 1:1 manner to receive either liraglutide or placebo. The mean age was 49 years (range 22 - 64); 28 % were women. 74 % were white, 19 % Black or African American and 12 % were Hispanic/Latino. Mean baseline body weight was 117,6 kg and mean BMI was 39,1 kg/m^2.

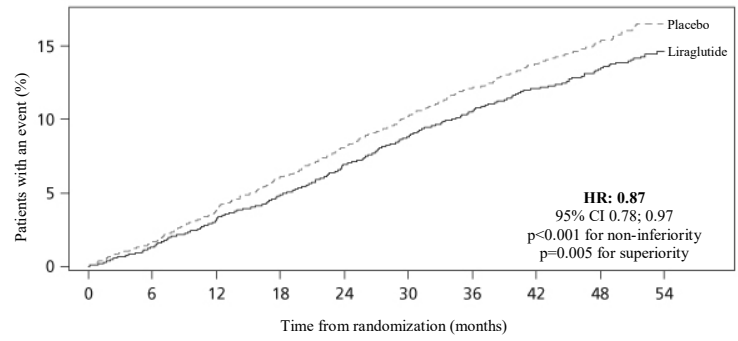
Trial 4 was a 56 week trial that enrolled 422 patients with obesity (BMI greater than or equal to 30 kg/m^2) or who were overweight (BMI 27 - 29,9 kg/m^2) and had at least one comorbid condition such as treated or untreated dyslipidaemia or hypertension. Patients were first treated with a low calorie diet (total energy intake 1200 - 1400 kcal/day) in the run-in period lasting up to 12 weeks. Patients who lost at least 5 % of screening body weight after 4 weeks and up to 12 weeks during the run-in were randomized in a 1:1 manner to receive either liraglutide or placebo for 56 weeks. The mean age was 46 (range 18 - 73); 81 % were women. 84 % were White and 13 % Black or African American. 7 % were Hispanic/Latino. Mean baseline body weight was 99,6 kg and mean BMI was 35,6 kg/m^2.

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. From the 5 double-blind controlled phase 2 and phase 3 clinical trials with liraglutide, there were 6 MACE for liraglutide treated patients 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 (see section 4.4 Special warnings and precautions for use).
The heart rate peaked after approximately 6 weeks. The change in heart rate was reversible upon discontinuation of liraglutide.
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 the patients 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 2).



Patients at risk

Placebo	4672	4587	4473	4352	4237	4123	4010	3914	1543	407
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424

FAS: full analysis set.

Figure 2 Kaplan Meier plot of time to first MACE – FAS population

Liraglutide also significantly reduced the risk of expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revascularisation, or hospitalisation due to heart failure) and other secondary endpoints (Figure 3).

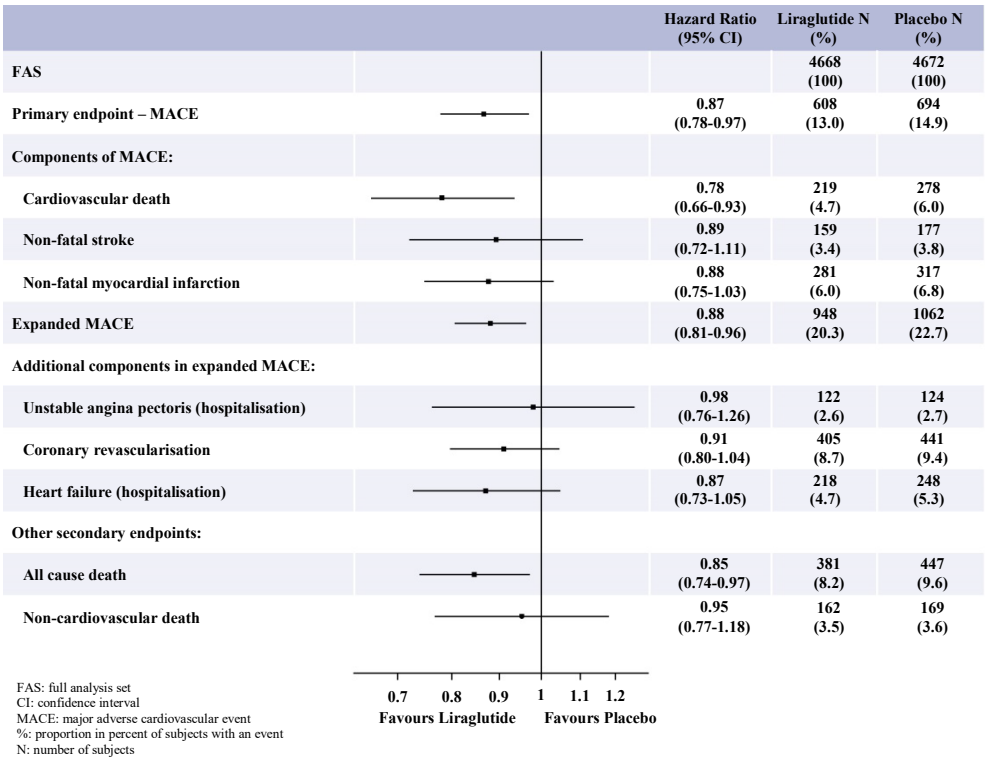
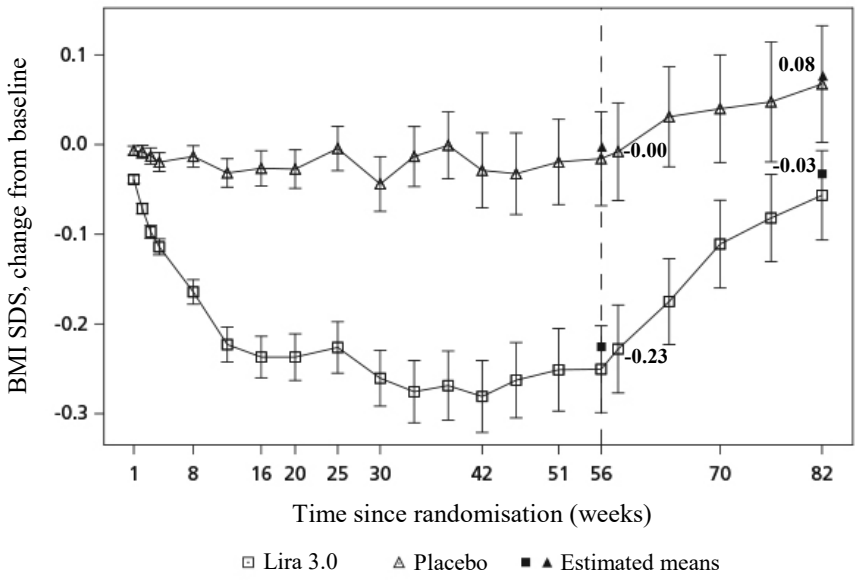


Figure 3 Forest plot of analyses of individual cardiovascular event types – FAS population

Paediatric population

In a double-blind trial comparing the efficacy and safety of liraglutide versus placebo on weight loss in adolescent patients aged 12 years and above with obesity, liraglutide was superior to placebo in reducing the BMI Standard Deviation Score (SDS) (measured to assess body weight loss) after 56 weeks of treatment resulting in an estimated treatment difference of - 0,22 [- 0,37; - 0,08] 95 % CI, p = 0,0022. After the 26 weeks of off-trial product follow-up period, weight regain was observed with liraglutide vs placebo (change in BMI SDS ETD: 0,15; [95 % CI 0,07 to 0,23], p = 0,0002) (Figure 4 and Table 4.)



BMI SDS : Body mass index standard deviation score, Line graphs are observed means, Error bar is :+/- standard error of mean Number at week 56 and 82 are estimated means using multiple imputation (jump to reference) for patients completing each scheduled visits

Figure 4 BMI SDS change from baseline

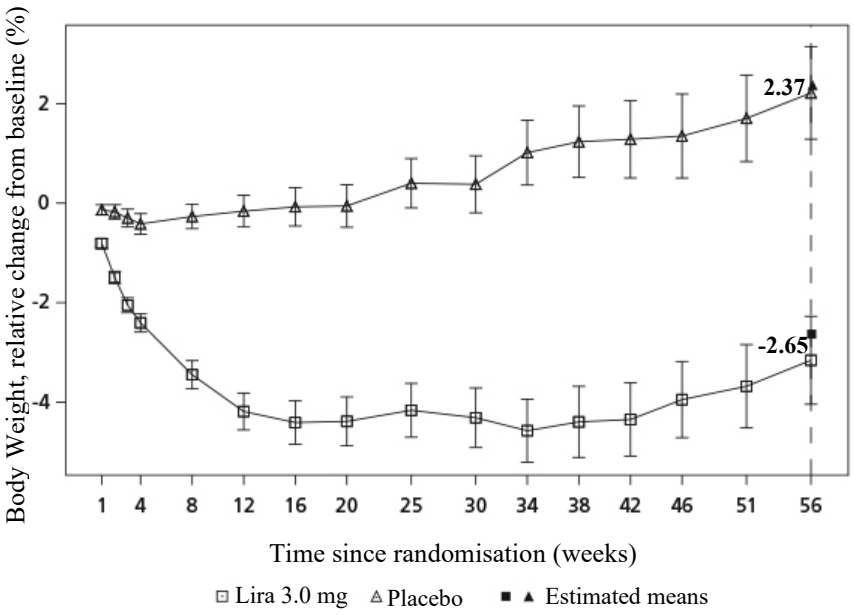
Patients were randomized in a 1:1 manner to receive liraglutide or placebo.

The mean age was 14,5 years, 59,4 % were females. 87,6 % were White, 8 % were Black or African. 22,3 % were Hispanic/Latino. Mean baseline body weight was 100,8 kg and mean BMI was 35,6 kg/m^2.

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.

At week 56, 43 % of patients in liraglutide group had lost ≥ 5 % of their baseline BMI vs. 19 % of patients in the placebo group (p = 0,0002). 26 % of patients in the liraglutide group lost ≥ 10 % of their baseline BMI vs. 8 % of the patients in the placebo group (p = 0,0006).

Greater reductions in BMI and body weight were observed with liraglutide vs placebo at week 56 (Figure 5 and Table 4).



Line graphs are observed means, Error bar is :+/- standard error of mean Number at week 56 are estimated means using multiple imputation (jump to reference) for patients completing each scheduled visit

Figure 5 Body weight, relative change from baseline (%)

Table 4 NN8022-4180 Changes from baseline in BMI SDS and body weight at week 56 and change in BMI SDS from week 56 to week 82

	Liraglutide (N = 125)	**Placebo (N = 126)**	**Liraglutide 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.*

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate

Propylene glycol

Sodium hydroxide

Hydrochloric acid

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 at or below 30 °C or store in a refrigerator (2 °C – 8 °C) for 30 days (1 month).

Discard any unused portion after 30 days.

Keep the cap on the pen in order to protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

3 ml solution in a cartridge made of colourless type 1 glass with a red rubber plunger (bromobutyl) and closed with a cream colour rubber stopper (bromobutyl/polyisoprene). The cartridge is contained in a pre-filled multidose disposable pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene. Each pen is able to deliver doses of 0,6 mg, 1,2 mg,1,8 mg, 2,4 mg and 3,0 mg.

Each pen is designed to be used with NovoFine® or NovoTwist® disposable needles of a length of 4 – 8 mm and a thickness of 30 – 32G.

The pen(s) is/are packed in hard cardboard paper
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.

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.

For detailed instructions for use, see the *Instructions for use of pre-filled pen-Patient Information Leaflet.*

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg

2196

8 REGISTRATION NUMBER(S)

50/21.13/1091

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 March 2020

10 DATE OF REVISION OF THE TEXT

08 February 2022