AUSTRALIAN PRODUCT INFORMATION

SAXENDA®
liraglutide solution for injection

1. NAME OF THE MEDICINE
liraglutide (rys)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
SAXENDA contains liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor (GLP-1R). Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*.

SAXENDA is a solution for injection in a pre-filled pen. One mL contains 6 mg salt-free anhydrous liraglutide. One pre-filled pen contains 18 mg liraglutide in 3 mL.
For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
SAXENDA is a solution for injection. It is a sterile, clear, colourless, isotonic solution, pH=8.15.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
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/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.

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

4.2 Dose and Method of Administration
SAXENDA has not been studied in patients taking insulin. SAXENDA and insulin should not be used together [see section 4.4 Special Warnings and Precautions for Use].

SAXENDA and VICTOZA both contain the same active ingredient, liraglutide, and therefore should not be used together. SAXENDA should not be used in combination with any other GLP-1 receptor agonist.

Dosage
The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg 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	0.6 mg	1
	1.2 mg	1
	1.8 mg	1
	2.4 mg	1
Maintenance dose	**3.0 mg**	

The need for continued treatment should be re-evaluated whenever a new prescription is written and at least annually.

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. SAXENDA pen is for use by one person only. It should be injected in the abdomen, thigh or upper arm. Injection sites should always be rotated within the same region in order to reduce the risk of cutaneous amyloidosis [see section 4.8 Adverse Effects (Undesirable effects)]. 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.

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.

SAXENDA should not be mixed with other injectable medicinal products (e.g. infusion fluids [see section 4.4 Special Warnings and Precautions for Use]).

Dosage Adjustment

Patients with type 2 diabetes

When initiating SAXENDA, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia [see section 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (Undesirable effects)].

SAXENDA is not a substitute for insulin.

Specific patient groups

Elderly (> 65 years old)

No dose adjustment is required based on age. Therapeutic experience with patients ≥75 years of age is limited and use in these patients is not recommended. SAXENDA should be used with caution in patients aged 65-74 years. [See section 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties.]

Patients with hepatic impairment

SAXENDA is not recommended in patients with hepatic impairment [see section 4.4 Special Warnings and Precautions for Use].

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 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties].

Children and adolescents
The safety and efficacy of SAXENDA in children and adolescents below 18 years of age have not been established [see section 5.1 Pharmacodynamic Properties]. No data are available. SAXENDA is not indicated for use in paediatric patients.

Special precautions for disposal and other handling
SAXENDA 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 disposable needles up to a length of 8 mm. Injection needles are not included.

The patient should be advised to discard the injection needle after each injection and store the pen without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

4.3 Contraindications
SAXENDA is not to be used in patients with hypersensitivity to liraglutide or any of its excipients.

4.4 Special Warnings and Precautions for Use

General
- SAXENDA must not be used as a substitute for insulin in patients with diabetes mellitus.
- SAXENDA and insulin should not be used together. SAXENDA has not been studied in patients taking insulin.
- SAXENDA is not indicated for the treatment of type 2 diabetes mellitus.
- SAXENDA is not indicated in patients with obesity secondary to endocrinological or eating disorders or to treatment with medicinal products that may cause weight gain.
- SAXENDA is not recommended in combination with other medicinal products intended for weight loss, including prescription medicines, over-the-counter medicines, and complementary medicines/herbal preparations. Efficacy and safety have not been established.

Aspiration in association with general anaesthesia or deep sedation
Cases of pulmonary aspiration have been reported in patients receiving GLP-1 RAs undergoing general anaesthesia (GA) or deep sedation despite reported adherence to preoperative fasting recommendations. Therefore, the increased risk of residual gastric content because of delayed gastric emptying should be considered prior to performing procedures with GA or deep sedation.

Cardiovascular events

Increase in heart rate
An increase in heart rate with SAXENDA was observed in clinical trials [see section 4.8 Adverse Effects (Undesirable effects)].

Heart rate should be monitored at regular intervals consistent with good 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 sustained increase in resting heart rate, SAXENDA should be discontinued.

The effect on the heart rate of co-administration of SAXENDA with other medicines that increase heart rate (e.g., sympathomimetic drugs) has not been evaluated. Consequently, co-administration of SAXENDA with these medicines should be undertaken with caution.

Dehydration, renal impairment and acute renal failure
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.

In patients treated with GLP-1 receptor agonists, including liraglutide, there have been reports of acute renal injury/failure and worsening of chronic renal failure, sometimes requiring haemodialysis [see section 4.8 Adverse Effects (Undesirable effects)]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, and diarrhoea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function and volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Use caution when initiating or escalating doses of SAXENDA in patients with renal impairment.

Use in hepatic impairment
The safety and efficacy of SAXENDA in patients with hepatic insufficiency has not been studied. SAXENDA is not recommended in patients with hepatic insufficiency.

Use in renal impairment
The safety and efficacy of SAXENDA in patients with severe renal impairment have not been established. SAXENDA is not recommended for use in patients with severe renal impairment, including end-stage renal disease.

Use in the elderly
In SAXENDA clinical trials, 232 (6.9%) of the SAXENDA-treated patients were 65 years of age and over, and 17 (0.5%) of the SAXENDA treated patients were 75 years of age and over. Patients ≥65 years may experience more gastrointestinal adverse reactions with SAXENDA than younger patients [see sub-sections above in section 4.4 Special Warnings and Precautions for Use on Dehydration, renal impairment and acute renal failure]. No overall differences in safety or effectiveness were observed between these patients and younger patients. Use caution in patients aged 65-74 years. SAXENDA is not recommended in patients 75 years or older.

Paediatric use
The efficacy and safety of SAXENDA have not been studied in paediatric patients. SAXENDA is not indicated for use in paediatric patients.

Pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. After initiation of SAXENDA, observe patients carefully for signs and symptoms of pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, SAXENDA should be discontinued and appropriate management initiated. If acute pancreatitis is confirmed, SAXENDA should not be restarted.

In SAXENDA clinical trials, acute pancreatitis was confirmed by adjudication more commonly in SAXENDA-treated patients versus placebo-treated patients [see section 4.8 Adverse Effects (Undesirable effects)].

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

SAXENDA is not recommended for use in patients with a history of pancreatitis.

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 the SAXENDA clinical trials, cholelithiasis or cholecystitis was reported more commonly in SAXENDA-treated patients than in placebo-treated patients [see section 4.8 Adverse Effects (Undesirable effects)]. The majority of SAXENDA-treated patients with cholelithiasis or cholecystitis required cholecystectomy. Substantial or rapid weight loss can increase the risk of acute gallbladder disease; however, the incidence was greater in SAXENDA-treated patients versus placebo-treated patients even after accounting for weight loss. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis.

Inflammatory bowel disease and diabetic gastroparesis

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis. SAXENDA is not recommended in these patients because it is associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Hypoglycaemia with concomitant use of anti-diabetic therapy

The risk of serious hypoglycaemia is increased when SAXENDA is used in combination with insulin secretagogues (e.g. sulfonylureas) in patients with type 2 diabetes [see Table 2 in section 4.8 Adverse Effects (Undesirable effects)]. The risk of hypoglycaemia can be lowered by a reduction in the dose of sulfonylurea.

The addition of SAXENDA in patients treated with insulin has not been evaluated. The SCALE-Diabetes trial excluded patients on insulin [see section 5.1 Pharmacodynamic Properties-Clinical trials]. SAXENDA and insulin should not be used together.

SAXENDA can lower blood glucose. Monitor blood glucose parameters before starting SAXENDA and during SAXENDA treatment in patients with type 2 diabetes. If needed, adjust co-administered anti-diabetic medicines based on glucose monitoring and risk of hypoglycaemia.

Malignancies

In the clinical development program for weight loss, there was no imbalance for all neoplasms, combined. However, when subgroup analyses were done by individual types of cancer,

imbalances were identified, including invasive breast cancer in women and colorectal neoplasms (mainly adenomas) [see section 4.8 Adverse Effects (Undesirable effects)].

Thyroid C-cell tumours
Liraglutide caused thyroid C-cell adenomas and carcinomas in two-year studies in mice and rats. Such medullary thyroid cancers are extremely rare cancers in humans. C-cell neoplasia was observed in mice at subcutaneous doses ≥1mg/kg/day (relative exposure based on plasma AUC, ≥8) and in rats at all doses tested (≥0.075mg/kg/day subcutaneously; relative exposure, ≥0.5). No tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months (≤5 mg/kg/day subcutaneously; relative exposure, ≤70). The findings in mice and rats are mediated by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot presently be completely excluded.

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. Cases of increased blood calcitonin were also observed in the weight management clinical trials. SAXENDA should be used with caution in patients with thyroid disease.

Hypersensitivity reactions
There have been reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide. If a hypersensitivity reaction occurs, then the patient should discontinue SAXENDA and other suspect medicines and promptly seek medical advice.

Angioedema has been reported with other GLP-1 receptor agonists. Do not use SAXENDA in patients with a history of angioedema with another GLP-1 receptor agonist because such patients may be predisposed to angioedema with SAXENDA.

Suicide behaviour and ideation
Suicidal behaviour and ideation have been reported with GLP-1 receptor agonists. Patients treated with SAXENDA should be monitored for the emergence of depression, suicide thoughts or behaviour, or any unusual changes in mood or behaviour. Discontinue SAXENDA in patients who experience suicidal thoughts or behaviours or who develop other symptoms of depression [see section 4.8 Adverse Effects (Undesirable effects)].

Patients with a history of major depressive disorder or other major psychiatric disorder were excluded from the SAXENDA clinical trials. Because of the lack of data on efficacy and safety in patients with a history of major depressive disorder or other major psychiatric disorder, SAXENDA is not recommended in these patients.

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicines and Other Forms of Interactions
No clinically significant drug interactions have been demonstrated with SAXENDA.

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

In vivo assessment of drug-drug interaction

The drug-drug interaction studies were performed at steady state with liraglutide 1.8 mg/day. The effect on rate of gastric emptying (paracetamol AUC_{0-5h}) was equivalent between liraglutide 1.8 mg and 3.0 mg [see section 5.1 Pharmacodynamic Properties]. Administration of the interacting drugs was timed so that C_{max} of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Oral Medications

The delay of gastric emptying caused by liraglutide may impact absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption of the compounds that were studied, however clinically relevant interactions with other compounds where the effect is dependent on C_{max} and t_{max}, drugs with narrow therapeutic index, or medications associated with local gastrointestinal irritation (e.g. bisphosphonates, potassium chloride) cannot be excluded.

Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Paracetamol

Liraglutide did not change the overall exposure (AUC) of paracetamol following a single dose of paracetamol 1000 mg, administered 8 hours after the dose of liraglutide at steady state. 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 (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of liraglutide at steady state. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 hour to 3 hours with liraglutide. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide.

Griseofulvin

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

Digoxin

A single dose of digoxin 1 mg was administered 7 hours after the dose of liraglutide at steady state. The concomitant administration with liraglutide resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximum concentration (t_{max}) was delayed from 1 hour to 1.5 hours. No dose adjustment of digoxin is required based on these results.

Lisinopril

A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide at steady state. The co-administration with liraglutide resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median t_{max} was delayed from 6 hours to 8 hours with liraglutide. No dose adjustment of lisinopril is required based on these results.

Oral contraceptives
A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide at steady state. Liraglutide lowered ethinylestradiol and levonorgestrel C_{max} by 12 and 13%, respectively. t_{max} was delayed by 1.5 hours with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the levonorgestrel $AUC_{0-\infty}$ by 18%. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

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.

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

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
No adverse effects on fertility were observed in male and female rats given subcutaneous doses of liraglutide at ≤1mg/kg/day, yielding exposure to liraglutide (plasma AUC) 12-14 times higher than that of patients at the maximum recommended human dose.

Use in pregnancy
Pregnancy Category: B3

Increased embryofetal death and minor fetal skeletal abnormalities (kinked ribs) were observed in rats given liraglutide at 1mg/kg/day by subcutaneous injection (yielding 12-times the plasma AUC in humans at the maximum recommended clinical dose). In rabbits treated at doses ≥0.01mg/kg/day (relative exposure, ≥0.2), there was retardation of fetal growth and an increased incidence of several minor skeletal and visceral abnormalities. Postnatal body weight gain was reduced in the offspring of rats treated with liraglutide during gestation and lactation. These findings may have occurred secondary to reduced maternal food consumption. Placental transfer of liraglutide and/or its metabolites was demonstrated in the animal species.

There are limited data from the use of SAXENDA in pregnant women. SAXENDA should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with SAXENDA should be discontinued.

Use in lactation
It is not known whether liraglutide is excreted in human milk. Studies in lactating rats 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. Due to lack of experience, SAXENDA must not be used during breast-feeding.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Patients with type 2 diabetes should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when SAXENDA is used in combination with a sulfonylurea.

4.8 Adverse Effects (Undesirable effects)

Summary of safety profile

Overall, gastrointestinal reactions were the most frequently reported adverse reactions during treatment with SAXENDA: nausea, vomiting, diarrhoea and constipation reported by > 10% of subjects, see section 'Description of selected adverse reactions' below.

Tabulated summary of adverse reactions

The data below reflect exposure to SAXENDA in four randomised, double-blind, placebo controlled, multicentre Phase 3 clinical trials, one of 32-weeks duration and three of 56-weeks duration, and one Phase 2 supportive trial in 469 adult patients.

In clinical trials, 9.8% of patients treated with SAXENDA prematurely discontinued treatment due to adverse reactions, compared with 4.3% of placebo-treated patients. Adverse reactions reported in greater than or equal to 1% of SAXENDA treated patients and more frequently than in placebo patients are shown in Table 2.

Table 2 Adverse reactions reported in ≥1% of patients on SAXENDA and more frequently than in placebo patients

System Organ Class Preferred Term	**SAXENDA** **N = 3384** **%**	**Placebo** **N = 1941** **%**
Gastrointestinal Disorders		
Nausea	39.3	13.8
Diarrhoea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Dyspepsia	9.6	2.7
Abdominal Pain Upper	5.1	2.7
Abdominal distension	4.5	3.0
Eructation	4.5	0.2
Flatulence	4.0	2.5
Gastroesophageal Reflux Disease	4.7	1.7
Dry Mouth	2.3	1.0
Gastritis	1.4	1.1
Metabolism and Nutrition Disorders		
Hypoglycaemia*	1.6	1.1
General Disorders and Administration Site Conditions		
Injection site reactions	9.0	1.7
Fatigue	7.5	4.6
Asthenia	2.1	0.8
Nervous System Disorders		
Dizziness	6.9	5.0
Dysgeusia	1.6	0.8
Hepatobiliary Disorders		
Cholelithiasis***	1.5	0.5
Psychiatric disorders		
Insomnia**	2.4	1.7
Investigations		
Increased lipase	5.3	2.2
Increased amylase	1.4	0.7

*Hypoglycaemia (based on self-reported symptoms by patients and not confirmed by blood glucose measurements) reported in patients

without type 2 diabetes treated with SAXENDA in combination with diet and exercise. Please see below for further information regarding hypoglycaemia.
** Insomnia was mainly seen during the first 3 months of treatment;
*** See section 4.4 Special Warnings and Precautions for Use

Nervous system disorders: Very common (≥1/10) – headache
Skin and subcutaneous tissue disorders: Common ((≥1/100 to <1/10) – Rash

Less common adverse events in Clinical Trials (<1%)
Adverse reactions are listed by system organ class using the frequency categories uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to < 1/1,000).

Gastrointestinal disorders: Uncommon – pancreatitis, delayed gastric emptying*
Metabolism and nutrition disorders: Uncommon – dehydration
General disorders and administration site conditions: Uncommon – malaise
Hepatobiliary disorders: Uncommon – cholecystitis
Immune system disorders: Rare – anaphylactic reaction
Cardiac disorders: Uncommon – tachycardia
Skin and subcutaneous tissue disorders: Uncommon – urticaria
Renal and urinary disorders: Rare – acute renal failure, renal impairment

*delayed gastric emptying based on clinical trial and post marketing data

Description of selected adverse reactions

Cardiovascular events
Heart rate increase
Mean increases in resting heart rate of 2 to 3 beats per minute (bpm) were observed with routine clinical monitoring in SAXENDA-treated patients compared to placebo in clinical trials. More patients treated with SAXENDA, compared with placebo, had changes from baseline at two consecutive visits of more than 10 bpm (34% versus 19%); and 20 bmp (5% versus 2%). At least one resting heart rate exceeding 100 bpm was recorded for 6% of SAXENDA-treated patients compared with 4% of placebo-treated patients, with this occurring at two consecutive study visits for 0.9% and 0.3%, respectively. Tachycardia was reported as an adverse reaction in 0.6% of SAXENDA-treated patients and in 0.1% of placebo-treated patients [see section 4.4 Special Warnings and Precautions for Use].

In a clinical pharmacology trial that monitored heart rate continuously for 24 hours, SAXENDA treatment was associated with a heart rate that was 4 to 9 bpm higher than that observed with placebo.

Major adverse cardiovascular events
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 there were 6 (0.1%) confirmed MACE for SAXENDA-treated patients and 10 (0.5%) for placebo-treated patients. The hazard ratio and 95% CI was 0.33 [0.12; 0.90] for Saxenda versus placebo. Favourable trends for cardiovascular disease in pre-market trials (that were not powered for this endpoint and who enrolled low-risk patients) did not necessarily provide reassurance of cardiovascular safety.

The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcomes Results (LEADER) study provides some supportive evidence for the use of liraglutide in cardiovascular disease. Extrapolation of the results of LEADER to SAXENDA is to be

performed with caution given that the maintenance dose of SAXENDA is 3.0 mg per day (versus 1.8 mg per day in the LEADER trial), and that the patient population treated in LEADER all had type 2 diabetes mellitus, were of a high CV risk, and were significantly older than SAXENDA patients on average. The duration of exposure to liraglutide 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%. 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%.

Cardiac conduction disorders and PR interval prolongation
A prolongation of the mean PR interval of up to 10 ms was reported with SAXENDA treatment in a clinical trial in healthy volunteers, using lower doses than recommended for weight management.

In SAXENDA clinical trials, the incidence of cardiac conduction disorders (e.g., first degree atrioventricular [AV] block) was higher with SAXENDA than placebo; 11 (0.3%) of 3384 SAXENDA-treated patients compared with none of the 1941 placebo-treated patients had a cardiac conduction disorder [see section 4.4 Special Warnings and Precautions for Use, Cardiac conduction disorders].

Hypoglycaemia in patients without type 2 diabetes
In clinical trials in overweight or obese patients without type 2 diabetes 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
In a clinical trial in overweight or obese patients with type 2 diabetes treated with SAXENDA in combination with diet and exercise, hypoglycaemic events were accompanied by blood glucose measurements and classified accordingly. 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 (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.

Gastrointestinal adverse reactions
In SAXENDA clinical trials, 68% of SAXENDA-treated patients and 39% of placebo-treated patients reported gastrointestinal disorders; the most frequently reported was nausea (39% versus 14%). The percentage of patients reporting nausea declined as treatment continued. Other common adverse reactions that occurred at higher incidence among SAXENDA-treated patients included diarrhoea, constipation, vomiting, dyspepsia, abdominal pain, dry mouth, gastritis, gastroesophageal reflux, flatulence, eructation, and abdominal distension. Episodes of gastrointestinal events leading to discontinuation of therapy were: SAXENDA 6.2% versus placebo: 0.8% [see section 4.4 Special Warnings and Precautions for Use].

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 older than 65 years of age may experience more gastrointestinal effects when treated with SAXENDA [see section 4.4 Special Warnings and Precautions for Use].

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, including liraglutide, there have been reports of acute renal injury/failure and worsening chronic renal failure, sometimes requiring haemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, or diarrhoea leading to volume depletion [see section 4.4 Special Warnings and Precautions for Use]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function and volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide.

Malignancy

Breast cancer
In SAXENDA clinical trials, breast cancer confirmed by adjudication was reported in 17 (0.7%) of 2379 SAXENDA-treated women compared with 3 (0.2%) of 1300 placebo-treated women, including invasive cancer (13 SAXENDA-treated versus 2 placebo-treated women) and ductal carcinoma in situ (4 versus 1). The majority of cancers were estrogen- and progesterone-receptor positive. There were too few cases to determine whether these cases were related to SAXENDA. In addition, there are insufficient data to determine whether SAXENDA has an effect on pre-existing breast neoplasia.

Colorectal neoplasms
In SAXENDA clinical trials, benign colorectal neoplasms (mostly colon adenomas) confirmed by adjudication were reported in 20 (0.6%) of 3291 SAXENDA-treated patients compared with 7 (0.4%) of 1843 placebo-treated patients. Six positively adjudicated cases of malignant colorectal carcinoma were reported in 5 SAXENDA-treated patients and 1 in a placebo-treated patient.

Papillary thyroid cancer
In SAXENDA clinical trials, papillary thyroid carcinoma, confirmed by adjudication, was reported in 8 (0.2%) of 3291 SAXENDA-treated patients compared with no cases among 1843 placebo-treated patients. Four of these papillary thyroid carcinomas were less than 1 cm in greatest diameter and 4 were diagnosed in surgical pathology specimens after thyroidectomy.

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

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

Pancreatitis
Few cases of acute pancreatitis have been reported during long-term clinical trials with liraglutide [See section 4.4 Special Warnings and Precautions for Use]. In SAXENDA clinical trials, acute pancreatitis was confirmed by adjudication in 9 (0.3%) of 3291 SAXENDA-treated patients versus 2 (0.1%) of 1843 placebo-treated patients. In addition, there were 2 cases of acute pancreatitis in SAXENDA-treated patients who prematurely withdrew from the clinical trials, occurring 74 and 124 days after the last dose. There were two additional cases in SAXENDA-treated patients, one during an off-treatment follow-up period within 2 weeks of discontinuing SAXENDA, and one that occurred in a patient who completed treatment and was off treatment for 106 days.

Allergic reactions
Few 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.

Suicidal behaviour and ideation
In the SAXENDA clinical trials, 9 (0.3%) of 3384 SAXENDA-treated patients and 2 (0.1%) of the 1941 placebo-treated patients reported suicide ideation; one of the SAXENDA-treated patients attempted suicide [See section 4.4 Special Warnings and Precautions for Use].

Hypotension

Adverse reactions related to hypotension (i.e., reports of hypotension, orthostatic hypotension, circulatory collapse, and decreased blood pressure) were reported more frequently with SAXENDA (1.1%) compared with placebo (0.5%) in SAXENDA clinical trials. Systolic blood pressure decreases to less than 80 mmHg were observed in 4 (0.1%) SAXENDA-treated patients compared with no placebo-treated patients. One of the SAXENDA-treated patients had hypotension associated with gastrointestinal adverse reactions and renal failure [See section 4.4 Special Warnings and Precautions for Use].
Laboratory Abnormalities

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

Serum Calcitonin
Calcitonin, a biological marker of MTC, was measured throughout the clinical development program [see section 4.4 Special Warnings and Precautions for Use]. More patients treated with SAXENDA in the clinical trials were observed to have high calcitonin values during treatment, compared with placebo. The proportion of patients with calcitonin greater than or equal to 2 times the upper limit of normal at the end of the trial was 1.2% in SAXENDA-treated patients and 0.6% in placebo-treated patients. Calcitonin values greater than 20 ng/L at the end of the trial occurred in 0.5% of SAXENDA-treated patients and 0.2% of placebo-treated patients; among patients with pre- treatment serum calcitonin less than 20 ng/L, none had calcitonin elevations to greater than 50 ng/L at the end of the trial.

Post-marketing adverse effects

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

Gastrointestinal disorders

- Acute pancreatitis, haemorrhagic and necrotising pancreatitis
- Intestinal obstruction*

*Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction

General disorders and administration site conditions

- Allergic reactions: Urticaria, rash and pruritus
- Malaise

Immune system disorders

- Angioedema and anaphylactic reactions

Metabolism and nutrition disorders

- Dehydration resulting from nausea, vomiting and diarrhoea

Renal and urinary disorders

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

Cardiac disorders

- Increased heart rate

Skin and subcutaneous tissue disorders

- Cutaneous amyloidosis

  Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing cutaneous amyloidosis. There may be a potential risk of change in SAXENDA absorption or effect following SAXENDA injections at sites with cutaneous amyloidosis.
- Alopecia

Infections and infestations

- Urinary Tract Infection

Hepatobiliary

- Elevation of liver enzymes

Nervous system disorders

- Dysaesthesia

Eye Disorders

- Non-arteritic anterior ischaemic optic neuropathy (NAION)*

*Cases of NAION have been reported with GLP-1 RAs, including liraglutide. A sudden loss of vision should lead to ophthalmological examination.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

From clinical trials and post-market use of liraglutide, deliberate or accidental administration of doses up to 24 times the recommended maintenance dose (72 mg) have been reported, including one case of a 6-fold overdose (18 mg daily) given for 7 months. These included instances where patients needed hospitalisation either due to severe events of vomiting, nausea and diarrhoea, or as a precaution. In some reports glucose infusion was administered. Severe hypoglycaemia has also been observed. All patients were reported to have recovered from the events without complications.

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

Mechanism of action

Liraglutide is an acylated human GLP-1 analogue with 97% amino acid sequence homology to endogenous human GLP-1. Like endogenous GLP-1, liraglutide binds to and activates the GLP-1R. Liraglutide is relatively stable against metabolic degradation and has a plasma half-life of 13 hours after subcutaneous administration.

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), binding to albumin and enzymatic stability towards the dipeptidyl peptidase (DPP-IV) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half-life.

GLP-1 is a physiological regulator of appetite and food intake and GLP-1R is present in several areas of the brain involved in appetite regulation as well as the intestine. 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 key satiety and decreased key hunger signals. Transient inhibition of gastric emptying was also observed.

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 the expression of genes related to inflammation in aortic tissue. In addition, liraglutide had a beneficial effect on plasma lipids, decreasing plasma triglyceride, total cholesterol, LDL and VLDL, and increasing HDL. Liraglutide did not reduce the plaque size of already established plaques.

Liraglutide lowers body weight through decreased food intake and loss of predominantly fat mass. Liraglutide does not increase 24-hour energy expenditure. Liraglutide affects the four main components of appetite. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption.

Liraglutide also has effects on glucose homeostasis, resulting in lowering of fasting and post-prandial glucose. Liraglutide stimulates insulin secretion, lowers inappropriately high glucagon secretion in a glucose-dependent manner and improves beta-cell function. The mechanism of blood glucose lowering also may involve a minor delay in gastric emptying. [see section 4.5 Interaction with Other Medicines and Other Form of Interactions].

Clinical trials

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

- **SCALE-Obesity and Pre-diabetes (NN8022-1839):** In this trial, a total of 3,731 patients with obesity (BMI ≥30 kg/m^2), or 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 medication/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 this trial assessed body weight loss in all the 3,731 randomised patients (2,590 completers). The 160 week part of this trial assessed time to onset of type 2 diabetes in the 2,254 randomised patients with pre-diabetes (1,128 completers).
- **SCALE-Diabetes (NN8022-1922):** A 56-week trial assessing body weight loss in 846 randomised (628 completers) obese and overweight patients with insufficiently controlled type 2 diabetes (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.
- **SCALE-Sleep Apnoea (NN8022-3970):** 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 (OSA).
- **SCALE-Maintenance (NN8022-1923):** A 56-week trial assessing body weight maintenance and weight loss in 422 randomised (305 completers) obese or overweight patients, with hypertension or dyslipidaemia, after a preceding ≥5% weight loss induced by a low caloric diet.

In all studies, patients received one-on-one instruction for a reduced calorie diet (approximately 500 kcal/day (2090 kJ/day) deficit) and exercise counselling (recommended increase in physical activity of minimum 150 mins/week) that began with the first dose of study medication or placebo and continued throughout the trial.

Body weight

Superior weight loss was achieved with SAXENDA compared to placebo in obese/overweight patients in all groups studied including those with and without pre-diabetes, type 2 diabetes and moderate or severe obstructive sleep apnoea. Across the trial populations, greater proportions of the patients achieved ≥5% and >10% weight loss with SAXENDA than with placebo (Tables 3-5). A significant body weight reduction was also observed in SCALE-Maintenance, where patients had achieved a mean weight loss of 6.0% on a low-calorie diet during a 12 week run-in period prior to treatment with SAXENDA. In SCALE-Maintenance, more patients maintained the weight loss achieved prior to treatment initiation with SAXENDA than with placebo (81.4% and 48.9%, respectively). Specific data on weight loss, responders and time course for all 4 trials are presented in Tables 3-6 and Figures 2-3.

In SCALE-Obesity and Pre-diabetes, patients treated with SAXENDA achieved a greater weight loss, as compared to placebo. The weight loss occurred mainly in the first year. 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 in this trial (Table 3).

Weight loss response after 12 weeks with SAXENDA (liraglutide 3.0 mg) treatment
Early responders were defined as patients who achieved a weight loss of ≥5% after 12 weeks on maintenance dose of SAXENDA (4 weeks of dose escalation and 12 weeks on maintenance dose). In the 56-week part of SCALE-Obesity and Pre-diabetes, 67.5% of the patients achieved ≥5% weight loss after 12 weeks. In SCALE-Diabetes, 50.4% of patients achieved ≥5% weight loss after 12 weeks. With continued treatment with SAXENDA, 86.2% of these early responders achieved a weight loss of ≥5% and 51% achieved a weight loss of ≥10% after one year of treatment. The mean weight loss in early responders who completed 1 year of treatment was 11.2% of their baseline body weight. For patients who achieved a weight loss of <5% after 12 weeks on maintenance dose and completed 1 year of treatment, the mean weight loss was 3.8% after 1 year.

Glycaemic control
Treatment with liraglutide significantly improved glycaemic parameters across sub-populations with normoglycaemia, pre-diabetes and type 2 diabetes.

In the 56-week part of SCALE-Obesity and Pre-diabetes, fewer patients treated with SAXENDA had developed type 2 diabetes 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 SCALE-Obesity and Pre-diabetes, the primary efficacy endpoint was the proportion of patients with onset of type 2 diabetes 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. More patients in the SAXENDA 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). The estimated time to onset of type 2 diabetes for patients treated with SAXENDA 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 was 0.2 for SAXENDA versus placebo.

During the entire 160 week treatment period, HbA_{1c} was lower in the Saxenda group than in the placebo group with a statistically significant estimated treatment difference of -0.21% $[-0.24; -0.18]_{95\%\ C.I}$, p<0.0001 at 160 weeks. After being off treatment for 12 weeks (week 172) a steep increase in HbA_{1c} was observed in the Saxenda group, while a more modest increase was seen in the placebo group. The same pattern was observed with fasting plasma glucose (FPG). During the entire trial FPG was lower with Saxenda than with placebo, and immediately after treatment cessation FPG reversed to baseline level in the Saxenda group, while no change was observed in the placebo group.

In SCALE-Diabetes, 69.2% of obese patients with type 2 diabetes treated with SAXENDA achieved an HbA_{1c}<7% (ADA) target compared to 27.2% for placebo and 56.5% of obese patients with type 2 diabetes treated with SAXENDA achieved an HbA_{1c}≤6.5% (IDF) target compared to 15.0% for placebo.

Cardiometabolic risk factors
Treatment with SAXENDA significantly improved systolic blood pressure, waist circumference and fasting lipids compared with placebo (Tables 3 and 4).

Apnoea-Hypopnoea Index (AHI)

Treatment with SAXENDA significantly reduced the severity of obstructive sleep apnoea as assessed by change from baseline in the AHI compared with placebo (Table 5).

SCALE-Obesity and Pre-diabetes: Weight management in obese and overweight patients with or without pre-diabetes

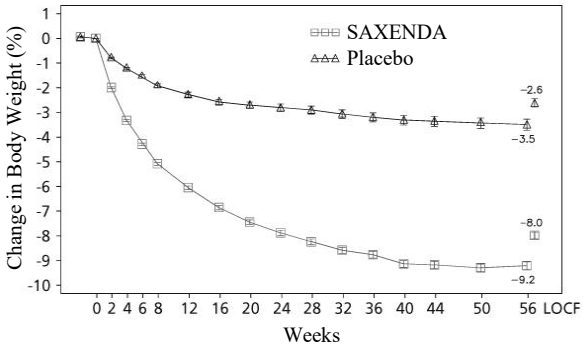


Figure 1: Change from baseline in body weight (%) by time in SCALE-Obesity and Pre-diabetes (0-56 weeks)

Table 3: SCALE-Obesity and Pre-diabetes: Changes from baseline in body weight, glycaemia and cardiometabolic parameters

	Results at week 56					Results at week 160[1]				
	Saxenda (N=2437)		**Placebo (N=1225)**		**Saxenda vs. placebo**	**Saxenda (N=1472)**		**Placebo (N=738)**		**Saxenda vs. placebo**
Body weight										
Baseline, kg (SD)	106.3 (21.2)		106.3 (21.7)		-	107.6 (21.6)		108.0 (21.8)		
Mean change, % (95% CI)	-8.0		-2.6		-5.4** (-5.8; -5.0)	-6.2		-1.8		-4.3** (-4.9; -3.7)
Mean change, kg (95% CI)	-8.4		-2.8		-5.6** (-6.0; -5.1)	-6.5		-2.0		-4.6** (-5.3; -3.9)
Proportion of patients losing ≥5% body weight, % (95% CI)	63.5		26.6		4.8** (4.1; 5.6)	49.6		23.4		3.2** (2.6; 3.9)
Proportion of patients losing >10% body weight, % (95% CI)	32.8		10.1		4.3** (3.5; 5.3)	24.4		9.5		3.1** (2.3; 4.1)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change		Baseline	Change	Baseline	Change	
HbA1c, %	5.6	-0.3	5.6	-0.1	-0.23** (-0.25; -0.21)	5.8	-0.4	5.7	-0.1	-0.21** (-0.24; -0.18)
FPG, mmol/L	5.3	-0.4	5.3	-0.01	-0.38** (-0.42; -0.35)	5.5	-0.4	5.5	0.04	-0.4** (-0.5; -0.4)
Systolic blood pressure, mmHg	123.0	-4.3	123.3	-1.5	-2.8** (-3.6; -2.1)	124.8	-3.2	125.0	-0.4	-2.8** (-3.8; -1.8)
Diastolic blood pressure, mmHg	78.7	-2.7	78.9	-1.8	-0.9* (-1.4; -0.4)	79.4	-2.4	79.8	-1.7	-0.6 (-1.3; 0.1)
Waist circumference, cm	115.0	-8.2	114.5	-4.0	-4.2** (-4.7; -3.7)	116.6	-6.9	116.7	-3.4	-3.5** (-4.2; -2.8)
Lipids										
Total cholesterol, mmol/L	5.0	-3.2%	5.0	-0.9%	-2.3** (-3.3; -1.3)	5.0	-2.9%	5.1	-1.2%	-1.8* (-3.3; -0.2)
LDL cholesterol, mmol/L	2.9	-3.1%	2.9	-0.7%	-2.4* (-4.0; -0.9)	2.9	-4.6%	3.0	-2.6%	-2.0 (-4.3; 0.4)
HDL cholesterol, mmol/L	1.3	2.3%	1.3	0.5%	1.9* (0.7; 3.0)	1.3	4.9%	1.3	3.9%	1.0 (-0.6; 2.7)
Triglycerides, mmol/L	1.4	-13.6%	1.5	-4.8%	-9.3** (-11.5; -7.0)	1.5	-11.7%	1.5	-5.91%	-6.2** (-9.4; -2.9)

[1]Changes from baseline in body weight, glycaemia and cardiometabolic parameters at week 160 in patients with pre-diabetes at randomisation

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at weeks 56 and 160 are estimated means (least-squares) and treatment contrasts at weeks 56 and 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 weeks 56 and 160 are relative changes, and treatment contrasts at weeks 56 and 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.

SCALE-Diabetes: Weight management in obese and overweight patients with type 2 diabetes

Table 4: SCALE-Diabetes 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	
HbA1c, %	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)
Lipids					
Total cholesterol, mmol/L	4.4	-1.4%	4.4	2.3%	-3.6* (-6.3; -0.8)
LDL cholesterol, mmol/L	2.2	0.8%	2.2	3.1%	-2.2 (-7.0; 2.8)
HDL Cholesterol, mmol/L	1.2	4.8%	1.2	2.0%	2.8* (0.2; 5.3)
Triglycerides, mmol/L	1.8	-14.6%	1.8	-1.1%	-13.7** (-19.5; -7.4)

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. For lipids, baseline values are geometric means, changes from baseline at week 56 are relative changes, and treatment contrasts at week 56 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.

SCALE-Sleep Apnoea: Weight management in obese patients with moderate or severe obstructive sleep apnoea

Table 5: SCALE-Sleep Apnoea 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, %	-5.7		-1.6		-4.2** (-5.2; -3.1)
Mean change at week 32, kg	-6.8		-1.8		-4.9** (-6.2; -3.7)
Proportion of patients losing ≥5% body weight at week 32, %	46.4		18.1		3.9** (2.4; 6.4)
Proportion of patients losing >10% body weight at week 32 %	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 intervals. SD=standard deviation.

SCALE-Maintenance: Weight loss in obese and overweight patients with at least one comorbid condition after initial ≥5% weight loss on low caloric diet

Table 6: SCALE-Maintenance: 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 intervals. SD=standard deviation.

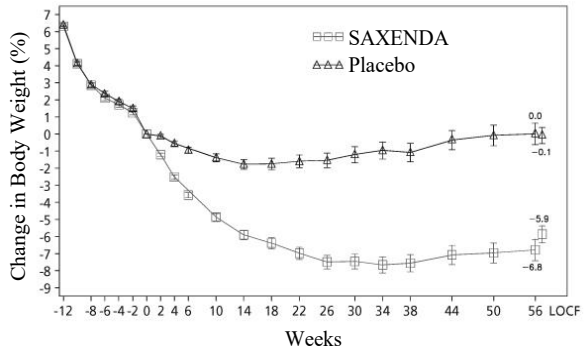


Figure 2 Change from randomisation (week 0) in body weight (%) during SCALE-Maintenance
Note: Before week 0 patients were only treated with low-calorie diet and exercise. At week 0 patients were randomised to receive either SAXENDA or placebo.

Concomitant medication
SAXENDA was more likely than placebo to reduce the use of antihypertensive and lipid lowering drugs after one year of treatment and in patients with type 2 diabetes, SAXENDA was also more likely than placebo to reduce the use of oral antidiabetic drugs after one year of treatment.

Patient reported outcomes
SAXENDA improved several patient reported outcomes compared to placebo. Significant improvements were seen in the IWQoL-Lite total score (SCALE-Obesity and Pre-diabetes and SCALE-Diabetes) and in all domains of the SF-36 (SCALE-Obesity and Pre-diabetes), indicating favourable effects on physical function and mental health.

Pharmacodynamics
In long term clinical trials involving overweight and obese patients SAXENDA, in conjunction with reduced calorie intake and increased physical activity, significantly lowered body weight.

Distribution of weight loss
In a sub-study of obese (BMI 30-40 kg/m2), non-diabetic patients, DEXA analysis and CT scans were performed at baseline and at Week 20 for 15 patients on SAXENDA and 14 patients on placebo. In the sub-study, weight loss was predominantly from fat mass rather than from lean body mass for both treatment groups. Mean visceral and subcutaneous adipose tissue area was reduced after 20 weeks of treatment compared to baseline. Moreover, with SAXENDA, relative reductions in visceral fat were greater than in subcutaneous fat.

Effects on appetite sensations, calorie intake and energy expenditure, gastric emptying, and fasting and postprandial glycaemia
A five week clinical pharmacology trial was conducted in 49 obese (BMI 30-40 kg/m^2) non-diabetic patients to investigate the pharmacodynamic effects of liraglutide.

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

Gastric emptying
SAXENDA caused a minor delay in gastric emptying during the first hour after the meal, thereby reducing the rate as well as the total level of postprandial glucose that appeared in the circulation.

Fasting and postprandial glucose, insulin and glucagon
Fasting and postprandial glucose, insulin and glucagon concentrations were assessed before and up to five hours after a standardised meal test. Compared to placebo, SAXENDA 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, SAXENDA decreased postprandial glucagon ($AUC_{0\text{-}300\ min}$) and 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 56 weeks of treatment in 3,731 overweight and obese patients with and without pre-diabetes [See section 5.1 Pharmacodynamic Properties-Clinical trials, SCALE-Obesity and Pre-diabetes]. Compared to placebo, SAXENDA reduced fasting and incremental glucose concentrations (Figure 1). The effect was more pronounced in patients with pre-diabetes. In addition, SAXENDA 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 SAXENDA, while on treatment, but remained unchanged with placebo. Additionally, post-challenge insulin AUC remained relatively stable with SAXENDA during the 160-week treatment period, while declining in the placebo group. The estimated treatment effects were all statistically significant in favour of SAXENDA.

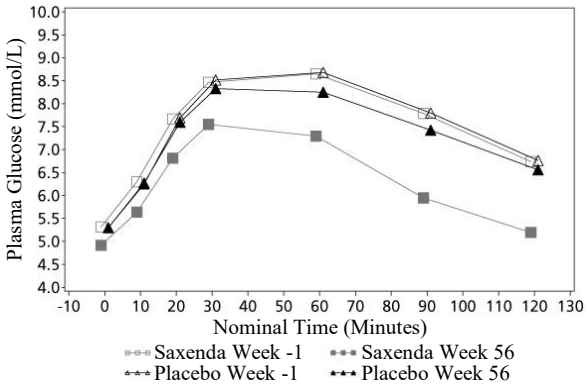


Figure 3: Oral glucose tolerance test - plasma glucose at week -1 and one-year – mean plot – Full Analysis Set

Effects on fasting and postprandial glucose increment in overweight and obese patients with type 2 diabetes
SAXENDA reduced fasting glucose and mean postprandial glucose increment (90 minutes after the meal, average over 3 daily meals), compared to placebo.

Beta-cell function
Clinical studies up to 52 weeks with SAXENDA in overweight and obese patients with and without diabetes mellitus have shown a durable secretagogue effect, as well as improvements from baseline in the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio.

Cardiac Electrophysiology (QTc)
In a cardiac repolarisation study, liraglutide at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation. The liraglutide exposure for overweight and obese subjects treated with SAXENDA is comparable to the exposure evaluated in the liraglutide QTc study.

5.2 Pharmacokinetic Properties

Absorption
The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration approximately 11 hours post dosing. The average steady state concentration of liraglutide ($AUC_{\tau/24}$) 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 to 3.0 mg. SAXENDA can be administered subcutaneously in the abdomen, thigh, or upper arm.

Distribution
The mean apparent volume of distribution after subcutaneous administration of a liraglutide 3.0 mg is 20-25 L (for a person weighing approximately 100 kg). The mean volume of distribution after intravenous administration of liraglutide is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

Metabolism/biotransformation
During the 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).

Excretion

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.

The apparent clearance following sub-cutaneous 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 subjects (18 to 82 years).

Gender

Based on results of population pharmacokinetic analyses, females have 24% lower weight adjusted clearance of liraglutide 3.0 mg compared to males. Based on the exposure response data, no dosage adjustment is required based on gender.

Ethnicity

No dosage adjustment is required based on ethnicity. Ethnicity had no clinically relevant effect on the pharmacokinetics of liraglutide 3.0 mg based on the results of a population pharmacokinetic analysis which included overweight and obese patients.

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 exposure 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 were evaluated in subjects with varying degrees of hepatic impairment in a single-dose trial (0.75 mg). Liraglutide exposure was decreased by 23% and 13% in subjects with mild or moderate hepatic impairment respectively, compared to healthy subjects. Exposure was significantly lower (44%) in subjects with severe hepatic impairment (Child Pugh score >9).

Renal impairment

Liraglutide exposure was mildly reduced in subjects 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 subjects 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.

Paediatrics

SAXENDA has not been studied in paediatric subjects.

5.3 Preclinical Safety Data

Genotoxicity
Liraglutide was not mutagenic in the bacterial Ames assay, and not clastogenic in human lymphocytes *in vitro*, or in rat lymphocytes and bone marrow *in vivo*.

Carcinogenicity
Refer to 4.4 Special Warnings and Precautions for Use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each mL of SAXENDA contains the following inactive ingredients: 1.42 mg dibasic sodium phosphate dihydrate, 14.0 mg propylene glycol, 5.5 mg phenol, hydrochloric acid q.s., sodium hydroxide q.s. and water for injections to 1 mL

6.2 Incompatibilities

Substances added to SAXENDA may cause degradation of liraglutide. SAXENDA must not be mixed with other medicinal products, e.g. infusion fluids.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store in a refrigerator (2°C to 8°C). Keep away from the cooling element. Do not freeze SAXENDA and do not use SAXENDA if it has been frozen.

After first use of the SAXENDA pen, the product can be stored for 1 month at room temperature (below 30°C) or in a refrigerator (2°C to 8°C).

Keep the pen cap on when the SAXENDA pen is not in use in order to protect from light.

SAXENDA should be protected from excessive heat and sunlight.

Always remove the injection needle after each injection and store the SAXENDA pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

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

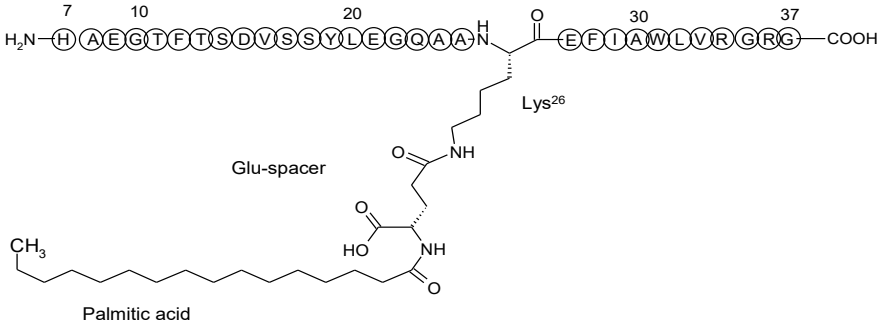
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 Physicochemical Properties

In liraglutide, the lysine at position 34 has been replaced with arginine, and a palmitic acid has been attached via a glutamoyl spacer to lysine at position 26.

Chemical structure

Liraglutide (rys) has the molecular formula $C_{172}H_{265}N_{43}O_{51}$ and a molecular weight of 3751.20 daltons.



CAS number

204656-20-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 10
118 Mount Street
North Sydney NSW 2060
www.novonordisk.com.au

9. DATE OF FIRST APPROVAL

24 December 2015

10. DATE OF REVISION

26 June 2026

Summary table of changes

Section changed	Summary of new information
4.8	Addition of NAION, alopecia and dysaesthesia as post-marketing adverse effects