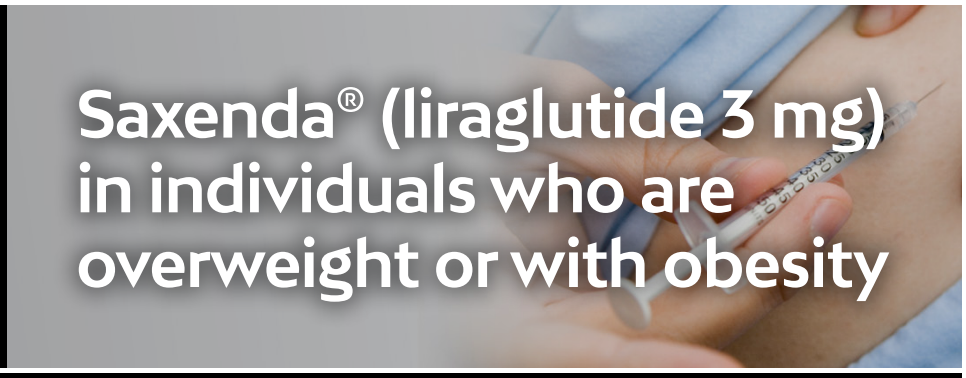
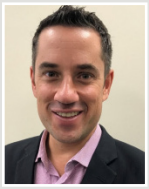
A RESEARCH REVIEW™
PRODUCT REVIEW

Saxenda® (liraglutide 3 mg) in individuals who are overweight or with obesity



Making Education Easy 2021

About the Reviewer



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Ryan is active in research in his roles as a Senior Lecturer at the University of Waikato and as a Clinical Associate of the Maurice Wilkins Centre. He also has a key role in teaching as a member of the Royal Australasian College of Physicians (RACP) New Zealand Endocrinology Advanced Training Subcommittee and leading the Diabetes Nurse Prescribers in New Zealand. Ryan is also a clinical advisor for Diabetes and Exercise and Sports Association (DESA) and Diabetes and Eating Disorder Awareness.

Ryan is the current President of the New Zealand Society of Endocrinology (NZSE) and an Executive Member of the New Zealand Society for the Study of Diabetes (NZSSD). He was awarded the New Zealand Clinical Educator of the Year by the New Zealand Medical Council in 2019.

The increased prevalence of weight gain and obesity has far-reaching consequences for individuals, society, and the economy. Liraglutide 3 mg (Saxenda®), a glucagon-like peptide-1 analogue, is indicated for weight management, as an adjunct to a reduced-calorie diet and increased physical activity, in adult patients with obesity or who are overweight with at least one weight-related comorbidity. This review focusses on the key characteristics of liraglutide 3 mg and provides a summary of the key data from the SCALE clinical trial program in individuals. This review is sponsored by an educational grant from Novo Nordisk.

Introduction

Obesity is a complex and heterogeneous chronic disease that does not present in the same way in all patients and that requires individualised treatment and long-term support like any other complex chronic disease.[1]

Globally, the prevalence of obesity has increased in the last few decades.[2, 3] In 2016, the WHO estimated that more than 1.9 billion adults were overweight, including 650 million with obesity.[4] The New Zealand Health Survey (2019/20) reported that 30.9% of adults (aged 15 years and over) had obesity, with the prevalence of obesity differing by ethnicity. Obesity rates were as high as 63.4% in Pacific Islanders, 47.9% in Māori, and 29.3% in Europeans, with fewer Asian adults being obese (15.9%).[5] The trends in weight gain and obesity have placed a significant burden on individuals, as well as society and the economy.[6-9]

Obesity is directly linked to the development and progression of other co-existing complications including type 2 diabetes, hypertension, dyslipidaemia, coronary artery disease, stroke, heart failure, osteoarthritis, obstructive sleep apnoea, malignancy and an increase in all-cause death.[10, 11] The prevalence of obesity-related comorbidities generally increases as body mass index (BMI) increases.[12]

Weight loss of 5 to 10% has been associated with a significant reduction in obesity-related complications and brings about a reduction in the risk of several co-morbidities.[13-16]

While lifestyle interventions (e.g. changes in eating habits and physical activity) can be effective in achieving weight loss, maintaining the weight loss with lifestyle intervention alone is difficult.[17] Treatment guidelines recommend the consideration of additional therapies such as pharmacotherapy and bariatric surgery when behavioral intervention alone has not achieved sufficient weight loss to improve health-related quality of life (HRQoL).[18, 19]

Currently, four medications are approved for the treatment of obesity in New Zealand and these include liraglutide 3 mg (Saxenda®),[20] orlistat (Xenical®),[21] phentermine (Duromine®),[22] and naltrexone hydrochloride/bupropion hydrochloride (Contrave® 8/90).[23]

This review will focus on the pharmacologic properties, efficacy, and safety profile of liraglutide 3 mg in patients with obesity or who are overweight with at least one weight-related co-morbidity.

Liraglutide 3 mg

The liraglutide 3 mg (Saxenda®) datasheet https://www.medsafe.govt.nz/profs/datasheet/s/saxendainj.pdf should be referred to before prescribing this agent.[20] Saxenda® is not currently listed on the Pharmaceutical Schedule and doctor´s fees and pharmacy charges may apply. A free patient-support programme, SaxendaCare®, is available to doctors and patients in New Zealand (saxendacare.co.nz).The recommended retail price of Saxenda® to pharmacies is $NZ499, with the final price depending on the mark up of the individual pharmacy. The prescription will be for a five-pen pack, which is approximately a one-month supply. This is equivalent to $NZ16.40 daily cost.Pen needles are provided free of charge.

Mechanism of action

Liraglutide 3 mg is an injectable acylated human glucagon-like peptide-1 (GLP-1) analogue, which regulates appetite and energy intake by binding to, and activating, GLP-1 receptors present in the periphery and brain.[20, 24] Liraglutide 3 mg is thought to act in the hypothalamus and other brain regions that regulate appetite, as well as acting directly on the gut, to reduce food intake via vagal signaling and delayed gastric emptying.[20] These actions induce early satiety, increased satiety, reduced hunger, and energy intake.[24, 25]

Indications

Liraglutide 3 mg 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 (obesity),[20] 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.[20]

Treatment with liraglutide should be discontinued if a patient has not lost at least 5% of their initial bodyweight, after receiving liraglutide 3.0 mg/day for 12 weeks.[20]

Dosage and administration

Liraglutide is for subcutaneous use only and it must not be administered intravenously or intramuscularly.[20] Liraglutide can be administered once daily at any time, independent of meals.[20] It should be injected in the abdomen, in the thigh, or in the upper arm.[20] The injection site and timing can be changed without dose adjustment.[20] However, it is preferable that liraglutide is injected around the same time of the day, when the most convenient time of the day has been chosen.[20]

Liraglutide should be initiated at a starting dosage of 0.6 mg once daily (**Figure 1**).[20] 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.[20] 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.

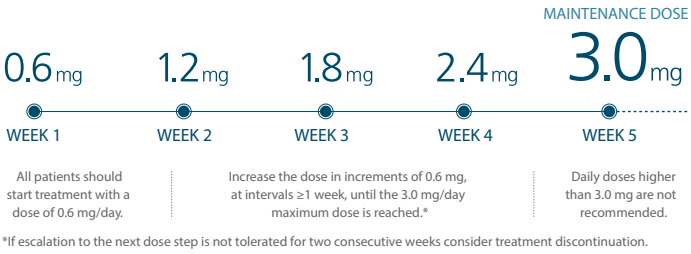

Figure 1. Dose-escalation schedule of liraglutide[20]

Saxenda® is supplied as a pre-filled pen containing liraglutide.[20] 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. Unused pens should be stored between 2°C and 8°C.[20] After the first use of the Saxenda® pen, the product can be stored for 1 month at room temperature (not above 30°C) or in a refrigerator (2 to 8°C).[20] With a Saxenda® prescription, a box of 100 NovoFine needles is provided free of charge with each pack of Saxenda®.

Contraindications

Saxenda® is not to be used in patients with hypersensitivity to liraglutide or any of its excipients.[20]

Other considerations

Since only limited safety data are available, liraglutide should not be used in pregnant women or in breast feeding women. If a patient wishes to become pregnant, or pregnancy occurs, treatment with liraglutide should be discontinued.[20]

Liraglutide has not been studied in children or adolescents aged <18 years, and is not indicated for use in this patient group.[20]

Liraglutide is not recommended in patients with severe renal impairment, hepatic insufficiency, or with a history of major depressive disorder or other major psychiatric disorder.[20]

Liraglutide 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.[20]

Drug interaction profile

In vitro assessment indicates that liraglutide has a very low potential for pharmacokinetic drug–drug interactions related to cytochrome P450 (CYP) and plasma protein binding.[20] No clinically significant drug interactions have been reported with liraglutide and paracetamol, oral contraceptives, digoxin, lisinopril, atorvastatin, griseofulvin, or insulin detemir.[20] No interaction study involving liraglutide and warfarin has been performed, but since a clinically relevant interaction cannot be excluded more frequent monitoring of INR (International Normalised Ratio) is recommended when liraglutide treatment is initiated.[20]

Since liraglutide causes a minor delay in gastric emptying during the first hour after a meal, the absorption of concomitantly administered oral medicinal products may be impacted.[20] 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 the maximum drug concentration and the time to maximum drug concentration, drugs with a narrow therapeutic index, or medications associated with local gastrointestinal irritation (e.g. bisphosphonates, potassium chloride) cannot be excluded.[20]

Pharmacokinetics

The pharmacokinetic properties of liraglutide do not differ when this agent is injected at various subcutaneous sites (abdomen, upper arm, and thigh).[20]

Following subcutaneous administration, the absorption of liraglutide is slow, reaching maximum concentration approximately 11 hours post dosing.[20] Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as a major route of elimination. Its elimination half-life is approximately 13 hours.[20]

Although renal elimination does not appear significant, liraglutide exposure was mildly reduced in subjects with mild-to-severe renal impairment compared to individuals with normal renal function.[20] Liraglutide 3 mg exposure was decreased by 23% and 13% in subjects with mild or moderate hepatic impairment, respectively, compared to healthy subjects, but exposure was significantly lower (44%) in subjects with severe hepatic impairment (Child Pugh score > 9).[20] Race, ethnicity, and gender have no effect on the pharmacokinetics of liraglutide and no dose adjustment is necessary.[20]

Pharmacodynamic properties

Effect on appetite

In clinical studies involving obese individuals, liraglutide reduced appetite and energy intake, but it did not increase 24-hour energy expenditure.[26, 27] Liraglutide regulated appetite by increasing feelings of fullness and satiety, but it reduced feelings of hunger and prospective food consumption.[26, 27]

Effect on glucose homeostasis

Liraglutide improves glucose homeostasis, by reducing fasting and post-prandial glucose by increasing glucose-dependent insulin secretion and decreasing glucose-dependent glucagon secretion.[20] Since the actions of liraglutide are glucose-dependent, it very rarely causes hypoglycaemia when used alone in combination with diet and exercise.

Liraglutide is not registered for the treatment of diabetes mellitus in New Zealand, but may be used to treat obesity in patients with type 2 diabetes.[20] Liraglutide may result in hypoglycaemia in patients with type 2 diabetes treated with insulin and/or sulfonylureas.[28] In these patients, when initiating liraglutide a reduction in dose (e.g. by 15 – 20%) of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) should be considered to reduce the risk of hypoglycaemia.[20] The doses of insulin and sulfonylureas can then be increased if hyperglycaemia persists.

Effect on fat mass

Studies indicate that the reduction in body weight in patients with obesity treated with liraglutide is predominantly due to the reduction in fat mass (including visceral fat and intrahepatic fat) and not lean mass.[20]

Adverse effects

Gastrointestinal reactions were the most frequently reported adverse reactions (reported in more than 10% of patients) during treatment with liraglutide 3 mg in the clinical trials, and include nausea, vomiting, diarrhoea, and constipation.[20]

Most episodes of gastrointestinal reactions were mild to moderate, transient, and the majority did not lead to discontinuation of therapy.[20] Nausea and vomiting usually occurred during the first few 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 liraglutide, so more cautious up-titration of liraglutide may be required in this age group.

Approximately 9% of patients develop injection site reactions, but the vast majority are mild, transient and dissipate on continued treatment.[20] Liraglutide 3 mg may result in hypoglycaemia in patients with type 2 diabetes treated with insulin and/or sulfonylureas that can typically be prevented as discussed above.[20] Liraglutide has

not been studied in patients taking insulin. Therefore, the Saxenda® data sheet advises against concomitant of liraglutide 3 mg and insulin use as a precaution.[20] Serious adverse effects with liraglutide 3 mg, such as anaphylactic reaction are extremely rare.[20]

Practical considerations for managing/preventing adverse events are described more fully in **Table 2**.

Key clinical trials

The efficacy and tolerability of liraglutide 3.0 mg/day was evaluated in the Satiety and Clinical Adiposity — Liraglutide Evidence in nondiabetic and diabetic individuals (SCALE) global clinical trial program, which involved more than 5,000 study participants with obesity (body mass index [BMI] ≥30 kg/m^2) or who were overweight (BMI ≥27 kg/m^2 to <30 kg/m^2) with weight-related comorbidities.[28-32]

In all SCALE studies, patients received instruction for lifestyle intervention including an energy-restricted diet (approximately 500 kcal/day deficit) and exercise counselling (recommended increase in physical activity of minimum 150 mins/week) as adjunct therapy. Liraglutide was initiated at 0.6 mg subcutaneously daily and titrated up 0.6 mg weekly to the target dose of 3.0 mg/day.

Overall, across the SCALE trials, weight reduction from baseline ranged from 5.7% to 8.0% after liraglutide 3.0 mg treatment (with adjunct improved nutrition and physical activity) and from 0.2 to 2.6% with placebo (**Table 1**).[28-32] In addition, significantly more individuals with obesity treated with liraglutide 3.0 mg lost ≥5% of baseline weight than with placebo (**Table 1 and Figure 2**).

SCALE-Obesity and Pre-diabetes[29, 30]

Study design: The Scale-Obesity and Pre-diabetes trial involved 3731 patients with obesity (BMI ≥30 kg/m^2), or who were overweight (BMI ≥27 kg/m^2) with dyslipidaemia and/or hypertension.[29] All patients were randomised to receive 56 weeks of liraglutide 3 mg or placebo to assess body weight loss.[29] Patients with pre-diabetes at screening (n=2254) continued randomised treatment with subcutaneous liraglutide 3 mg versus placebo for a total of 160 weeks after completion of the initial 56-weeks, followed by a 12-week off medication/placebo observational follow-up period.[30] The 160-week (3-year) part of this trial assessed time to onset of type 2 diabetes patients with pre-diabetes.

One year outcomes: At week 56, liraglutide 3 mg recipients lost a mean 8.0% of bodyweight compared with a loss of 2.6% in placebo recipients (p<0.001).[29] Significantly more patients in the liraglutide 3 mg than in the placebo group lost at least 5% of their bodyweight (p<0.001) or more than 10% of their bodyweight (p<0.001) (**Figure 2** and **Table 1**).[29]

Liraglutide 3 mg, compared with placebo, was also associated with improvements in glycaemia and cardio-metabolic risk factors (including blood pressure, waist circumference, and lipid levels; **Table 1**). There were improvements in HRQoL, notably physical function, with liraglutide 3 mg, compared with placebo.[29]

The most frequently reported adverse events with liraglutide were mild or moderate nausea, diarrhoea, and constipation. Serious events occurred in 6.2% of the patients treated with liraglutide 3 mg and in 5% of those receiving placebo.[29]

Three-year outcomes: Among patients with pre-diabetes, liraglutide 3 mg compared with placebo appeared to be beneficial, with an associated 79% reduction in the risk of developing type 2 diabetes (p<0.0001).[30] By week 160 (approximately 3 years), the cumulative probability of a diagnosis of type 2 diabetes was 3% of individuals in the liraglutide 3 mg group compared with 11% in the placebo group.[30] Among all randomised patients, the time-to onset of diabetes over 160 weeks while on treatment was 2.7-times longer with liraglutide than with placebo (p<0.0001).[30] A limitation of the trial was that a large proportion of individuals in both treatment arms withdrew from follow-up.

Weight loss with liraglutide 3 mg treatment was sustained over 3 years. Although the weight loss generally occurred in the first year, the mean percent change in bodyweight (–6.1% vs –1.9%; p<0·0001; **Figure 3**) and the proportions of patients achieving ≥5% (p<0.0001) and >10% (p<0.001) weight loss over the 160 weeks of treatment were also significantly greater with liraglutide 3 mg compared with placebo (**Table 1**).[30] After treatment was stopped at week 160, some weight was regained in the liraglutide 3 mg group (**Figure 3**), although the treatment difference was still significant at week 172 (–3.2%, p<0.0001).[30]

Liraglutide 3 mg was generally well tolerated over the 160-week period, with no new safety signals observed compared with the 56-week initial treatment period.[30]

Figure 2. Patients losing **A)** ≥5% or **B)** >10% of bodyweight across the SCALE clinical trial program

ETD, estimated treatment difference; OR, odds ratio; EOR, estimated odds ratio.

Adapted from Fitch A, Ingersoll AB. Postgrad Med. 2020 Dec 3:1-10.[33]

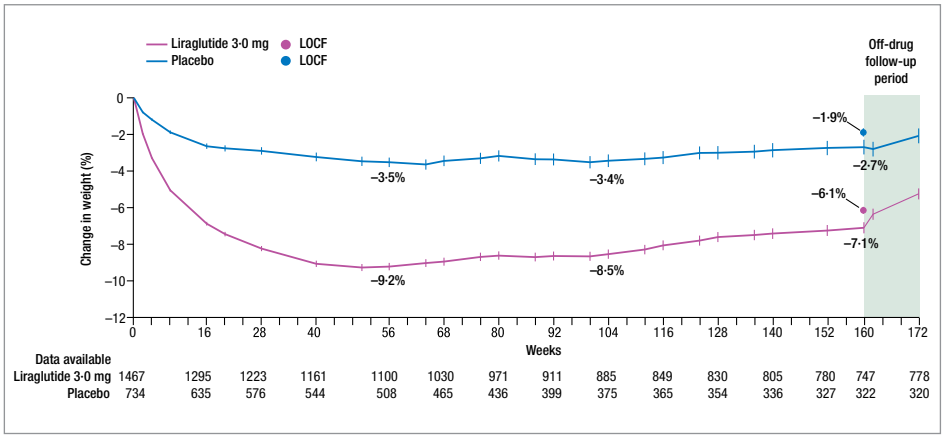

Figure 3. Change from baseline in bodyweight (%) over time in the SCALE-Obesity and Pre-diabetes trial in individuals with prediabetes and a body-mass index of at least 30 kg/m², or at least 27 kg/m² with comorbidities[32, 33]

LOCF, last observation carried forward.

Figure adapted from le Roux CW, et al. Lancet. 2017;389:1399-409.[30]

SCALE–Diabetes[28]

Study design: A 56-week, randomised, placebo-controlled trial assessed body weight loss in 846 (628 completers) patients with obesity or who were overweight with insufficiently controlled type 2 diabetes.[28] At completion of the 56-week treatment phase of the trial, patients entered a 12-week observational off-drug follow-up period.[28] The background treatment at trial start was either diet and exercise alone, metformin, a sulfonylurea, a thiazolidinedione as single agents or any combination hereof.[28]

Study outcomes: At week 56, weight loss was significantly greater with liraglutide 3.0 mg/day than placebo (6.0% [6.4 kg] vs 2.0% [2.2 kg]; p<0.001) (**Table 1**).[28] Weight loss of ≥5% and >10% occurred in significantly more patients treated with liraglutide 3.0 mg than with placebo (p<0.001; **Figure 2**).[28] Of those patients treated with liraglutide 3.0 mg/day, 69.2% achieved an HbA1c <7% and 56.5% an HbA1c ≤6.5% compared with 27.2% and 15%, respectively, in the placebo group.

SCALE– Sleep Apnoea[32]

Study design: This 32-week, randomised, placebo-controlled trial assessed sleep apnoea severity and body weight loss in 359 randomised (276 completers) patients with obesity and moderate or severe obstructive sleep apnoea (apnoea–hypopnoea index [AHI] 15–29.9 events/hour) or severe sleep apnoea (AHI ≥30 events/hour).[32]

Treatment with liraglutide 3.0 mg/day, compared with placebo, significantly reduced the severity of obstructive sleep apnoea as assessed by change from baseline in the AHI (-12.2 vs -6.1 events/hour; p=0.02).[32] Liraglutide 3.0 mg was associated with a greater mean percentage weight loss compared with placebo (–5.7% vs –1.6%; p<0.0001).[32] Greater proportions of liraglutide 3.0 mg versus placebo-treated participants lost either ≥5% or >10% of baseline bodyweight at week 32 (**Table 1; Figure 2**).[32] A *post hoc* analysis demonstrated a statistically significant association between the degree of weight loss and the improvement in obstructive apnoea endpoints (p<0.01).[32]

SCALE–Maintenance[31]

Study design: This 56-week trial assessed body weight maintenance and weight loss in 422 randomised (305 completers) patients with obesity or overweight, with hypertension or dyslipidaemia, after a preceding ≥5% weight loss induced by a low caloric diet.[31]

Study outcomes: During the 56-week treatment period, weight decreased by an additional 6.2% with liraglutide 3 mg and 0.2% with placebo (p<0.0001) (**Table 2**). More participants receiving liraglutide 3 mg (81.4%) maintained the ≥5% weight loss (achieved during the run-in period with the low-calorie diet) than placebo recipients (48.9%; p<0.001). More liraglutide 3 mg than placebo recipients (50.5% vs 21.8%; p<0.001; **Figure 2**) lost >5% of the weight at randomisation during the 56-week maintenance trial. Liraglutide 3 mg was associated with small but statistically significant improvements in several cardio-metabolic risk factors compared with placebo (**Table 2**).

Table 1. Outcomes in the SCALE trial programme involving patients with obesity or overweight treated with liraglutide (LIR) 3.0 mg/day or placebo (PL)

Endpoints[a]	SCALE Obesity and Pre-diabetes [56 weeks][29]		SCALE Obesity and Pre-diabetes[b] [106 weeks][30]		SCALE-Diabetes [56 weeks][28]		SCALE–Sleep Apnoea [32 weeks][32]		SCALE-Maintenance [56 weeks][31]	
	LIR (n=2437)	PL (n=1225)	LIR (n=1472)	PL (n=738)	LIR (n=412)	PL (n=211)	LIR (n=180)	PL (n=179)	LIR (n=212)	PL (n=210)
Bodyweight										
Baseline, kg	106.2	106.2	107.5	108.0	105.7	106.6	116.5	118.7	100.4	98.7
Change from baseline in bodyweight, %	-8.0***	-2.6	-6.1***	-1.9	-6.0***	-2.0	-5.7***	-1.6	-6.2***	-0.2
Lost ≥5% bodyweight, % pts	63.2***	27.1	49.6***	23.7	49.9***	13.8	46.3***	18.5	50.5***	21.8
Lost >10% bodyweight, % pts	33.1***	10.6	24.8***	9.9	23.4***	4.3	23.4***	1.7	26.1***	6.3
Glycaemic endpoints										
HbA1c at baseline, %	5.6	5.6	5.8	5.7	7.9	7.9	5.7	5.6	5.6	5.6
HbA1c change from baseline, %	-0.30	-0.06	-0.35	-0.14	-1.3***	-0.3	-0.4***	-0.2	-0.1***	0.1
Fasting glucose at baseline, mmol/L[c]	5.3	5.3	5.5	5.5	8.8	8.6	5.4	5.4	5.4	5.5
Fasting glucose change from baseline, mmol/L[c]	-0.4***	-0.01	-0.37***	0.05	-1.9***	-0.1	-0.2***	0.2	-0.5***	-0.2
Blood pressure (BP)										
Systolic BP at baseline, mm Hg	123.0	123.2	124.7	125.0	128.9	129.2	125.8	127.1	116.6	117.8
Diastolic BP at baseline, mm Hg	78.7	78.9	79.4	79.8	79.0	79.3	81.2	82.2	74.2	75.9
Change from baseline in systolic BP, mm Hg	-4.2***	-1.5	-3.2***	-0.5	-2.8*	-0.4	-3.4***	0.0	0.2**	2.8
Change from baseline in diastolic BP, mm Hg	-2.6***	-1.9	-2.3	-1.9	-0.9	-0.5	-0.7	-0.4	1.4	1.2
Waist circumference										
Baseline, cm	115.0	114.5	116.5	116.7	118.0	117.3	122.3	122.7	109.4	107.8
Change from baseline, cm	-8.2***	-3.9	-6.9***	-3.4	-6.1***	-2.7	-6.4***	-3.1	-4.7***	-1.2
Fasting lipid profile										
Cholesterol (%)										
Total	-3.1***	-1.0			-1.5**	3.8			0.2	0.3
LDL	-3.0**	-1.0			0.6	5.0			0.2	0.3
HDL	2.3***	0.7			4.7*	1.9			0.2	0.1
VLDL	-13.1***	-5.5			-14.1***	-8.1			-0.2	-0.1
Non-HDL	-5.1***	-1.8								
Triglycerides	-13.3***	-5.5			-14.7***	0.4			0*	0.1
Free fatty acids	1.7**	3.5			-13.6	-9.0			-0.1	-0.1

[a]Mean values unless otherwise stated; [b]Pre-diabetes patients only; [c]Data obtained from the prescribing information.
AHI, apnoea–hypopnea index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.
***p≤0.001, **p≤0.01, *p <0.05 vs placebo.

S-LITE trial[34]

Study design: A randomised, double-blind, placebo-controlled trial in patients with obesity (n=215) who had undergone 8-weeks of a very low calorie diet (800 kcal/day) to induce a body weight loss of ≥5%. Participants were randomised to 1-year of treatment with liraglutide 3.0 mg/day without planned exercise; placebo plus exercise 150 min/week; liraglutide 3.0 mg/day plus exercise 150 min/week; or placebo without planned exercise.[34, 35]

Study outcomes: Following weight loss from a very low calorie diet, a year of regular exercise combined with liraglutide 3 mg was more effective in maintaining weight loss than placebo alone, liraglutide alone, or exercise alone.[34, 35] Over the 1-year study period, weight loss occurred in the liraglutide 3 mg plus exercise arm, with an average reduction in body weight of 3.7 kg ($p<0.001$).[34, 35] Patients in the placebo arm experienced an average increase in body weight of 5.6 kg ($p<0.001$). Those in the liraglutide 3 mg group (without the exercise) had a loss of -1.5 kg over the year, while those in the exercise only group had an increase in weight of 1.5 kg.[34, 35]

Real-world studies

Real-world clinical effectiveness of liraglutide 3.0 mg, in combination with diet and exercise, was investigated in Canadian study in patients with obesity (mean BMI 40.68 kg/m^2) attending specialist weight loss clinics.[36] The patients who persisted with treatment for ≥6 months (n=167) had a mean weight reduction of -8.0 kg ($p<0.001$), representing a decrease of 7.1%. Among these individuals, nearly two-thirds (64.1%) lost ≥5% and over one-third (34.5%) lost >10% body weight. However, since this trial was conducted in a specialist care setting, it may not be directly applicable to a primary care setting.

Practical considerations

Practical considerations for the initiation and maintenance of liraglutide 3.0 mg treatment in patients with obesity are shown in **Table 2**, with aspects related to dose titration, managing gastrointestinal adverse events, administration, maintaining adherence, and managing weight reduction expectations being outlined.

Scan this QR code for further information about Saxenda's mechanism of action.

Scan this QR code for further information about how to use Saxenda®.

Expert commentary on the SCALE and real-world studies

The relatively large SCALE randomised, controlled trials (RCTs) show that liraglutide 3 mg daily is an effective and safe weight loss agent in obese and overweight patients, with approximately two thirds and one third of patients losing 5% and 10% of their body weight, respectively, after one year of therapy (SCALE-Obesity and Prediabetes). The mean weight loss of 8.4 kg for obese patients in the SCALE-Obesity and Prediabetes Trial has been confirmed in real world settings (e.g. Canadian study).

Weight loss appears to largely plateau after one year of therapy (SCALE-Obesity and Prediabetes and SCALE-Diabetes), and is maintained over at least three years if liraglutide is continued, with persistent weight loss three months after cessation of therapy versus placebo (SCALE-Obesity and Prediabetes). Liraglutide was also effective in maintaining weight initially lost through lifestyle interventions (SCALE-Maintenance and S-LITE), and was still effective and safe in those with diabetes (SCALE-Diabetes).

Liraglutide-induced weight loss is predominantly loss of visceral fat rather than subcutaneous fat or lean mass, which likely explains, at least in part, the improvements in cardio-metabolic outcomes such as reductions in blood pressure (all SCALE trials), serum LDL, VLDL and triglyceride levels, and progression from prediabetes to type 2 diabetes (SCALE-Obesity and Prediabetes), sleep apnoea events (SCALE-Sleep Apnoea) and improved glycaemic control in type 2 diabetes (SCALE-Diabetes, SCALE-Maintenance).

Treatment with liraglutide is also associated with improved physical and mental quality of life (SCALE-Obesity and Prediabetes). Importantly, liraglutide appears to be tolerated well. Although mild gastrointestinal adverse effects such as nausea are common, serious adverse effects and the need to withdraw treatment were similar in the liraglutide and placebo groups (SCALE-Obesity and Prediabetes and SCALE-Maintenance).

Although there are no direct head-to-head trials, there is a meta-analysis suggesting that liraglutide is a more effective agent in inducing significant weight loss than other available pharmacological agents for obesity in New Zealand, such orlistat and phentermine.[1]

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Table 2. Recommendations for the initiation and maintenance of liraglutide 3 mg in patients with obesity[33]

Aspect of treatment	Practical recommendations
Managing gastrointestinal adverse events(GI AEs)	Remind patients that most gastrointestinal (GI) adverse events tend to be transient and mild to moderate in nature, and do not lead to discontinuation Gradually increasing the dose during escalation may help to minimise the rate of GI AEs. Inform patients that dietary modifications may minimise GI AEs, and that anti-emetics may be prescribed if necessary Discuss reflux precautions (eating smaller meals, not eating 2 hours before bedtime) Recommend that patients increase their water consumption Discuss with patient the steps to follow in the event of missing a dose, as per prescribing information
Administration	Pen does not need to be refrigerated while patients are using it Recommend patients store the pen in a place that they will remember to take it, and that they set a reminder alarm on their phone Provide training on using pens, especially if the individual is new to using a treatment that requires injections
Maintaining adherence	Remind patients that weight-reduction pharmacotherapies are not a 'quick fix', but a long-term option for managing obesity Explain that a 5–10% reduction in weight and management of obesity has many health benefits Discuss the benefits of liraglutide beyond weight reduction, such as the improvement of cardiovascular-associated risk factors
Managing weight reduction expectations	Remind patients of their success and celebrate their accomplishments Show patients a graph of their weight reduction over time and improvement in metabolic markers Remind individuals that when medication is stopped, most patients regain weight over time

Adapted from Fitch A, Ingersoll AB, 2020.

EXPERT CONCLUSION

Liraglutide is an effective and safe adjunct for weight loss when combined with lifestyle intervention and in obese or overweight patients with co-morbidities such as prediabetes, type 2 diabetes, hypertension, obstructive sleep apnoea or dyslipidaemia.

A 3-month trial of liraglutide is useful to determine whether patients will respond to therapy. Treatment can be stopped in those patients who have not achieved at least 5% loss of bodyweight after 3 months, but should ideally be continued for at least 12 months to maximize and maintain weight loss in those that do respond. These patients will typically lose more than 5-10% of their body weight that is associated with clinically significant improvements in their blood pressure, lipid profile, glycaemic control, sleep apnoea and quality of life.

Although mild gastrointestinal side effects are initially common, patients should be reassured that these adverse effects are typically transient and dissipate despite continued treatment. Liraglutide is otherwise well tolerated and should be considered in all obese patients or overweight patients with at least one weight-related comorbidity where lifestyle intervention alone for weight loss has been ineffective.

KEY MESSAGES

- Liraglutide 3 mg (Saxenda®) is a human glucagon-like peptide-1 (GLP-1) analogue that reduces appetite and energy intake
- In the phase III SCALE trials in individuals with obesity or overweight (with or without diabetes), subcutaneous liraglutide 3 mg (as an adjunct to a reduced-calorie diet and increased physical activity) was associated with clinically relevant reductions in bodyweight, with approximately 1 in 3 individuals losing >10% of the baseline bodyweight
- Improvements in bodyweight were maintained after 3 years of liraglutide 3 mg therapy
- Liraglutide 3 mg was associated with simultaneous improvements in cardio-metabolic risk factors (lowered blood glucose levels, decreased blood pressure, lower lipid levels) and improvements in HRQoL
- In people with prediabetes, liraglutide 3 mg was effective in delaying the progression to type 2 diabetes
- In adults with obesity or overweight with moderate to severe obstructive sleep apnoea, liraglutide 3 mg improved AHI scores, which was associated with the reductions in bodyweight
- Liraglutide 3 mg was generally well tolerated, with gastrointestinal events that were mild to moderate and transient being most commonly reported
- In conclusion, liraglutide 3 mg as an adjunct to a reduced-calorie diet and increased physical activity, is a suitable option for chronic bodyweight management in adults with obesity or overweight, including those with diabetes

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