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ADIS DRUG EVALUATION

Liraglutide: A Review of Its Use in the Management of Obesity

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Abstract Globally, obesity has reached epidemic proportions and poses an ever increasing burden from a societal and healthpayer perspective. Although lifestyle interventions are fundamental in its management, in the real world setting most obese or overweight adults require adjunctive pharmacotherapy to achieve clinically relevant reductions in bodyweight (i.e. a ≥5 % reduction). Subcutaneous liraglutide (Saxenda®) 3 mg once daily is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic bodyweight management in adults with an initial body mass index (BMI) of ≥30 kg/m^2 (obese) or a BMI of ≥27 kg/m^2 (overweight) and at least one bodyweight-related comorbidity [e.g. hypertension, dyslipidaemia, type 2 diabetes mellitus or obstructive sleep apnoea (OSA)]. In phase III trials (32 or 56 weeks' duration) in these populations, subcutaneous liraglutide was associated with clinically relevant reductions in fasting bodyweight and was generally well tolerated. Liraglutide was significantly more effective than placebo in terms of reductions in fasting bodyweight and waist circumference, and improvements in some biomarkers of cardiovascular risk. Improvements in bodyweight were maintained after up 2 years of liraglutide therapy. In nondiabetic adults with moderate to severe OSA, liraglutide improved apnoea-hypopnoea index scores at 32 weeks, which was largely driven by significant reductions in bodyweight. In the absence of head-to-head trials, the relative position of individual anti-obesity drugs remains to be fully determined. In the meantime, liraglutide is an emerging option, as an adjunct to a reduced-calorie diet and increased physical activity, for chronic bodyweight management in obese adults and overweight adults with at least one bodyweight-related comorbidity.

Liraglutide in obesity: a summary

Glucagon-like peptide-1 receptor agonist that lowers bodyweight (BW) by reducing calorie intake
Reduces BW to a significantly greater extent than placebo at 56 weeks in obese adults or overweight adults with ≥1 BW-related comorbidity
Significantly higher 5 and 10 % responder rates than placebo (i.e. ≥5 and >10 % reduction in BW)
Maintains BW reductions in the long term (≤2 years)
Improves apnoea-hypopnea index scores [obstructive sleep apnoea (OSA) severity score] in obese adults with moderate to severe OSA; largely driven by significant reductions in BW
Generally well tolerated; most adverse events are of a GI nature, transient and of mild to moderate intensity

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1 Introduction

Obesity is a mainly preventable disease state that has reached epidemic proportions worldwide, with the number of individuals affected more than doubling since 1980 [1]. In 2008, of the more than 1.4 billion adults (aged ≥20 - years) who were overweight [defined by WHO as a body mass index (BMI) of ≥25 kg/m^2], ≈500 million of them were obese (defined by WHO as a BMI of ≥30 kg/m^2) [1]. Obesity is associated with a significant increase in the risk of morbidity, including an increased risk of diabetes mellitus, metabolic syndrome, cardiovascular (CV) disease, musculoskeletal disorders and non-alcoholic fatty liver disease [1–3]. It also associated with an increased risk of mortality at BMIs of >22.5–25 kg/m^2, with this BMI range associated with the lowest mortality rate [4, 5]. Globally, obesity and overweight is estimated to account for ≈3.4 million adult deaths each year, 44 % of the diabetes burden, 23 % of the ischaemic heart disease burden and 7–41 % of certain cancer burdens [1]. At BMIs of ≥25 kg/m^2, there is a 30 % increase in the risk of death for each 5 kg/m^2 increase in BMI, based on a pooled analysis of mortality studies involving ≈900,000 individuals [5]. Reductions in bodyweight have been shown to significantly improve health outcomes and thereby reduce healthcare costs [4, 6]. Indeed a bodyweight loss of 5–10 % is associated with clinically relevant benefits, including reductions in CV risk factors (mainly in those with pre-existing CV risk factors) and the risk of developing type 2 diabetes [4, 6], improvements in health-related quality of life (HRQOL) such as increased physical activity [7] and a reduction in the severity of obstructive sleep apnoea (OSA) [8].

A fundamental part of obesity management is adopting new behavioural approaches, including healthy eating and increased physical activity [1, 4, 6, 9, 10]. Adjunctive options to these lifestyle changes include pharmacotherapy and bariatric surgery (the latter only once all other interventions have failed to achieve meaningful bodyweight reductions in individuals with a BMI of ≥35 kg/m^2 and at least one bodyweight-related comorbidity or with a BMI of ≥40 kg/m^2) [6, 10]. One pharmacological strategy involves targeting the incretin hormone glucagon-like peptide-1 (GLP-1). GLP-1 is a gut derived hormone released from L cells after food intake and exhibits pleiotropic effects throughout the body, including physiological regulation of appetite and calorie intake; GLP-1 levels are reduced in obese patients [11–14].

The exact mechanisms whereby gut-derived endogenous GLP-1 affects the brain are not yet known, although both direct and indirect mechanisms are postulated to be involved in GLP-1-mediated satiation. GLP-1 may act indirectly via stimulation of intestinal vagal afferents, with subsequent actions at satiation centres in the CNS, but also may act directly by entering the brain via the circumventrilcular organs (a region where peptides from the peripheral circulation are not blocked by the blood-brain barrier) to activate CNS nuclei involved in satiation [11–15]. Evidence from animal studies suggests that weight lowering effects of liraglutide are primarily mediated through central effects, specifically via GLP-1 receptors on arcuate nucleus neurons expressing propiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) [16]. Extensive clinical experience has firmly established that GLP-1 receptor agonists (including liraglutide [17]) are associated with significant bodyweight reductions when used as antihyperglycaemic therapy in patients with type 2 diabetes.

This article reviews the pharmacology, efficacy and tolerability of liraglutide (Saxenda®; 3 mg dose) for chronic bodyweight management in obese adults or overweight adults with bodyweight-related comorbidities, such as type 2 diabetes, hypertension or dyslipidaemia. The efficacy of liraglutide (Victoza®; 1.8 mg dose) for the management of hyperglycaemia in patients with type 2 diabetes is well established (reviewed in *Drugs* [17]); discussion of its use in this indication is beyond the scope of this review.

2 Pharmacodynamic Properties

Liraglutide is an acylated GLP-1 analogue that shares 97 % amino acid sequence homology to human endogenous GLP-1 (7–37) [17, 18]. Following subcutaneous administration, liraglutide has a prolonged plasma half-life compared with endogenous GLP-1 (≈13 h vs. 1.5–2 min), with the formation of a heptameric liraglutide structure delaying its absorption from the injection site and providing protection against degradation by dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidases [17, 18].

Like endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenyl cyclase activation via the stimulatory G-protein Gs [11–14]. GLP-1 receptors are widely distributed throughout the body, including in the pancreas, stomach, intestine, lung, kidney, heart, peripheral nervous system and CNS [19]. Activation of GLP-1 receptors triggers several responses, including glucose-dependent stimulation of pancreatic insulin secretion and inhibition of pancreatic glucagon secretion (glucoregulatory effects) and regulation of appetite and calorie intake [11–14]. This section focuses on the effects of liraglutide in reducing bodyweight.

In obese adults with or without type 2 diabetes, short-term liraglutide treatment reduced bodyweight by decreasing calorie intake and improving eating behaviour and

food choices, with no increase in 24-h energy expenditure, [20–23]. For instance, at 5 weeks, the mean estimated energy intake during an ad libutum lunch was significantly reduced (by ≈16 %) in liraglutide 1.8 and 3 mg/day recipients compared with placebo recipients (estimated mean energy intake 3004 and 3024 vs. 3592 kJ; $p \leq 0.003$) [21]. This reduction was reflected in appetite rating scores, with mean ratings, maximum ratings and 15-min postprandial ratings significantly ($p \leq 0.01$) improved for overall appetite, satiety, fullness and 100-prospective food consumption scores in both liraglutide groups compared with the placebo group [21].

After 5 weeks of liraglutide therapy, equivalence was shown between the 1.8 mg and 3 mg doses, and between liraglutide and placebo, in terms of gastric emptying during a 5-h meal test in obese, nondiabetic adults (primary endpoint) [21]. However, there was a significant delay in 1-h gastric emptying with liraglutide 3 mg/day (by 23 % vs. placebo; $p = 0.007$), but not with liraglutide 1.8 mg/day (reduced by 13 % vs. placebo), although the clinical relevance of this slight delay remains to be elucidated.

Liraglutide also improved body fat mass and some anthropometric parameters and biomarkers of cardiovascular risk in patients with type 2 diabetes (reviewed in Drugs [17]). For example, data from the 26-week LEAD-2 and 52-week LEAD-3 trials in patients with inadequately controlled type 2 diabetes indicated that bodyweight loss with liraglutide treatment (±metformin) mainly reflected reductions in fat tissue, with significant ($p < 0.05$) reductions in body fat mass and fat percentage in liraglutide versus glimepiride recipients [24]. Liraglutide-induced bodyweight loss may also be mediated, at least in part, by increases in cardiac natriuretic peptides (CNPs; reduce body fat accumulation by increasing adipocyte lipolysis), with a significant correlation between increased CNP levels and bodyweight loss in patients with type 2 diabetes treated with liraglutide (plus oral antihyperglycaemic drugs) [25]. The effects of liraglutide on bodyweight, cardiometabolic biomarkers and anthropometric parameters in the obesity clinical trial programme are discussed in Sect. 4.

In a thorough corrected QT (QTc) study in healthy volunteers, steady-state concentrations of liraglutide (≤1.8 mg/day) did not produce prolongation of the QTc interval [18]. The maximum plasma concentration in obese and overweight individuals treated with liraglutide 3 mg was similar to that observed in this QTc study [18].

3 Pharmacokinetic Properties

The pharmacokinetic profile of subcutaneous liraglutide did not differ to a clinically relevant extent when different injection sites were used (upper arm, abdomen and thigh) [18, 26]. Following subcutaneous administration, liraglutide is slowly absorbed, with maximum plasma concentrations attained at 11 h. In obese individuals (BMI 30–40 kg/m^2), the average steady-state concentration of liraglutide over a 24-h period was 116 ng/mL following a 3 mg dose of liraglutide. Following subcutaneous administration, the absolute bioavailability of liraglutide is ≈55 % and the mean apparent volume of distribution after a 3 mg dose is 20–25 L (in a 100 kg person). Liraglutide is extensively (>98 %) bound to plasma protein [18, 26].

No specific organ has been identified as a major route of elimination for liraglutide, with its metabolism occurring in a manner similar to that of large proteins [18]. During the 24-h period post administration of a single radiolabelled dose to healthy volunteers, the major component in plasma was unchanged drug. Intact liraglutide was not detected in the urine or faeces, with 6 and 5 % of the administered radioactivity excreted in the urine and faeces as liraglutide-related metabolites during the first 6–8 days. Following a single subcutaneous dose of liraglutide, the mean apparent clearance of the drug is 0.9–1.4 L/h and the elimination half-life is ≈13 h [18].

Age (in adults), gender, race and ethnicity had no clinically relevant effect on the pharmacokinetics of liraglutide, based on results of population pharmacokinetic analyses [18, 26]. In patients with mild, moderate or severe renal impairment or end-stage renal disease, liraglutide exposure was reduced by an average of 35, 19, 29 and 30 %, respectively, compared with healthy individuals [18]. Exposure to liraglutide was reduced by 11, 14 and 42 % in patients with mild, moderate or severe hepatic impairment, respectively, compared with healthy individuals [18]. Local prescribing information should be consulted regarding the use of liraglutide in patients with renal or hepatic impairment (Sect. 6).

Based on in vitro studies, liraglutide has a low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 and plasma protein binding displacement [18, 26]. There are no clinically relevant interactions between steady-state liraglutide (1.8 mg/day) and single doses of digoxin, lisinopril, atorvastatin, acetaminophen, griseofulvin, insulin detemir or oral contraceptives [18, 26].

4 Therapeutic Efficacy

The efficacy of once-daily subcutaneous liraglutide, as an adjunct to an energy-deficit low-calorie diet and exercise counselling, for chronic bodyweight management in adults was established in a 20-week phase II trial in obese patients [27] and in 56-week phase III trials in obese adults (i.e. BMI ≥30 kg/m^2) or overweight adults (i.e. a BMI ≥27 kg/

m^2) with at least one bodyweight-related comorbidity [28–30]. All trials were of a double-blind, multinational design. Results for the NCT01272219 (SCALE Obesity and Prediabetes) [29, 31–34] and NCT01272232 (SCALE Diabetes) [30, 35] phase III trials are currently only available as abstract presentations, with these data supplemented with information from the US FDA briefing document [36]. Discussion focuses on data from phase III trials and the recommended dosage of liraglutide 3 mg/day (Sect. 6). Patients with type 1 or 2 diabetes were excluded from the SCALE Maintenance [28] and SCALE Obesity and Prediabetes [36] trials.

In 56-week phase III trials, coprimary endpoints were evaluated using hierarchical testing [28, 36]. The first coprimary endpoint was the change in fasting bodyweight from baseline; the second (third in the SCALE Maintenance trial) was the proportion of patients achieving a ≥5 % reduction in fasting bodyweight from randomization (i.e. 5 % responders) or, in the SCALE Maintenance trial, the proportion of patients who maintained the ≥5 % reduction in fasting bodyweight achieved during the low-calorie diet run-in period; and, in the SCALE Obese and Pre-Diabetes and the SCALE Diabetes trials, the third coprimary endpoint was the proportion of patients achieving a >10 % reduction in fasting bodyweight from randomization (i.e. 10 % responder rates) [28, 36]. In the SCALE Maintenance trial, patients had to achieve a ≥5 % reduction in fasting bodyweight during the variable length (4–12 weeks) run-in period to be eligible for randomization [28].

OSA is a bodyweight-related comorbidity that is improved with bodyweight reductions. The 32-week, double-blind, multinational, phase III trial (SCALE Sleep Apnoea) in nondiabetic, obese adults who had moderate to severe OSA evaluated the effects of liraglutide 3 mg on OSA severity (primary endpoint), with bodyweight endpoints evaluated as secondary endpoints (abstract presentation) [37]. Moderate and severe OSA were defined as having an apnoea-hypopnoea index (AHI) of 15–29.9 and ≥30 events/h of sleep, respectively. All patients followed an energy-deficit low-calorie diet and received exercise counselling. The primary endpoint was the change in AHI at 32 weeks.

Efficacy data relating to glycaemic efficacy endpoints (e.g. glycated haemoglobin levels, fasting plasma glucose levels, post-load glycaemia, post-load insulin levels and/or insulin sensitivity) are generally not discussed (secondary endpoints). In brief, in 56-week phase III trials, liraglutide 3 mg/day significantly ($p < 0.001$) improved glycaemic control and/or insulin secretion and action compared with placebo in overweight and obese adults without diabetes [28, 29, 33] and in overweight or obese adults with type 2 diabetes (liraglutide ± concomitant oral antihyperglycaemic drugs) [30, 35]. These data are supported by results from the SCALE Sleep Apnoea trial [36, 37].

In the SCALE Obesity and Prediabetes trial, an ongoing primary objective is to determine whether long-term liraglutide 3 mg/day delays the onset of type 2 diabetes in obese patients with prediabetes and in overweight patients with prediabetes and hypertension and/or dyslipidaemia [36]. At 56 weeks, significantly fewer liraglutide than placebo recipients had developed type 2 diabetes (4 vs. 14 events; 0.2 vs. 1.3 events/100 patient-years of exposure; $p = 0.0003$) [33]. In addition, a significantly greater proportion of liraglutide than placebo recipients had reverted to normoglycaemia after 56 weeks' treatment (19.9 vs. 6.9 %; $p < 0.001$) [34].

4.1 Effects on Bodyweight

4.1.1 In Patients Without Diabetes Mellitus

In phase III trials, liraglutide treatment significantly improved bodyweight compared with placebo at 56 weeks, in terms of coprimary endpoints [28, 29], with these data supported by results from the 32-week SCALE Sleep Apnoea trial [37] (secondary endpoints) (Table 1). Reductions in fasting bodyweight (by 6.2 and 8 % with liraglutide 3 mg/day) and 5 and 10 % responder rates all significantly favoured liraglutide treatment over placebo in the SCALE Maintenance [28] and SCALE Obesity and Prediabetes [29] trials (Table 1). Moreover, in the SCALE Maintenance trial, the ≥5 % reduction in fasting bodyweight achieved during the run-in period was maintained at 56 weeks in significantly more liraglutide than placebo recipients (81.4 vs. 48.9 %; odds ratio 4.8; 95 % CI 3.0–7.7; $p < 0.0001$) [coprimary endpoint] [28]. Prespecified sensitivity analyses confirmed that all primary endpoint results were robust, including sensitivity analysis in the per-protocol completer population, a repeated measures analysis and using fasting and non-fasting observations [28].

Patients discontinuing liraglutide treatment experienced an increase in bodyweight during the 12-week follow-up phases of the SCALE Maintenance trial (off-treatment phase) [28] and the SCALE Obesity and Prediabetes trial (liraglutide recipients without prediabetes were re-randomized to liraglutide 3 mg/day or placebo) [29]. In the SCALE Maintenance trial, patients treated with liraglutide during the double-blind phase maintained a 4.1 % reduction in baseline bodyweight at the end of the follow-up phase (week 68; $p < 0.0001$ vs. placebo), whereas placebo recipients had a 0.3 % increase in baseline bodyweight [28]. In the SCALE Obesity and Prediabetes trial, bodyweight gain during the 12-week re-randomized phase was lower in the patients re-randomized to liraglutide than in

Table 1 Efficacy of once-daily liraglutide, as an adjunct to an energy-deficit low-calorie diet and exercise counselling, in reducing bodyweight in obese (BMI ≥30 kg/m^2) and/or overweight (BMI ≥27 kg/m^2) adults participating in double-blind, multinational trials; with the exception of one trial (only in obese patients) [27], all trials were phase III. Results[a] at the primary study timepoint

Study (duration; weeks)	Regimen (mg/day)	No. of pts[a]	Mean BW change (BL) [kg]	↓ in BW (%)	≥5 or >5 % ↓ in BW[b] (% pts)	>10 % ↓ in BW (% pts)
In pts without diabetes mellitus (obese pts or overweight pts with ≥1 bodyweight-related comorbidity[c])						
NCT00422058 (20) [27][d]	LIR 3.0	93	−7.2**[†e] (97.6)		76.1**[†]	28.3
	PL	98	−2.8[e] (97.3)		29.6	2
	ORL 360 (ol)	95	−4.1[e] (96.0)		44.2	9.5
SCALE Maintenance[f] (56) [28]	LIR 3.0	207	−6.0** (100.4)	6.2**[e]	50.5[e] (OR 3.9; 95 % CI 2.4–6.1**)	26.1 (OR 5.3; 95 % CI 2.8–10.1**)
	PL	206	−0.1 (98.7)	0.2[e]	21.8[e]	6.3
SCALE Obesity and Pre-diabetes (56) [29, 31][g]	LIR 3.0	2432	−8.4**[e,h] (106.2)[i]	8.0**[e,h]	63.5[e,h] (OR 4.8; 95 % CI 4.1–5.6**)	32.8 [h] (OR 4.3; 95 % CI 3.5–5.3**)[e]
	PL	1220	−2.8[e, h] (106.2)[i]	2.6[e, h]	26.6[e,h]	10.1[e, h]
In obese or overweight pts with type 2 diabetes						
SCALE Diabetes (56) [35, 36][g]	LIR 1.8	202	(106.1)	4.6**[e,h]	35.0[e] (OR 3.7; 95 % CI 2.2–6.1**)	13.3 (OR 3.8; 95 % CI 1.8–8.4*)
	LIR 3.0	411	(105.6)	5.9**[‡e,h]	49.9[e] (OR 6.8; 95 % CI 4.3–10.7**[‡‡])[j]	22.1 (OR 7.1; 95 % CI 3.5–14.5**[‡]) [j]
	PL	210	(106.7)	2.0[e, h]	12.7[e]	3.9
In obese nondiabetic pts with moderate to severe obstructive sleep apnoea						
SCALE Sleep Apnoea (32) [37][g]	LIR 3.0	180	(117.6)[i]	5.7**[h]	46.4[h] (OR 3.9**)	22.4[h] (OR 19.0**)
	PL	179	(117.6)[i]	1.6[h]	18.1[h]	1.5[h]

BL baseline, *BMI* body mass index, *BW* fasting bodyweight, *LIR* subcutaneous liraglutide, *LSM* least-square mean, *ol* open-label, *OR* odds ratio vs. PL, *ORL* oral orlistat, *PL* subcutaneous placebo, *pts* patients, ↓ indicates reduction

* $p < 0.001$, ** $p \leq 0.0001$ vs. PL, [†]$p \leq 0.0001$ vs. ORL, [‡]$p < 0.01$, [‡‡]$p < 0.001$ vs. LIR 1.8 mg

[a] Analyses conducted in the intent-to-treat (phase II trial) or full analysis set (phase III trials) populations

[b] BW ↓ of ≥5 % [28, 29, 35, 37] or >5 % [27]

[c] Treated or untreated dyslipidaemia and/or treated or untreated hypertension

[d] Only the LIR 3.0 mg/day (approved dosage) data are tabulated; this trial also included LIR 1.2, 1.4 and 1.8 mg/day groups (n = 90–95/group)

[e] Primary or coprimary endpoints, with coprimary endpoints evaluated using a hierarchical testing procedure

[f] To be eligible for randomization, pts had to have achieved ≥5 % ↓ in BW during the variable length (4–12 weeks) low-calorie diet run-in period; a coprimary endpoint was the percentage of pts who maintained the ≥5 % reduction in BW at 56 weeks (81.4 vs. 48.9 % in the LIR vs. PL group; OR 4.8; 95 % CI 3.0–7.7**)

[g] Abstract presentation. In the SCALE Diabetes trial, BL data and, for the most part, results were obtained from the FDA briefing document [36]

[h] Least-square mean

[i] BL BW for all randomized pts (values for individual groups were not reported in the abstract)

[j] BW ↓ of ≥5 % OR for LIR 3 mg vs. 1.8 mg 1.84 (95 % CI 1.29–2.64; $p = 0.0008$); BW ↓ of >10 % OR for LIR 3 mg vs. 1.8 mg 1.85 (95 % CI 1.16–2.95; $p = 0.0099$)

patients switched to placebo (0.7 vs. 2.9 %; $p < 0.0001$) [29].

Mean bodyweight reductions observed at 20 weeks in obese adults participating in a phase II trial (data for 3 mg group shown in Table 1) [27] were sustained after 2 years of treatment in an extension study [38]. At 1 year, mean bodyweight reductions were significantly ($p \leq 0.0001$) greater in the liraglutide 3 mg/day group than in the placebo group (7.8 vs. 2.0 kg) or in the open-label orlistat group (7.8 vs. 3.9 kg) [38]. Significantly ($p \leq 0.001$) more liraglutide 3 mg/day recipients than placebo or orlistat recipients achieved a >5 % (73 vs. 28 and 44%, respectively) or >10 % (37 vs. 10 and 14 %) reduction in bodyweight. At 2 years, mean bodyweight reductions in the liraglutide and orlistat groups were 6.2 and 4.5 kg, with 5 % responder rates of 52 and 29 % ($p < 0.001$) and 10 % responder rates of 26 and 16 % ($p < 0.05$). In this study, double-blind treatment (liraglutide 1.2–3 mg/day or

placebo) was continued until week 52, after which all liraglutide recipients were switched to liraglutide 2.4 mg/day (optimum dosage based on 20-week results) and then to 3.0 mg/day (switched at week 70–96 after 1-year data indicated this was the optimal dosage) [38].

4.1.2 In Patients with Type 2 Diabetes

In the SCALE Diabetes trial, improvements in bodyweight (reduced by 5.9 % with liraglutide 3 mg/day) and the 5 and 10 % responder rates were all significantly better in the liraglutide groups than in the placebo group, with liraglutide 3 mg/day more effective than liraglutide 1.8 mg/day for all of these parameters (Table 1) [35, 36]. During the subsequent 12-week, off-treatment follow-up period (week 56–68), patients in all treatment groups regained some bodyweight [30]. However, at week 68, mean percentage changes from baseline in bodyweight continued to favour liraglutide 3 mg/day treatment over placebo (−4.7 vs. +2.5 %; $p = 0.0002$), with no significant differences between the liraglutide 3 and 1.8 mg/day groups (−4.7 vs. −3.7 %) or between the liraglutide 1.8 mg/day and placebo groups [30].

4.2 Effects on Anthropometric and Cardiometabolic Parameters

Waist circumference is an established surrogate marker for abdominal fat mass (both subcutaneous and intra-abdominal), with increases in waist circumference associated with an increased cardiometabolic risk [39]. Cardiometabolic risk increases in men with waist circumferences of >102 cm and in women with waist circumferences of >88 cm, which correlate with a BMI of ≥30 kg/m^2 [39]. In phase III trials, compared with placebo, liraglutide 3 mg/day was associated with significantly ($p < 0.0001$) greater reductions from baseline to week 56 in waist circumference and BMI in nondiabetic patients [28, 31] and greater ($p < 0.001$) reductions in waist circumference in patients with type 2 diabetes (changes in BMI not reported) [35]. For example, in the SCALE Maintenance trial, mean waist circumference was reduced from baseline by 4.7 cm in the liraglutide group compared with 1.2 cm in the placebo group ($p < 0.0001$; baseline mean 109.4 and 107.8 cm), with respective mean reductions in BMI of 2.1 and 0 kg/m^2 ($p < 0.0001$; baseline mean 36.0 and 35.2 kg/m^2) [28].

At 56 weeks, changes from baseline in systolic blood pressure (SBP), diastolic BP (DBP) and pulse rate were relatively small in all treatment groups in phase III trials [28, 35, 36]; where reported, ≈31 % [28] and 35 % [36] of participants had hypertension at baseline. For example, in the SCALE Maintenance trial, mean SBP was significantly lower at 56 weeks in the liraglutide than placebo group (estimated treatment difference −2.7 mmHg; $p = 0.007$; baseline mean SBP 117.2 mmHg), although there were no significant between-group differences for mean changes in DBP or pulse rate [28]. In the SCALE Diabetes trial, there were significant ($p < 0.05$) differences for changes in SBP [least-square mean (LSM) change −3.0 vs. −0.4 mmHg; baseline ≈130 mmHg] and pulse rate (+2 vs. −1.5 beats/min) between the liraglutide 3 mg/day and placebo groups at 56 weeks, with no significant between-group differences for LSM changes in DBP [35].

There were also minimal changes in lipid parameters from baseline to 56 weeks in all treatment groups in phase III trials, including for total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), very low-density lipoprotein-cholesterol (VLDL-C) and triglycerides [28, 35, 36]. In the SCALE Maintenance trial, there were no significant differences between the liraglutide and placebo groups, except for changes in triglyceride levels (mean change 0 vs. +0.1 mmol/L; $p < 0.05$); ≈30 % of patients had dyslipidaemia at baseline [28]. In the SCALE Obesity and Prediabetes trial, liraglutide recipients experienced statistically significant ($p < 0.05$), improvements from baseline to 56 weeks in all lipid parameters compared with placebo, including in total cholesterol (−3.1 vs. −1.0 %), LDL-C (−3.0 vs. −1.0 %), HDL-C (+2.3 vs. +0.7 %), VLDL-C (−13.1 vs. −5.5 %) and triglyceride (−13.3 vs. −5.5 %) levels; 29.4 % of patients had a medical history of dyslipidaemia at baseline and ≈15 % of patients were taking lipid-lowering drugs [36]. In the SCALE Diabetes trial, liraglutide 3 mg/day significantly ($p < 0.05$) reduced total cholesterol (by 4 %), VLDL-C (by 13 %) and triglycerides (by 14 %) and increased HDL-C (by 3 %) compared with placebo, with no significant between-group differences for changes in LDL-C and free fatty acid levels [35]; 67 % of patients had dyslipidaemia at baseline [36].

Results from the SCALE Obesity and Prediabetes [36] and the SCALE Diabetes [35] trials suggest that liraglutide improves some biomarkers of CV risk. In the SCALE Obesity and Prediabetes trial, mean changes at 56 weeks in high sensitivity C-reactive protein (hsCRP) in the liraglutide and placebo groups were −38 and −10 % and those for adiponectin levels were 11 and 3 % (no p values reported), with no between-group differences for changes in fibrinogen levels and urinary albumin/creatinine clearance ratios [36]. In the SCALE Diabetes trial, treatment with liraglutide 3 mg/day also improved CV biomarkers compared with placebo at 56 weeks [35]. Relative to placebo, mean percentage reductions in hsCRP levels, plasminogen activator inhibitor-1 levels and the urinary albumin/creatinine clearance ratio in the liraglutide 3 mg/day group

were 27, 24 and 20 % (all $p < 0.05$), respectively, and fibrinogen levels increased by 5 % ($p < 0.05$) [35].

4.3 Effects on Obstructive Sleep Apnoea

At 32 weeks, liraglutide treatment improved the AHI score to a significantly greater extent than placebo (LSM decrease −12.2 vs. −6.1 events/h; $p = 0.015$) in the SCALE Sleep Apnoea trial (primary endpoint), largely driven by the significant reductions in bodyweight that occurred during this period (Table 1) [37]. At 32 weeks, there was no significant between-group difference for LSM changes from baseline in total sleep time (23.2 min in the liraglutide group vs. 15.5 min in the placebo group) or the percentage of wake time after sleep onset (−4.6 vs. −2.9 %) [37].

5 Tolerability

Subcutaneous liraglutide 3 mg/day was generally well tolerated in clinical trials discussed in Sect. 4, with most treatment-emergent adverse events (TEAEs) being of mild to moderate intensity and transient [27, 28, 37, 40, 41]. In a pooled analysis of overweight or obese patients participating in five double-blind trials of 32–56 weeks' duration ($n = 3384$ and 1941 in the liraglutide and placebo groups), 9.8 % of liraglutide recipients and 4.3 % of placebo recipients discontinued treatment because of an adverse event [18]. Nausea (2.9 % in the liraglutide group vs. 0.2 % in the placebo group), vomiting (1.7 vs. <0.1 %) and diarrhoea (1.4 vs. 0 %) were the most common TEAEs leading to treatment discontinuation. Most adverse events were of a gastrointestinal nature. Adverse reactions occurring with an incidence of ≥10 % in liraglutide recipients and with a higher incidence than placebo are summarized in Fig. 1. In this pooled analysis, the mean duration of liraglutide treatment was 45.9 weeks, with 1087 liraglutide recipients and 497 placebo recipients treated beyond the primary endpoint period for an additional mean duration of 53 weeks [18].

Liraglutide reduces blood glucose and thus, there is a potential for hypoglycaemia to occur. In the SCALE Diabetes trial in obese and overweight patients with type 2 diabetes, documented symptomatic hypoglycaemia [plasma glucose <3.9 mmol/L (≤70 mg/dL) and symptoms of hypoglycaemia [18, 40]] rates in the liraglutide 1.8 mg/day, liraglutide 3 mg/day and placebo groups were 0.95, 0.87 and 0.31 events/patient-years' exposure, respectively, with a higher incidence in patients receiving concomitant sulfonylureas compared with those not receiving sulfonylureas [40]. The incidence of documented symptomatic hypoglycaemia with liraglutide 3 mg/day or placebo was 43.6 and 27.3 % in patients taking a concomitant sulfonylurea, with respective rates in patients not taking a concomitant sulfonylurea of 15.7 and 7.6 % [18]. Severe hypoglycaemia (i.e. hypoglycaemia requiring the assistance of another person) occurred in 0.7 % of patients in the liraglutide 3 mg/day group (five events in three patients, all of whom were taking concomitant sulfonylureas) and no patients in the placebo group [18, 40]. As per-protocol, the dosage of sulfonylureas was reduced by 50 %

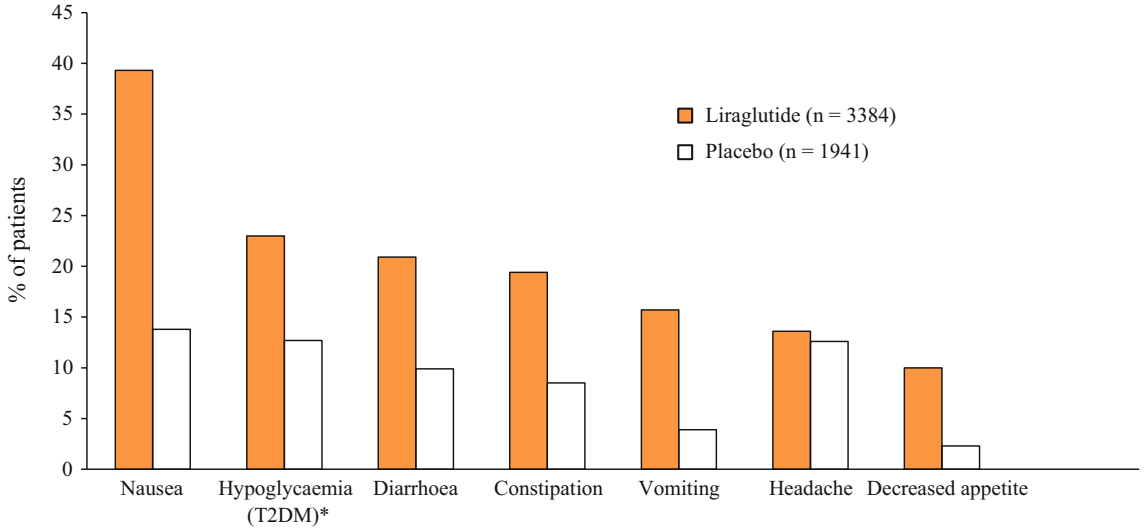

Fig. 1 Adverse reactions reported in ≥10 % of liraglutide recipients and with a higher incidence than with placebo in a pooled analysis of five clinical trials in overweight or obese adults [18]. *Documented symptomatic hypoglycaemia in patients with T2DM (SCALE Diabetes trial); there was no systematic capturing or reporting of these events in nondiabetic patients. *T2DM* type 2 diabetes mellitus

at the beginning of this study [18]. In clinical trials in nondiabetic patients, there was no systematic capturing or reporting of hypoglycaemia, as patients were not provided with blood glucose metres or hypoglycaemia diaries [18]. Spontaneously reported symptomatic episodes of unconfirmed hypoglycaemia occurred in 1.6 % of liraglutide recipients ($n = 2962$ evaluable) versus 1.1 % of placebo recipients ($n = 1729$), with 3.1 and 0.8 % of patients reported as having hypoglycaemia (irrespective of symptoms), based on fasting blood glucose values of ≤70 mg/dL in samples collected at routine clinic visits [18].

Overall, injection-site reactions occurred in ≈13.9 % of liraglutide recipients versus 10.5 % of placebo recipients [18]. The most common (incidence 1–2.5 %) injection site reactions occurring with a higher incidence in liraglutide than placebo recipients included erythema, pruritus and rash at the injection site, with 0.6 and 0.5 % of patients discontinuing treatment because of injection site reactions [18].

There have been postmarketing reports of acute renal failure in patients receiving GLP-1 receptor agonists, with most of these occurring in patients experiencing nausea, vomiting or diarrhoea leading to volume depletion [18, 26].

Tachycardia occurred in 0.6 % of liraglutide recipients and 0.1 % of placebo recipients in clinical trials [26]. The mean heart rate increased from baseline by 2.5 beats/min (range 1.6–3.6 beats/min) in liraglutide recipients. These increases in heart rate peaked at 6 weeks and most were of mild to moderate intensity and resolved during continued treatment [26]. Heart rate should be regularly monitored during liraglutide treatment [18, 26]. In long-term clinical trials of liraglutide (Saxenda®), six major adverse CV events (MACE; adjudicated by an external independent group) occurred in liraglutide recipients and ten such events occurred in placebo recipients (hazard ratio 0.33; 95 % CI 0.12–0.90) [26].

There have been spontaneous postmarketing reports of acute pancreatitis, including fatal and nonfatal haemorrhagic or necrotizing pancreatitis, in patients treated with liraglutide [18]. In clinical trials in obese and overweight individuals, confirmed acute pancreatitis occurred in 0.3 % of liraglutide recipients ($n = 3291$ evaluable) and 0.1 % of placebo recipients ($n = 1843$), with two additional cases reported in liraglutide recipients who prematurely withdrew from these trials. An additional case occurred during the off-treatment follow-up period within 2 weeks of discontinuing liraglutide therapy. At any timepoint in clinical trials, serum lipase levels of ≥3 × the upper limit of normal (ULN) were reported in 2.1 % of liraglutide recipients and 1.0 % of placebo recipients, with serum amylase levels of ≥3 × ULN occurring in 0.1 % of patients in both groups. The clinical relevance of these elevations is unknown in the absence of signs and symptoms of pancreatitis. When initiating liraglutide treatment, patients should be carefully monitored for signs and symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued and, if pancreatitis is confirmed, liraglutide should not be restarted [18].

In the postmarketing period, there have been reports of cases of medullary thyroid carcinoma (MTC) in patients treated with liraglutide (Sect. 6) [18]. The data in these reports are insufficient to establish or exclude a causal relationship between liraglutide and these cases of MTC. Serum calcitonin, a biological marker of MTC, was routinely measured in individuals participating in the clinical development program, with 1.2 % of liraglutide recipients and 0.6 % of placebo recipients having calcitonin levels ≥2 × ULN [18]. Of interest, there appeared to be no evidence that therapeutic concentrations of liraglutide (0.6–1.8 mg/day) stimulated calcitonin release from human C cells, including in patients with elevated calcitonin levels at baseline, after up to 2 years' treatment, based on longitudinal data from patients with type 2 diabetes and obese subjects without type 2 diabetes participating in randomized clinical trials ($n > 5000$) [42].

Papillary thyroid carcinoma (PTC) confirmed by adjudication was reported in 0.2 % of liraglutide recipients ($n = 3291$ evaluable) and no placebo recipients ($n = 1843$) in clinical trials in obese and overweight individuals [18]. Four of the seven cases of PTC were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings identified prior to treatment [18].

6 Dosage and Administration

In the USA [18], Canada [43] and the EU [26], once-daily subcutaneous liraglutide (3 mg dose; Saxenda®) is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for chronic bodyweight management in adult patients with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one bodyweight-related condition (e.g. hypertension, type 2 diabetes, dyslipidaemia, OSA); in Canada [43], individuals in the latter overweight category also have to have failed a previous weight management intervention.

The initial recommended dosage of liraglutide is 0.6 mg once daily for 1 week, with the dose increased by 0.6 mg at weekly intervals until a dosage of 3 mg/day is attained [18, 26]. Liraglutide should be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and time of administration may be changed without dose adjustment. Liraglutide is contraindicated in patients with a personal history of MTC or multiple endocrine neoplasia syndrome type 2, in patients with a hypersensitivity to the drug or any product components, and in pregnancy [18, 26].

In the USA [18], liraglutide should be used with caution in patients with renal or hepatic impairment. In the EU [26], no dosage adjustment of liraglutide is required in patients with mild or moderate renal or hepatic impairment, with caution advised with its use in patients with mild or moderate hepatic impairment; liraglutide is not recommended in patients with severe renal (creatinine clearance <30 mL/min) or hepatic impairment.

Local prescribing information should be consulted for detailed information, including contraindications, drug interactions, precautions and use in special patient populations.

7 Place of Liraglutide in the Management of Obesity

Obesity is a serious disease that is growing in prevalence globally and, with its negative impacts on morbidity, mortality and HRQOL, poses an ever increasing burden on healthpayer systems in both developed and under developed countries [1, 44]. In the real world setting, high-intensity lifestyle interventions for managing obesity are relatively ineffective for most individuals, with most requiring adjunctive pharmacotherapy to achieve clinically relevant reductions in bodyweight [44]. Current US [6] and UK [10] guidelines recommend pharmacotherapy, as an adjunct to diet, exercise and/or behavioural approaches, for overweight individuals with a BMI of ≥27 kg/m^2 [6] or ≥28 kg/m^2 [10] plus at least one bodyweight-related comorbidity or obese adults (BMI ≥30 kg/m^2). No one pharmacotherapy is recommended over another in these guidelines [6, 10].

Pharmacotherapy options for reducing and maintaining bodyweight loss include orlistat (inhibitor of pancreatic and gastric lipases; approved in numerous countries, including the EU and USA), lorcaserin (a selective serotonin C2 receptor agonist; approved in numerous countries, including the USA, but not in the EU), phentermine/topiramate (a sympathomimetic anorectic/anti-epileptic combination; approved in the USA, but not in the EU) and, most recently, liraglutide (approved in the USA, Canada and the EU) and naltrexone/bupropion extended-release (ER), which combines an opioid antagonist and a norepinephrine and dopamine reuptake inhibitor (approved in the USA [45] and the EU [46]). With the exception of liraglutide, which is given subcutaneously, all of these newer anti-obesity drugs have the convenience of oral administration. Ultimately, the choice of anti-obesity drug will depend upon numerous factors, including the benefit/risk ratio, drug characteristics (e.g. route of administration, costs, potential drug-drug interactions, safety) and patient characteristics (e.g. disease status).

In well-designed 56-week phase III trials, subcutaneous liraglutide 3 mg/day was associated with significantly greater reductions in fasting bodyweight and higher 5 and 10 % responder rates than placebo in obese adults or overweight adults with at least one comorbidity (Sect. 4.1), including in patients with type 2 diabetes (Sect. 4.1.2). Moreover, the ≥5 % reduction in fasting bodyweight achieved during the run-in period was maintained at 56 weeks in significantly more liraglutide than placebo recipients in the SCALE Maintenance trial (Sect. 4.1.1). In an extension study, the clinically relevant reductions in fasting bodyweight attained after 20 weeks of liraglutide therapy, were maintained after up to 2 years treatment (Sect. 4.1.1). Liraglutide therapy was also associated with improvements in waist circumference and in some biomarkers of cardiovascular risk in phase III trials (secondary endpoints; Sect. 4.2), although whether these outcomes are driven by weight loss per se or some additional drug action remains to be elucidated. In the 32-week SCALE Sleep Apnoea trial, liraglutide improved AHI scores to a significantly greater extent than placebo in nondiabetic obese adults with moderate to severe OSA, with these improvements largely driven by liraglutide-induced reductions in bodyweight (Sect. 4.3). In the absence of direct head-to-head trials, the relative efficacy of liraglutide to that of other anti-obesity drugs remains to be fully determined.

Subcutaneous liraglutide was generally well tolerated in clinical trials, with most adverse events of a gastrointestinal nature, mild to moderate in intensity and transient (Sect. 5). Since liraglutide reduces blood glucose levels, there is a risk of hypoglycaemia occurring during treatment. In obese or overweight patients with type 2 diabetes, documented symptomatic hypoglycaemia was reported approximately twice as often in the liraglutide group as in the placebo group and with a higher incidence in patients taking a concomitant sulfonylurea than in those not taking a sulfonylurea. In nondiabetic obese or overweight adults, the incidence of spontaneously reported hypoglycaemia and hypoglycaemia detected in blood samples collected at routine clinic visits was relatively low (there was no systematic capturing of these events in this population). The manufacturer's prescribing information recommends that patients with type 2 diabetes who are taking liraglutide 3 mg/day for bodyweight management concomitantly with an insulin secretagogue (e.g. a sulfonylurea) may need to reduce the dosage of the insulin secretagogue [18]. The clinical significance of elevations in heart rate (Sect. 5) remains to be fully determined, especially for patients with CV and cerebrovascular disease, since exposure to liraglutide in these patients is limited [26].

Tolerability and safety are important considerations in determining the choice of anti-obesity drug. Although

some safety concerns have been raised regarding the potential risk of relatively rare cases of pancreatitis and pancreatic and thyroid cancer with long-term use of GLP-1 receptor agonists, including liraglutide, and DPP-4 inhibitors in patients with type 2 diabetes, the evidence remains equivocal [47]. Ongoing clinical experience should help to clarify these concerns regarding incretin mimetics. Long-term treatment with orlistat may be limited by the potential risk of gastrointestinal adverse events unless a low-fat diet is strictly adhered to [44]. Adverse events associated with lorcaserin therapy include the risk of valvulopathy, serotonin syndrome or neuroleptic malignant syndrome, psychiatric disorders and priapism [48]. With phentermine/topiramate combination treatment, safety concerns include the risk of foetal toxicity, suicidal behaviour and ideation, mood or sleep disorders, metabolic acidosis, and acute myopia and secondary angle closure glaucoma [49]. Naltrexone/bupropion ER is contraindicated in patients with uncontrolled hypertension or seizure-related disorders and in those taking monoamine oxidase inhibitors, and has warnings/precautions regarding the risk of suicidality, seizures, increased blood pressure and heart rate (especially in those with CV disease or cerebrovascular disease), hepatotoxicity and angle-closure glaucoma [50]. Liraglutide, lorcaserin, phentermine/topiramate and naltrexone/bupropion ER are all contraindicated in pregnancy [18, 48–50]. Ultimately the choice of anti-obesity therapy requires careful balancing of the benefits and risks associated with their use, with the long-term safety profiles of these agents in the chronic management of obesity remaining to be fully determined.

To date, the effects of liraglutide on CV morbidity and mortality remain to be established [18], as is the case for other anti-obesity drugs such as lorcaserin, phentermine/topiramate and naltrexone/bupropion ER [48–50]. The FDA recently raised concerns that routine disclosure of detailed interim analyses of CV outcomes trials (CVOTs) at the time of drug approval may subsequently compromise the integrity of final analyses of CVOTs [51]. Given this recent FDA concern, although interim data are available from an ongoing, phase 3 CVOT (NCT 01601704; LIGHT study) evaluating naltrexone/bupropion ER treatment, a postmarketing CVOT for naltrexone/bupropion ER treatment has also been requested by the FDA [45, 51].

Globally, obesity is associated with significant costs from a societal and healthpayer perspective, with costs being an important consideration in contemporary healthcare systems. Given the very recent approval of liraglutide for the chronic management of obesity, there are no published data regarding its cost effectiveness in this indication.

In conclusion, in phase III trials, subcutaneous liraglutide 3 mg once daily was associated with clinically relevant reductions in fasting bodyweight and was generally well tolerated in obese adults and in overweight adults with at least one bodyweight-related comorbidity. Liraglutide was significantly more effective than placebo in terms of reductions in fasting bodyweight and waist circumference, and improvements in some biomarkers of cardiovascular risk. Liraglutide also improved AHI scores (largely driven by reductions in bodyweight) in nondiabetic obese adults with moderate to severe OSA. In the absence of head-to-head trials and with a paucity of pharmacoeconomic and long-term safety data for newer anti-obesity drugs, the relative position of these drugs remains to be fully determined. In the meantime, liraglutide is an emerging option, as an adjunct to a reduced-calorie diet and increased physical activity, for chronic bodyweight management in adults with an initial BMI of $\geq$30 kg/m^2 or a BMI of $\geq$27 kg/m^2 in the presence of at least one bodyweight-related comorbidity, such as hypertension, dyslipidaemia, type 2 diabetes or OSA.

Data selection sources: Relevant medical literature (including published and unpublished data) on liraglutide was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 24 April 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Liraglutide, Saxenda, Victoza, obesity, obese*, over weight*, weight
Study selection: Studies in obese adults or overweight adults with at least one bodyweight-related comorbidity who received liraglutide. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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