

# Liraglutide (Saxenda®) as a Treatment for Obesity

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## Abstract

Obesity is a significant concern in the United States, affecting approximately 35% of the population. Comorbidities, such as diabetes, hypertension, and hyperlipidemia, significantly increase one's risk of heart attack, stroke, and even death. Liraglutide, a medication originally used to treat diabetes, has been approved for the treatment of obesity. Clinical trials have shown significant improvements in body weight and body mass index (BMI) at a dose of up to 3.0 mg daily. The most common adverse effects are gastrointestinal in nature, however, these often subside with time. Safety concerns with regards to thyroid tumors and pancreatitis should be carefully considered prior to use of this agent. Liraglutide should be considered an additional tool in the treatment of obesity, especially in patients with concomitant diabetes.

## Keywords

Diabetes, Liraglutide, Obesity, Treatment

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## 1. Introduction

The American Heart Association has adopted body mass index (BMI) as the accepted measurement for adiposity. BMI is calculated by taking a patient's weight in kilograms and dividing by their height in meters squared ( $\text{kg}/\text{m}^2$ ). Individuals with a BMI of 30 or greater are considered obese [1]. As of 2014, 34.9% of the United States (US) adult population was defined as obese. Although obesity rates do not appear to have significantly increased overall in the past decade, the rate of obesity in women over the age of 60 has increased significantly [2]. This increased rate of obesity in older women corresponds to the two-fold increase in diabetes in persons aged 65 or older since 1980 [3]. The association between obesity and diabetes has been well studied, with obese men having a seven times greater chance of developing diabetes and obese women having a twelve fold

increased risk [4]. However, other comorbidities such as hypertension, hyperlipidemia, asthma, arthritis and general poor health have also been associated with obesity [5] making it one of leading causes of preventable death [6].

Limited options exist for the treatment of obesity. This is due in part to weight loss medications being removed from the market. For example, sibutramine was removed due to the increased risk of cardiovascular events discovered in the SCOUT (Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects) trial [7]. Saxenda (liraglutide) was approved in December 2014 for the treatment of obesity. Prior to its approval, liraglutide was used exclusively for diabetes at a lower dose (1.2 to 1.8 mg daily) and under a different brand name, Victoza<sup>®</sup>. To gain approval for weight loss, medications must produce a weight loss of  $\geq 5\%$  from baseline; this requirement was met in early clinical trials with liraglutide [8].

With the large number of individuals in the U.S. who are diabetic as well as obese, having a medication which could potentially treat both conditions is crucial. This article will explore the use of liraglutide as a weight loss medication including its mechanism of action, safety profile, and clinical evidence of efficacy.

## 2. Pharmacology

Research connecting the gastrointestinal system and insulin secretion dates back to the 1960s stemming from an observation that oral glucose administration produced a greater insulin response compared to an intravenous glucose infusion [9] [10]. This was later termed the incretin effect. The incretin effect is primarily mediated by two insulinotropic gut hormones, glucagon-like peptide (GLP-1) and gastric inhibitory polypeptide (GIP), and accounts for approximately 50% - 70% of the total insulin secreted following oral glucose administration [11]. GLP-1 is a peptide released from L-cells in the intestine in response to nutrient ingestion and subsequently enhances glucose-stimulated insulin secretion. Circulating GLP-1 and GIP are found within minutes post meal ingestion, suggesting both neuronal and endocrine signals are responsible for the release of the hormone [12]. The incretin effect is greatly impaired in patients with type 2 diabetes (T2DM) and GLP-1 secretion is noticeably deficient.

Liraglutide is a GLP-1 analogue, produced by recombinant DNA technology, which shares 97% amino acid sequence homology to endogenous human GLP-1 [13] [14]. Native GLP-1 is rapidly degraded by endogenous DPP-4 enzyme promoting a short half-life of 1.5 - 2 minutes. Liraglutide is stable against DPP-4 degradation and has a prolonged plasma half-life of 13 hours [15] [16]. Similar to endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor. GLP-1 receptors are found in the pancreas, stomach, intestine, heart, kidney, peripheral and central nervous system [16] [17]. Once activated, several responses occur including glucose-dependent stimulation of pancreatic insulin secretion and inhibition of inappropriately high glucagon secretion.

In addition to its glucoregulatory mechanisms, activation of GLP-1 receptors regulates appetite and caloric intake, slow gastric emptying and promote weight loss [13]. This has promoted further research with GLP-1 receptor agonists in the treatment of obesity. In clinical trials, subjects taking liraglutide with a BMI between 30 - 40 kg/m<sup>2</sup> with or without diabetes, observed short term reduction in body weight by decreasing calorie intake and improving eating behaviors without an increase in 24-h energy expenditure [18] [19]. Mean estimated energy intake during a meal was significantly reduced in liraglutide 1.8 and 3 mg subjects when compared to placebo ( $p < 0.003$ ). This reduction translated into improved appetite rating scores consisting of reduced appetite, satiety, and fullness in both liraglutide arms compared with placebo. Gastric emptying rates were similar between the three groups during a 5-h meal test. The 1-h gastric emptying rates, however, were 23% lower in the liraglutide 3 mg arm and 13% lower in the 1.8 mg arm when compared to placebo ( $p = 0.007$ ,  $p = 0.14$ , respectively). The clinical significance of this finding is unknown [19].

Liraglutide's effect on cardiac repolarization was tested in a QTc trial. A randomized, placebo-controlled, cross-over study, found no clinically relevant prolongation in the QTc interval after daily doses up to 1.8 mg were given [20]. The maximum plasma concentrations (C<sub>max</sub>) in overweight and obese subjects treated with liraglutide 3 mg was similar to the C<sub>max</sub> observed in healthy volunteers.

## 3. Pharmacokinetics

The pharmacokinetic properties of liraglutide (outlined in **Table 1**) do not differ to a clinically relevant extent when comparing various subcutaneous injection sites (abdomen, upper arm, and thigh) [13]. Liraglutide is highly

**Table 1.** Pharmacokinetic properties of liraglutide [13]-[16].

<b>Absorption</b>	<ul style="list-style-type: none"> <li>• Max plasma concentration in 9 - 14h</li> </ul>
<b>Distribution</b>	<ul style="list-style-type: none"> <li>• Bioavailability <math>\approx</math> 55%</li> <li>• Volume of distribution 20 - 25 L for a 100 kg person</li> <li>• Plasma protein binding (&gt;98%)</li> </ul>
<b>Metabolism</b>	<ul style="list-style-type: none"> <li>• Similar to that of large proteins</li> <li>• <i>In vitro</i> studies suggest metabolism by DPP-4 and neutral endopeptidase</li> </ul>
<b>Excretion</b>	<ul style="list-style-type: none"> <li>• No specific organ is major route of elimination (drug is metabolized) <ul style="list-style-type: none"> <li>◦ Some metabolites excreted in feces (5%) and urine (6%)</li> </ul> </li> <li>• Mean apparent clearance 0.9 - 1.4 L/h</li> <li>• Half-life <math>\approx</math>13 h</li> </ul>

protein bound (98%), and has reduced susceptibility from DPP4 degradation [21]. Liraglutide demonstrates a relatively slow rate of absorption, with maximum concentrations observed at 9 - 14 hours [22]. Absolute bioavailability is approximately 55% upon subcutaneous administration with a mean apparent volume of distribution of 20 - 25 L (100 kg person) [13].

Liraglutide is metabolized in a manner similar to large proteins; no specific route has been identified as a major route of elimination [13]. Intact liraglutide is not found in feces or urine and only low levels of liraglutide related metabolites are detected during the first 6 - 8 days [17] [23]. The elimination half-life is approximately 13 hours, allowing for once daily administration. Although renal elimination does not appear significant, liraglutide area under the curve (AUC) was lower in patients with mild to severe renal impairment. There have been reports of acute renal failure with GLP-1 receptor agonists including liraglutide, however some of these reports were in patients with underlying renal disease and the majority occurred in volume depleted patients [13]. Data in hepatic impairment is limited. Caution should be utilized in patients with renal or hepatic impairment.

Race, ethnicity and gender have no effect on the pharmacokinetics of liraglutide and no dose adjustment is necessary [13]. This drug demonstrated little to no inhibition of cytochrome P450 enzymes thus indicating low potential for pharmacokinetic cytochrome P450 mediated and plasma protein binding drug-drug interactions [24]. No clinically significant drug interaction has been identified with oral contraceptives, digoxin, lisinopril, atorvastatin, acetaminophen, griseofulvin, and insulin detemir with coadministration of steady state liraglutide 1.8 mg/day [13].

#### 4. Clinical Trials

Several clinical trials have investigated the efficacy of liraglutide on weight loss in non-diabetic as well as diabetic patients (Table 2).

The efficacy of liraglutide as a weight loss agent was evaluated in a 56-week randomized, controlled clinical trial [25]. Patients without diabetes were enrolled in the trial if BMI was  $\geq 30$  (or  $\geq 27$  with other comorbidities). In a 2:1 ratio, patients were randomized to receive liraglutide (n = 2487) or placebo (n = 1244). The dose of liraglutide was initiated at 0.6 mg subcutaneously daily and titrated up 0.6 mg weekly to the target dose of 3.0 mg daily. Both groups received counseling on lifestyle modifications. The primary endpoints in this trial were weight change from baseline, the proportion of patients who lost at least 5% of their weight from baseline, and the proportion of patients who lost more than 10% of their baseline body weight. After 56 weeks, patients in the liraglutide group lost 8.4 kg  $\pm$  7.3 kg while patients in the placebo group lost 2.8 kg  $\pm$  6.5 kg from baseline (p < 0.001 vs placebo). The percentage of patients who lost at least 5% of their body weight from baseline was 63.2% in the liraglutide group vs. 27.1% in the placebo group (p < 0.001 vs placebo). Likewise, 33.1% of patients in the liraglutide group vs 10.6% of patients in the placebo group lost at least 10% of their body weight from baseline (p < 0.001). Patients in the liraglutide group most commonly reported gastrointestinal related adverse events; with nausea and vomiting reported primarily within the first 4 - 8 weeks of treatment. Based on the results of this trial, the authors concluded liraglutide 3.0 mg once daily, in combination with diet and exercise, produced clinically meaningful weight loss in obese patients without diabetes.

A small trial involving 44 obese binge-eaters aimed to evaluate the efficacy of liraglutide 1.8 mg daily for 12 weeks [26]. Subjects were randomized to receive liraglutide 1.8 mg plus diet and exercise or diet and exercise alone. Subjects were excluded if they were taking medications which affect weight or appetite and if they had diabetes, impaired glucose tolerance, or cardiovascular disease. Among the primary endpoints were changes in

**Table 2.** Clinical trials of Liraglutide in weight loss.

Reference	N	Design	Duration	Treatment	Change in Weight	BMI	Results	
							% of pts lost $\geq 5\%$ of BW	% of patients lost $> 10\%$ of BW
Pi-Sunyer	3731	R, DB, PC	56 weeks	LJR up to 3.0 mg daily or PBO	LJR -8.4 kg PBO -2.8 kg*	N/A	LJR 63.2% PBO 27.1%*	LJR 33.1% PBO 10.6%*
Robert	44	R, PRO	12 weeks	LJR 1.8 mg daily or PBO	LJR -4.4 kg PBO -0.76 kg*	LJR -1.75 kg/m <sup>2</sup> PBO -0.28 kg/m <sup>2</sup> *	N/A	N/A
Rasmussen	84	OBS	$\geq 4$ weeks	LJR up to 1.8 mg daily	LJR -9 kg <sup>^</sup>	LJR -3.2 kg/m <sup>2</sup> <sup>^</sup>	N/A	N/A
Jensterle	84	R	12 weeks	LJR 1.2 mg daily or MET 1000 mg BID	LJR -3 kg MET -2.3 kg <sup>#</sup>	LJR -1.1 kg/m <sup>2</sup> MET -0.9 kg/m <sup>2</sup> <sup>#</sup>	N/A	N/A
Davies	846	R, DB, PC, PG	56 weeks	LJR 3 mg daily, LJR 1.8 mg daily, OR PBO	LJR 3 mg -6.4 kg <sup>†</sup> LJR 1.8 mg -5 kg <sup>†</sup> PBO -2.2 kg	N/A	LJR 3 mg 54.3% <sup>†</sup> LJR 1.8 mg 40.4% <sup>†</sup> PBO 21.4%	LJR 3 mg 25.2% <sup>†</sup> LJR 1.8 mg 15.9% <sup>‡</sup> PBO 6.7%
Feng	328	OL	24 weeks	LJR up to 1.8 mg daily	LJR -7.34 kg	LJR -1.8 kg/m <sup>2</sup> <sup>2b</sup>	N/A	N/A
Bashier	365	PRO, OBS	24 weeks	LJR up to 1.8 mg daily	LJR -1.51 kg <sup>#</sup>	N/A	N/A	N/A

R = randomized; DB = double blind; PC = placebo controlled; PRO = prospective; OBS = observational; PG = parallel group; OL = open label; LJR = liraglutide; PBO = placebo; MET = metformin; BID = twice daily; BW = body weight  
<sup>\*</sup>p < 0.001 between groups  
<sup>^</sup>p < 0.0001 from baseline  
<sup>#</sup>p < 0.001 from baseline  
<sup>†</sup>p < 0.001 compared to PBO  
<sup>‡</sup>p = 0.006  
<sup>2b</sup>p < 0.01 from baseline

Binge Eating Scale (BES) scores, BMI, and waist circumference from baseline. Liraglutide treatment resulted in significant decreases in BES score, BMI, and waist circumference from baseline; while subjects in the control group only saw a significant decrease in BES from baseline. The investigators concluded that 12 weeks of liraglutide treatment in non-diabetic binge-eating patients resulted in significant improvements in BES and body weight.

An observational study reported the results from 84 overweight or obese women with polycystic ovary syndrome (PCOS) who were treated with up to 1.8 mg of liraglutide daily for at least 4 weeks [27]. Patients were included in the study if they had failed to lose any weight despite therapy with metformin and lifestyle interventions for 6 months. The primary endpoints were change in body weight and BMI from baseline. Mean body weight at baseline was 98.9 kg and the mean duration of treatment with liraglutide was 27.8 weeks. Results of this study showed a mean weight loss of 9kg (95% CI 7.8 - 10.1;  $p < 0.0001$ ) and a mean change in BMI of 3.2 kg/m<sup>2</sup> (95% CI 2.8 - 3.6;  $p < 0.0001$ ) from baseline. When evaluating these parameters in patients who were treated for  $\geq 20$  weeks, the mean weight loss and change in BMI compared to baseline were even greater. Based on the results of this study, the authors concluded liraglutide may be an effective adjunct to metformin, diet, and exercise in overweight and obese women with PCOS.

The efficacy of liraglutide was evaluated in another trial of 84 overweight or obese women who had a diagnosis of PCOS [28]. In this 12 week trial, 32 obese women with newly diagnosed PCOS were randomized to receive metformin 1000 mg twice daily or liraglutide 1.2 mg daily. Changes in BMI, body weight, waist circumference, and body fat mass were the primary endpoints. After 12 weeks, significant changes in BMI, body weight, waist circumference, and body fat mass were experienced by patients in both groups compared to baseline. Adverse effects reported by both groups were gastrointestinal in nature with nausea and diarrhea most commonly reported. Based on the results of this study, the investigators concluded short term treatment with liraglutide was associated with significant weight loss in obese women with PCOS.

The SCALE trial investigated the safety and efficacy of liraglutide for weight loss in 846 overweight or obese patients with T2DM over a period of 56 weeks [29]. Patients were included in this trial if they had a BMI  $\geq 27$  with a stable body weight over the past 3 months, were treated with 0 to 3 diabetic agents, and had a hemoglobin A1c between 7% - 10%. In a 2:1:1 ratio, patients were randomly assigned to receive liraglutide 3 mg, liraglutide 1.8mg, or placebo. The primary endpoints of this trial were relative change in body weight, proportion of patients losing  $\geq 5\%$  of their baseline body weight, and the proportion of patients losing  $>10\%$  of their body weight from baseline. At week 56, the mean weight loss was 6.4 kg, 5 kg, and 2.2 kg for the liraglutide 3 mg, liraglutide 1.8 mg, and placebo groups, respectively. These results were statistically significant for both liraglutide groups compared to placebo. The proportion of patients losing  $\geq 5\%$  of their body weight from baseline was 54.3% in the liraglutide 3 mg group, 40.4% in the liraglutide 1.8 mg group, and 21.4% in the placebo group. Again, these results were statistically significant for both liraglutide groups when compared to placebo. Finally, the proportion of patients who lost  $>10\%$  of their body weight from baseline was 25.2%, 15.9%, and 6.7% in the liraglutide 3 mg, liraglutide 1.8 mg, and placebo groups, respectively. Based on these results, the study investigators concluded liraglutide 3 mg daily leads to significant weight loss over 56 weeks of treatment compared to placebo.

A smaller study involving 328 patients, aimed to assess the effect of liraglutide on body weight and waist circumference in overweight and obese Chinese patients with T2DM [30]. In this open-label study, patients received up to 1.8 mg daily of liraglutide over 24 weeks. The primary endpoints were defined as changes in body weight, BMI, and waist circumference to height ratio (WHR) from baseline. After 24 weeks of treatment, significant reductions in all primary outcomes were observed. The authors compared their results to clinical trials conducted in Western countries and concluded that liraglutide is more effective in Chinese patients than Western patient populations. It is important to note here, the trials being compared were not designed to evaluate weight loss as a primary outcome and thus this conclusion warrants further investigation.

The efficacy of liraglutide in reducing A1c and weight was investigated in a prospective, observational study of Arab patients with T2DM [31]. This study was conducted at 3 centers in Dubai, and included all adult patients with T2DM between 18 - 70 years of age who received a prescription for liraglutide. The dose of liraglutide was initiated at 0.6 mg and titrated to 1.2 mg or 1.8 mg daily as tolerated. The primary endpoints were defined as change in weight and A1c from baseline to 6 months. The mean change in body weight from baseline to 6 months was 2.5% ( $p < 0.001$ ). In addition, the mean A1c decreased from 8.3% at baseline to 7.6% after 6 months ( $p < 0.001$ ). Based on these results, the investigators concluded liraglutide as add on therapy for diabetes,

produced significant reductions in weight and A1c in this Arab population.

## 5. Adverse Effects

The most common adverse effects reported by patients using liraglutide include nausea, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, and abdominal pain [13]. Hypoglycemia is a concern when using liraglutide with other antidiabetic agents especially insulin or sulfonylureas. The prescribing information for liraglutide recommends against the use of liraglutide in combination with insulin [13]. However, combination therapy with long acting insulin has been evaluated in two studies [32] [33]. The results of these trials showed low rates of hypoglycemia with combination therapy. Little information is available regarding the use of liraglutide with other types of insulin, therefore, providers should encourage regular glucose monitoring with initiation of therapy or dose changes and make adjustments as necessary. The prescribing information for liraglutide states there is an increased risk of serious hypoglycemia in combination with insulin secretagogues (ex: sulfonylureas, meglitinides) [13]. Thus, a decreased dose of the insulin secretagogue should be considered when initiating therapy with liraglutide.

Thyroid C-cell tumors and acute pancreatitis are among the most serious warnings and precautions with liraglutide use. The package insert for liraglutide contains a black box warning for the risk of thyroid C-cell tumors [13]. These tumors have only been seen in mice and rats; the ability of liraglutide to cause such tumors in humans is unknown. The use of liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Patients should be educated about symptoms of potential thyroid tumors including a mass in the neck, dysphagia, dyspnea, and persistent hoarseness [34]. Postmarketing reports of acute pancreatitis have surfaced with liraglutide use. Providers should monitor patients for signs and symptoms of pancreatitis after initiation of liraglutide and with any dose increases. In addition, patients should be educated to seek medical help immediately if they experience persistent, severe abdominal pain with liraglutide use [13] [34]. The use of liraglutide is currently being monitored under a FDA REMS (Risk Evaluation and Mitigation Strategy) program. A fact sheet for this program can be found at [www.SAXENDA.com/REMS](http://www.SAXENDA.com/REMS).

## 6. Dosage and Administration

Saxenda<sup>®</sup> (liraglutide) is available as multi-dose, prefilled syringes. Each pen contains 18 mg of drug (6 mg/mL, 3 mL) and can deliver doses of 0.6 mg, 1.2 mg, 2.4 mg, or 3 mg. Saxenda comes in packs of 3 or 5 pens depending on the patient's need. The pens should be stored in the refrigerator prior to use but can be kept at room temperature for up to 30 days once the pen has been used [13].

In an effort to minimize gastrointestinal adverse effects, liraglutide should be initiated at 0.6 mg daily for one week. The dose should be titrated weekly by 0.6 mg until the target dose of 3 mg daily has been reached. If a patient is not able to tolerate the dose increase, delay titration for one additional week. Liraglutide should be injected subcutaneously once daily in the abdomen, thigh, or upper arm. Patients should be educated to rotate between all three sites if needed as absorption has been shown to be equivalent in clinical studies [14]. Liraglutide can be administered without regard to meals, however, patients should be encouraged to inject themselves at the same time each day [13].

## 7. Therapeutic Considerations

In addition to the adverse effects and precautions previously mentioned, there are other factors practitioners should take into consideration when considering the use of Saxenda<sup>®</sup>. Cost is a serious concern as very few insurance companies cover weight loss medications [35]. This leaves patients to decide whether or not they will pay for the medication out of pocket [36]. Studies have shown only 2/3 of all medications that are prescribed are actually filled [37]. Therefore, it is pertinent that clinicians discuss a patient's financial situation prior to providing a prescription for any weight loss medication. Saxenda<sup>®</sup> costs approximately \$1200 per month for cash paying patients. This is substantially more expensive than many of the other agents available for weight loss. To avoid this, some clinicians have considered placing patients on Victoza<sup>®</sup> for weight loss. However, it is important to keep in mind that the highest dose recommended for Victoza<sup>®</sup> is 1.8 mg of liraglutide which has not been shown to have the same efficacy for weight loss as Saxenda<sup>®</sup> at 3.0 mg of liraglutide.



Another factor to take into consideration is dosage form. Saxenda® is a subcutaneous injection which may be undesirable to some patients. For diabetic patients who may already be injecting insulin, this may not be a concern. However, patients may be unwilling to inject themselves or may have a fear of injections and/or needles. Because of this, it is important that clinicians discuss these fears with patients before prescribing a medication like Saxenda®.

Lastly, with a substantial number of patients experiencing nausea and vomiting with this medication, careful consideration should be given to individuals who may be more sensitive to these adverse effects. In addition, providers should use caution in those whom vomiting could exacerbate an underlying condition such as recent abdominal surgery or respiratory problems.

## 8. Conclusion

Rate of obesity worldwide continues to climb and presents as a major public health concern. Obesity is frequently coupled with other debilitating diseases such as heart disease and diabetes. Reduced caloric intake and increased physical activity are the cornerstones of obesity treatment. However, in some patients pharmacological treatment may be warranted. High dose liraglutide has been shown to reduce food intake and promote weight loss in patients with or without diabetes, for up to a year. Liraglutide may also have a role in obese patients with PCOS. Overall, liraglutide is well tolerated, with gastrointestinal complaints reported most commonly. Monitoring for safety, efficacy and tolerability are important. Liraglutide is an attractive option for chronic weight management in overweight or obese patients. Additional research is warranted for its role in combination weight loss treatments.

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