Liraglutide: A New Option for the Treatment of Obesity

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Obesity continues to pose a major public health risk to the United States and across the world, with an estimated one-third of adult Americans being defined as obese. Obesity treatment guidelines recommend the use of pharmacologic therapy in adults who have a body mass index (BMI) of 30 kg/m^2 or higher or in patients with a BMI of 27 kg/m^2 or higher who have at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus). Liraglutide is a glucagon-like peptide-1 receptor agonist that has been successfully used in the treatment of type 2 diabetes for several years. Weight loss has been well described as an additional benefit with liraglutide therapy, which prompted the manufacturer to evaluate and develop a higher dose formulation specifically for the treatment of obesity. Liraglutide 3 mg/day was approved by the U.S. Food and Drug Administration for this indication in December 2014. We performed a search of the Medline database to identify relevant literature focused on liraglutide's role specifically in treating obesity. Five clinical trials with this primary end point were identified. Data demonstrated that liraglutide can successfully achieve weight-loss benchmarks of 5% or more and 10% or more loss from baseline. The most common adverse effects were gastrointestinal and mild to moderate in intensity. The cost of therapy is high, averaging over $1000/month for out-of-pocket expenses if insurance coverage is not available. Liraglutide is also available for delivery only by subcutaneous injection, which may represent a barrier for patients. Liraglutide 3 mg/day represents another pharmacologic option for the treatment of obesity.

Key Words obesity, liraglutide, glucagon-like peptide-1 receptor agonist, GLP-1, weight loss, Saxenda.
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The prevalence of obesity among adults in the United States has more than doubled from the mid-1970s to 2000 and has remained mostly stable since 2000.[1, 2] Most recent data indicate that more than one-third (34.9%, or 78.6 million) of adults in the United States are obese.[3, 4] Obesity is a known risk factor for several common chronic conditions including cardiovascular disease, diabetes mellitus, osteoarthritis, obstructive sleep apnea, cancer, and back pain.[5] The estimated medical cost associated with obesity in 2008 was $147 billion.[6] The cause of obesity is typically multifactorial and includes an imbalance between energy consumption and energy expenditure as well as other social, behavioral, biologic, and environmental factors. Due to the persistently high prevalence, risk, and associated cost, obesity is one of the most pressing public health issues in the United States.

Overweight and obesity ranges are determined by using height and weight to calculate a body mass index (BMI). Weight classifications in adults according to BMI are as follows: less than 18.5 kg/m^2 = underweight; 18.5–24.9 kg/m^2 = normal weight; 25–29.9 kg/m^2 = overweight; and 30 kg/m^2 or more = obese.[5] The BMI correlates with the amount of body fat, but it does not directly measure body fat.[5]

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With continued advances in the surgical treatment of obesity, as well as the approval of several new weight-loss medications, the treatment of obesity is becoming increasingly complex. Selecting the most appropriate patient-specific treatment recommendation depends on several factors, such as the patient's BMI, the presence of other comorbid conditions, and patient preferences. To aid clinicians in this decision-making process, several clinical practice guidelines for the management of overweight and obesity have recently been published.[5, 7–10] In general, treatment guidelines recognize that diet, exercise, and behavioral modifications are the cornerstone of treatment for obesity, and pharmacologic interventions should be considered only as adjunctive therapy in certain patients. Significant and sustainable weight loss through lifestyle interventions alone, however, remains elusive for the vast majority of patients. Weight-loss medications can be considered adjunct therapy to lifestyle modifications in patients with a BMI of 30 kg/m^2 or greater or in patients with a BMI of 27 kg/m^2 or greater who have at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, insulin resistance, and type 2 diabetes mellitus [T2DM]). Medication selection should be based on specific weight-loss goals and patient preferences, along with a comparison of the benefits and potential risks of each product. Regardless of which medication is selected, the response should be monitored after 3 months of initiation. Weight loss of 5–10% of body weight is considered clinically meaningful and is associated with improvements in many obesity-related chronic conditions.[11]

Medications that are currently approved for the treatment of obesity include phentermine, topiramate/phentermine, lorcaserin, orlistat, naltrexone/bupropion, and liraglutide. Each medication has distinctive advantages and disadvantages with regard to efficacy, adverse effects, drug interactions, and dosing requirements. Liraglutide (Saxenda; Novo Nordisk, Clayton, NC) is the most recent of these agents to be approved for weight loss by the U.S. Food and Drug Administration (FDA). Although liraglutide was approved by the FDA on January 25, 2010, for the treatment of T2DM at lower doses (Victoza 1.2 and 1.8 mg/day; Novo Nordisk), the higher dose formulation (Saxenda 3 mg/day) gained FDA approval on December 23, 2014, specifically as a treatment option for chronic weight management. This article reviews the pharmacology, efficacy, and safety of the more recently approved high-dose liraglutide medication.

Pharmacology

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist with 97% structural homology to endogenous human GLP-1. Whereas native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and thus has a short elimination half-life of 1–2 minutes, liraglutide is stable against metabolic degradation by DPP-4 and has a half-life of 13 hours after subcutaneous administration, allowing for once/day dosing.[12, 13] Liraglutide was originally developed for the treatment of T2DM and has been shown to lower hemoglobin A_{1c} (A1C) effectively at daily doses of 1.2 and 1.8 mg.[14–18] Liraglutide functions at the pancreas to enhance glucose-stimulated insulin secretion and reduce inappropriately elevated levels of glucagon. It also delays gastric emptying and increases satiety by central effects on the hypothalamus. Because GLP-1 receptor agonists stimulate insulin release and inhibit glucagon secretion in a glucose-dependent fashion, the risk of hypoglycemia with these agents is low. This is an important consideration with the new indication for the treatment of obesity because patients without diabetes are not likely to face risks of low blood glucose levels due to the nature of the drugs in this class to only lower glucose when patients' glucose levels are physiologically high.

Liraglutide is also associated with a dose-dependent weight loss. The mechanism for liraglutide's weight loss is likely a combination of effects on the brain and the gastrointestinal tract. Centrally, the GLP-1 receptor is present in many different areas of the brain that regulate appetite including the hypothalamus. Peripherally, GLP-1 released from L cells within the gut may reduce food intake[19, 20] through vagal sensory afferent nerves signaling to the brain[21] as well as by the direct effects on the stomach by delaying gastric emptying, which causes satiety.[22]

Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of liraglutide have been well described with the drug's earlier approval for the treatment of T2DM. As stated, liraglutide is 97% homologous to the endogenous GLP-1 hormone, with substitutions made at position 34 (replacing lysine with arginine) and a lipophilic

moiety added to lysine at position 26 (a palmitic acid added through a glutamoyl spacer).[23] The prolonged activity of the molecule is achieved through self-association because liraglutide forms heptamers in solution, as well as high plasma protein binding (more than 98%) and stability from degradation by the DPP-4 enzyme.[23, 24] Bioavailability for subcutaneously administered liraglutide is ~55%, with similar absorption when administered in the abdomen, thigh, and upper arm.[25] The maximum concentration of liraglutide is seen ~11 hours after dosing.[23, 25] The high protein binding also produces a relatively small volume of distribution. The 3-mg dose for a 100-kg person has a mean volume of distribution of ~20–25 L.[25] Liraglutide is fully metabolized in the body, with no single organ dominating as the primary route of clearance.[23, 25] The elimination half-life after administration of a single dose is ~13 hours, allowing for once/day dosing.[23–25]

Clinical Trials

An English-language literature search (1966–May 2015) of the PubMed/Medline and Scientific Citation Index databases was performed using the following search terms: Saxenda, liraglutide, obesity, and weight loss. Reference lists of identified publications were further reviewed to identify any additional articles. Results were narrowed down to those trials specifically evaluating liraglutide for the treatment of obesity.

Five clinical trials were identified that evaluated liraglutide's effectiveness in the treatment of obesity. The first of these, Trial 1807, was a 20-week phase II dose-ranging trial that included an 84-week open-label extension, with a primary end point of change in body weight.[26] This double-blind placebo-controlled trial randomized 564 patients with a BMI of 30–40 kg/m^2 to one of four liraglutide doses (1.2, 1.8, 2.4, or 3.0 mg), an open-label orlistat (120 mg 3 times/day) comparator group, or placebo.[26] All patients received a low-fat diet with a 500-kcal/day energy deficit (based on basic metabolic rate estimates), and they were encouraged to increase their exercise, with the assistance of a pedometer. At week 20, all patients receiving liraglutide demonstrated statistically significant weight reductions compared with placebo ($p=0.003$ for liraglutide 1.2 mg vs placebo, $p<0.0001$ for all other liraglutide doses vs placebo), and those patients receiving the two highest liraglutide doses had significantly more weight loss compared with orlistat ($p=0.003$ for liraglutide 2.4 mg vs orlistat, $p<0.0001$ for liraglutide 3.0 mg vs orlistat). Mean weight losses observed at 20 weeks for liraglutide 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg were 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg, respectively, compared with a 2.8-kg average weight loss with placebo and 4.1-kg average loss with orlistat. A reported 76% of patients receiving liraglutide 3 mg attained a 5% or higher weight loss at 20 weeks compared with 30% of placebo-treated patients and 44% of patients in the orlistat group.[26] Gastrointestinal adverse effects were the most common across all treatment groups and did appear to be dose related in the liraglutide groups. Nausea and vomiting was ~7-fold more prevalent in the liraglutide 2.4-mg and 3.0-mg groups compared with placebo, although they were predominantly described as mild to moderate in intensity. Most (80%) of the nausea events and half (50%) of the vomiting occurred in the first 4 weeks of the trial. The orlistat group demonstrated rates of nausea and vomiting at 4.2% and 2.1%, respectively, which were both very similar to the placebo group. Withdrawal rates due to adverse events were as follows: 3 (3.1%) in the placebo group, 4 (4.2%) with liraglutide 1.2 mg, 5 (5.6%) with liraglutide 1.8 mg, 9 (9.7%) with liraglutide 2.4 mg, 5 (5.4%) with liraglutide 3.0 mg, and 3 (3.2%) in the orlistat group. Weight loss across all groups was associated with reductions in systolic and diastolic blood pressure.

Three phase III clinical trials were conducted that fell under the Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals (SCALE) acronym: Trial 1839 (SCALE-Obesity and Prediabetes),[27] Trial 1922 (SCALE-Diabetes),[28] and Trial 1923 (SCALE-Maintenance).[29] Table 1 outlines the enrollment and completion rates for these three trials. Weight changes at 1 year for each trial are shown in Table 2.

Trial 1839 (SCALE-Obesity and Prediabetes) was a randomized double-blind placebo-controlled parallel-group 56-week trial involving 3731 patients with a BMI of 30 kg/m^2 or higher or 27 kg/m^2 or higher with a comorbidity of hypertension or dyslipidemia.[27] Patients with diabetes or those who met diagnostic criteria for diabetes (based on A1C, fasting blood glucose level, or oral glucose tolerance test criteria) were excluded. Of the 3731 patients, 2285 (61.2%) were classified as having prediabetes, whereas

Table 1. Number of Patients Enrolled and Completion Rates of the SCALE Trials

Variable	Trial 1839: SCALE-Obesity and Prediabetes[27]		Trial 1922: SCALE-Diabetes[28]	Trial 1923: SCALE-Maintenance[29]
	Patients with prediabetes	Patients without prediabetes		
Duration, wks	56		56	56
No. of patients randomized to liraglutide	1528	959	Liraglutide 3.0 mg: 423 Liraglutide 1.8 mg: 211	212
No. of patients randomized to placebo	757	487	212	210
No. (%) of completers in the liraglutide groups	1110 (72.6)	679 (70.8)	Liraglutide 3.0 mg: 324 (76.6) Liraglutide 1.8 mg: 164 (77.7)	159 (75.0)
No. (%) of completers in the placebo groups	505 (66.7)	296 (60.8)	140 (66.0)	146 (69.5)

SCALE = Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals.

Table 2. Weight Change Results at 56 weeks in the SCALE Trials

Parameter	Trial 1839: SCALE-Obesity and Prediabetes[27]		Trial 1922: SCALE-Diabetes[28]		Trial 1923: SCALE-Maintenance[29]	
	Liraglutide group (n=2437)	Placebo group (n=1225)	Liraglutide 3 mg/day group (n=412)	Placebo group (n=211)	Liraglutide group (n=207)	Placebo group (n=206)
Weight						
Baseline, mean ± SD, kg	106.2 ± 21.2	106.2 ± 21.7	105.7 ± 21.9	106.5 ± 21.3	100.4 ± 20.8	98.7 ± 21.2
% change from baseline	−8.0 ± 6.7	−2.6 ± 5.7	−6.0	−2.0	−6.2 ± 7.3	−0.2 ± 7.0
% Δ vs placebo, LSMean (95% CI)	−5.4 (−5.8 to −5.0)*		−4.00 (−5.10 to −2.90)*		−6.1 (−7.5 to −4.6)*	
Loss of ≥ 5% body weight, % of patients	63.2	27.1	54.3	21.4	50.5	21.8
Loss of ≥ 10% body weight, % of patients	33.1	10.6	25.2	6.7	26.1	6.3

CI = confidence interval; LSMean = least squares mean.
*$p<0.001$ for liraglutide vs placebo.

1446 (38.8%) did not. Patients in both groups were randomized in a 2:1 ratio to once/day liraglutide 3 mg or placebo. The first 4 weeks of the trial followed a fixed-dose escalation, where patients in the active treatment group titrated up from 0.6 mg in 0.6-mg intervals until they could tolerate the fixed 3.0-mg dose, which was held stable across the next 52 weeks. The primary objective was to evaluate efficacy with liraglutide 3 mg compared with placebo in both inducing and maintaining weight loss across 56 weeks. The prediabetes group was randomized to a total of 160 weeks of treatment to address the second primary objective, which was to investigate the long-term ability of liraglutide 3 mg to delay the onset of progression to T2DM. That part of the trial is still ongoing. The three co-primary end points to demonstrate superiority were percentage change in body weight from baseline to week 56, proportion of patients who lost 5% or more of baseline body weight at week 56, and proportion of patients who lost 10% or more of baseline body weight at week 56.

Table 2 outlines and compares the weight changes across the treatment and placebo groups. A larger proportion of patients withdrew from the placebo group (35.6%) than the treatment group (28.1%), although a larger proportion of patients in the liraglutide group withdrew due to adverse events (9.9% vs 3.8%). At 56 weeks, liraglutide demonstrated a superior change in body weight as well as superior rates in attaining both the 5% and 10% weight-loss benchmarks. During the 56-week treatment

period, four patients in the liraglutide group (0.2%) and 14 patients in the placebo group (1.1%) developed T2DM. Secondary end points showed a greater reduction of A1C in the liraglutide group versus the placebo group (−0.30%± 0.28 vs −0.06% ± 0.30, between-group difference −0.23% [95% confidence interval (CI) −0.25 to −0.21], p<0.001) as well as a greater reduction in fasting plasma glucose level in the liraglutide group (−7.1 mg/dl ± 10.8 vs 0.1 mg/dl ± 10.4, between-group difference −6.9 mg/dl [95% CI −7.5 to −6.3], p<0.001).

Trial 1922 (SCALE-Diabetes) was designed to measure the potential for liraglutide to produce and maintain weight loss in overweight or obese patients with T2DM.[28] This 56-week randomized double-blind, placebo-controlled trial had three arms: placebo, liraglutide 1.8 mg, and liraglutide 3.0 mg. Patients had a dose-escalation period of 2–4 weeks followed by stable dosing for 52–54 weeks. A total of 846 enrolled patients were randomized in a 2:1:1 ratio to once/day liraglutide 3 mg, liraglutide 1.8 mg, or placebo, respectively. Enrollment criteria included T2DM patients who controlled their glucose levels with lifestyle management or one of three oral antihyperglycemics (metformin, sulfonylurea, or glitazone). A BMI of 27 kg/m^2 or higher and an A1C in the range of 7–10% were also enrollment requirements. The trial specified the same three co-primary end points as Trial 1839: percentage change in body weight as well as the proportions of patients who achieved 5% or more and 10% or more loss from baseline body weight.

The primary end points for the liraglutide 3.0-mg group compared with placebo are outlined in Table 2. Both active liraglutide groups demonstrated statistically significant weight loss compared with placebo, with the liraglutide 3.0-mg group also demonstrating statistically significant weight loss compared with the 1.8-mg liraglutide group (difference in least squares mean −1.44%, 95% CI −2.49 to −0.38, p=0.0078).[28] Of note, the outcomes for this population were more modest than with the obese or overweight individuals without T2DM, seen in Trial 1839.

The third SCALE trial—SCALE-Maintenance (Trial 1923)—was designed to enroll patients with a BMI of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 with the comorbidities of dyslipidemia or hypertension after an initial run-in period of 4–12 weeks.[29] During this run-in period, patients needed to demonstrate a weight loss of 5% or more of their baseline weight to qualify for randomization. They were given a prescribed low-calorie diet of 1200–1400 kcal/day during the run-in period and had weekly face-to-face or telephone interactions with a nutritionist to reinforce dietary adherence. They were provided pedometers and also encouraged to engage in moderate activity (150 min/week of brisk walking) during this time. Once patients successfully attained the 5% or more weight loss, they were randomized in a 1:1 ratio to either liraglutide 3.0-mg (212 patients) or placebo (210 patients). Patients were stratified according to comorbidity status (presence or absence of hypertension or dyslipidemia) as well as their BMI. Both active drug and placebo were delivered through FlexPen devices, and the dosing was titrated, beginning with 0.6 mg and increasing weekly over 4–5 weeks to reach the full 3.0-mg dose. Patients were also given a diet with a 500-kcal/day deficit, based on estimated 24-hour energy expenditures, and they were instructed to continue their moderate activity. In addition, 15- to 20-minute lifestyle counseling sessions were provided face-to-face weekly during the dose titration interval, and once every 4 weeks across the duration of the trial. The three co-primary end points were mean percentage change in body weight from randomization, proportion of patients who maintained their 5% or greater weight loss from the run-in period, and proportion of patients who attained 5% or greater weight loss after randomization.

During the run-in period, the 422 patients attained a mean ± SD of 6.0 ± 0.9% weight loss. After this run-in period, patients in the liraglutide group had an additional weight loss of 6.2 ± 7.3%, on average, compared with 0.2 ± 7.0% average weight loss with placebo. A total of 81.4% of patients receiving liraglutide were able to maintain the 5% or greater weight loss from the run-in period compared with 48.9% in the placebo group (estimated odds ratio [OR] 4.8, 95% CI 3.0–7.7, p<0.0001). It was reported that 50.5% of patients receiving liraglutide achieved an additional 5% or greater weight loss after the run-in period compared with 21.8% in the placebo group (estimated OR 3.9, 95% CI 2.4–6.1, p<0.0001).

The final phase III trial evaluated the effects of liraglutide 3 mg in obese subjects who had moderate or severe sleep apnea.[30] Trial 3970 (SCALE-Sleep Apnoea) was conducted over 32 weeks, enrolling 359 patients with the primary end point of change in the apnea-hypopnea index from baseline. Weight changes were

specified as secondary end points for the trial, and statistical analysis was not performed but summarized descriptively. At the end of 32 weeks, the liraglutide group demonstrated a greater mean percentage body weight loss compared with placebo (−5.73% vs −1.58%), with a between-group difference of −4.15%.[30]

Safety

Table 3 lists the pooled adverse events that were reported in at least 5% of patients in the liraglutide treatment group. The highest rates of adverse events were gastrointestinal; the top four were nausea, diarrhea, constipation, and vomiting.[25] With regard to serious adverse events, pooled data reflected a rate of 6.3% (213 patients) in the liraglutide 3.0-mg treatment groups compared with 4.6% (89 patients) in the placebo groups.[25] This translated to an estimated incidence of 93/1000 patients in the treatment groups compared to 71/1000 patients in the placebo groups. The most common serious adverse events in the liraglutide groups were hepatobiliary disorders and gallbladder disorders, whereas infections were most common in the placebo groups.[25]

When examining the adverse events that resulted in withdrawal from trials, pooled data showed a total of 331 patients (9.8%) who withdrew across the liraglutide 3.0-mg treatment groups compared with 83 (4.3%) who withdrew from placebo groups.[25] Gastrointestinal disorders or symptoms were the most prevalent reasons for withdrawal in both the treatment and placebo groups, totaling 63% of all treatment group withdrawals and 30% of placebo withdrawals.[25] Of note, most of the withdrawals across both groups occurred early, in the first 4–8 weeks of treatment.[25]

Table 3. Combined Adverse Events Reported in at Least 5% of Patients Receiving Liraglutide across the Five Phase II or III Trials[25]

Adverse event	Liraglutide 3-mg groups (n=3384)	Placebo groups (n=1941)
Gastrointestinal disorders		
Nausea	39.3	13.8
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Dyspepsia	9.6	2.7
Abdominal pain	5.4	3.1
Upper abdominal pain	5.1	2.7
Metabolism or nutritional disorders		
Hypoglycemia (in patients with type 2 diabetes mellitus)	23.0	12.7
Decreased appetite	10.0	2.3
Nervous system disorders		
Headache	13.6	12.6
Dizziness	6.9	5.0
Other		
Fatigue	7.5	4.6
Increased lipase level	5.3	2.2

Data are percentages of patients.

Due to previous concerns with GLP-1 receptor agonists potentially being linked to cases of pancreatitis in patients with diabetes, pancreatitis was carefully monitored for across the five phase II or phase III trials. Acute pancreatitis was diagnosed if patients met two of the following three criteria: characteristic abdominal pain, amylase and/or lipase levels that exceeded three times the upper limit of normal, or characteristic findings on imaging of the pancreas. Pooled data showed a total of nine (0.3%) confirmed events in the treatment group compared with one (0.1%) in the placebo group.[25] The estimated incidence of pancreatitis based on these data would be 2.4/1000 patients in the liraglutide 3.0-mg groups compared with 0.6/1000 patients in the placebo groups.[25] This 4:1 increased pancreatitis event rate is consistent with clinical trials conducted for approval of the 1.8-mg liraglutide product (Victoza).

Thyroid cancer was another risk monitored across these trials, based on mouse and rat data that suggested a dose-dependent and treatment duration–dependent increased risk of thyroid c-cell tumors with the use of liraglutide.[25] Pooled data showed that two patients (less than 0.1%) developed thyroid cancer in the liraglutide treatment groups compared with one patient (less than 0.1%) in the placebo group.[25]

Due to liraglutide's established ability to lower blood glucose levels, hypoglycemia was monitored across these trials. Patients without diabetes did not have blood glucose meters, so no systematic capturing of hypoglycemic episodes occurred. A total of 46 liraglutide-treated patients (1.6%) reported symptomatic episodes of unconfirmed hypoglycemia compared with 19 placebo-treated patients (1.1%).[25] In patients with diabetes, the incidence of hypoglycemia was strongly related to sulfonylurea use; 48 (43.6%) of the 110 patients reported confirmed hypoglycemia in the liraglutide group compared with 15 (27.3%) of the 55 patients in the placebo group.[25] This was after a 50% reduction in sulfonylurea dose in all patients on starting the

trial according to the study protocol. In the diabetic patients studied who were not taking a sulfonylurea, documented symptomatic hypoglycemia occurred in 49 (15.7%) of 312 patients treated with liraglutide compared with 12 (7.6%) of 157 patients in the placebo group.[25] This higher rate of hypoglycemia is surprising because earlier liraglutide trials showed the rate of hypoglycemia to be similar to placebo.[15] Patients with diabetes who use liraglutide 3 mg should be counseled to monitor their blood glucose levels more frequently for a possible risk of hypoglycemia.

Dosage and Administration

Liraglutide dispensed for the treatment of obesity is supplied as prefilled multidose pens that deliver doses in intervals of 0.6 mg, similar to the previous pen devices used for the treatment of diabetes, only with a maximum dose of 3.0 mg. Each pen has a concentration of 6 mg/ml in a 3-ml volume. It is available in packages of three or five pens. Unused pens should be stored in the refrigerator; once used, the pen is stable in the refrigerator or at room temperature for 30 days. The drug should be clear and colorless in appearance. Disposable pen needles should be attached to the liraglutide pen device for single use. Liraglutide should be injected once/day by subcutaneous injection into the abdomen, upper arm, or thigh. It can be given without consideration to timing with meals.[25] Injection sites can be rotated or the dose timing changed without an adjustment in dose. Needles should not be stored on the device to avoid contamination from the environment, and the cap should be placed on the pen when not in use. Patients should titrate the dose by starting at 0.6 mg and increasing by one interval (0.6 mg) weekly to reach the full 3.0-mg dose by week 5. The titration should help the patient tolerate some of the gastrointestinal adverse effects caused by the drug. Patients who do not tolerate an increased dose should consider delaying the titration by ~1 week. It is recommended, however, to discontinue the drug if the full 3.0-mg dose cannot be tolerated because efficacy has not been established with lower doses.

Place in Therapy

Liraglutide provides a new option for long-term weight management in combination with a reduced-calorie diet and increased physical activity in obese patients. The drug has demonstrated superior weight loss compared with orlistat but has not been directly compared to other weight-loss medications. Tolerability may be problematic in some patients. The most common adverse effects of liraglutide are nausea, diarrhea, constipation, and vomiting; initial dose titration is required to minimize these adverse effects. Liraglutide also requires daily subcutaneous injections, which may be a deterrent for some patients, although problems with adherence and patient acceptance were not reported in clinical trials.[25] Patients with a history of medullary thyroid cancer should not take liraglutide.[25] The benefits and potential risks of liraglutide should be weighed carefully in patients with a history of pancreatitis.

Liraglutide is expensive. The average wholesale price of liraglutide 3 mg subcutaneously once/day is $1281.96/30-day supply compared with $239.40 for naltrexone/bupropion, $204.78 for topiramate/phentermine, and $239.40 for lorcaserin.[31] The manufacturer currently offers a patient assistance program for privately insured patients, but the program is not available for patients insured by Medicare, Medicaid, or other government-sponsored insurance. The program reduces the co-pay to $30/month for any insurance plans that cover the medication or provides a $200/month reimbursement to patients who pay out-of-pocket charges.

Patients who may particularly benefit from liraglutide are those who have tried and did not tolerate other weight-loss medications or those who have prediabetes. Patients must be willing to self-administer a daily subcutaneous injection and will likely require prescription drug benefits. Liraglutide may be particularly appealing to patients with prediabetes due to the glucose-lowering effects and potential to delay the progression from prediabetes to diabetes; however, high-dose liraglutide (Saxenda) is not FDA approved for the prevention or treatment of T2DM. Liraglutide should not be used in patients who are already taking a GLP-1 agonist for T2DM.[25]

The appropriate duration of treatment for liraglutide is not established. The Endocrine Society guidelines on pharmacologic management of obesity recommend that a weight-loss medication be continued if a patient achieves a weight loss of 5% or greater of body weight at 3 months and is tolerating the medication without adverse effects.[7] Studies have demonstrated that weight-loss effects of medications are only

sustained as long as they are taken, thus making the theoretical argument that weight-loss medications should be considered as long-term medications to treat a chronic condition.[32,33] However, high-dose liraglutide has been evaluated in clinical studies over a period of only 1–2 years. The long-term safety of liraglutide is not known, and long-term cardiovascular safety studies of liraglutide are still ongoing.

Conclusion

High-dose liraglutide (3.0 mg) is an effective medication available for the treatment of obesity in patients with a BMI of 30 kg/m^2 or greater or a BMI of 27 kg/m^2 or greater in patients with a weight-related comorbid condition. It is dosed at 3 mg/day by subcutaneous injection, and the most frequently occurring adverse effects appear to be gastrointestinal. Cost appears to be a major consideration because it is currently priced much higher than other pharmacologic agents for the treatment of obesity.

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