

From The Medical Letter on Drugs and Therapeutics

Liraglutide (Saxenda) for Weight Loss

The injectable glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide, previously approved by the FDA for treatment of type 2 diabetes as Victoza,¹ has now also been approved at a higher dose as Saxenda (Novo Nordisk) for chronic weight management in adults with a BMI ≥ 30 , or a BMI ≥ 27 with a weight-related comorbidity such as hypertension, dyslipidemia, or diabetes (Table 1).

Drugs for Weight Loss

Pharmacologic treatment of obesity has been limited by modest efficacy, adverse effects, low adherence rates, and regain of weight with drug cessation.² Drugs approved by the FDA for long-term treatment of obesity are listed in Table 2.

Phentermine/topiramate ER (Qsymia) is the most effective drug available to date for weight loss. Lorcaserin (Belviq) is only modestly effective, but is generally well tolerated.³ The lipase inhibitor orlistat (Xenical, Alli) is also modestly effective, but it can cause unpleasant adverse effects such as flatulence with discharge, oily spotting, and fecal urgency. The fixed-dose combination (Contrave) of bupropion (Wellbutrin SR, Zyban, and others) and naltrexone (ReVia, and others) has been effective, but nausea is common, and serious neuropsychiatric reactions have been reported.⁴

Table 1. Liraglutide Clinical Trials^a

Study Design	Drug Regimen	Mean Weight Loss (%)	% of Patients With Weight Loss $\geq 5\%$
Patients with Diabetes			
RA DeFronzo et al ^{b,c} 56 weeks (n = 846)	Liraglutide 3 mg	5.9%	49.9%
	Liraglutide 1.8 mg ^d	4.6%	35.6%
	Placebo	2.0%	13.8%
Patients without Diabetes			
X Pi-Sunyer et al ^e 56 weeks (n = 3731)	Liraglutide 3 mg	8.0%	63.2%
	Placebo	2.6%	27.1%
Patients without Diabetes after $\geq 5\%$ Initial Weight Loss^f			
TA Wadden et al ^g 56 weeks (n = 422)	Liraglutide 3 mg	6.2% ^h	50.5% ^h
	Placebo	0.2% ^h	21.8% ^h

^a In addition to diet and exercise in adults with a BMI ≥ 30 or a BMI ≥ 27 with a weight-related comorbidity.

^b RA DeFronzo et al. Effects of liraglutide 3.0 mg and 1.8 mg on body weight and cardiometabolic risk factors in overweight and obese adults with type 2 diabetes mellitus (T2DM): the SCALE Diabetes randomized, double-blind, placebo-controlled, 56-week trial. The Endocrine Society's 96th annual meeting and expo, Chicago, June 21-24, 2014. Poster SAT-0930.

^c Effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes: SCALE Diabetes. Available at <https://clinicaltrials.gov>. Accessed June 11, 2015.

^d FDA-approved as a titration dose, but not for maintenance.

^e X Pi-Sunyer et al. N Engl J Med 2015; 373:11.

^f Patients were first treated with a low-calorie diet and lost $\geq 5\%$ of initial body weight in 4-12 weeks during the run-in phase.

^g TA Wadden et al. Int J Obes (Lond) 2013; 37:1443.

^h Weight loss observed after randomization.

Pronunciation Key

Liraglutide: lir' a gloo' tide Saxenda: sax end ah

Mechanism of Action

Liraglutide decreases caloric intake. The exact mechanism is unknown; delayed gastric emptying and agonist effects on GLP-1 receptors in areas of the brain involved in appetite regulation have been implicated.

Clinical Studies

Table 1 summarizes the results of some randomized trials of liraglutide for weight loss in overweight or obese adults.

Adverse Effects

Common adverse effects of liraglutide include nausea, diarrhea, constipation, vomiting, hypoglycemia, headache, decreased appetite, and dyspepsia. Acute pancreatitis and cholelithiasis, acute renal failure and worsening of chronic renal failure, increased heart rate, suicidal thoughts, and neuropsychiatric reactions have been reported in clinical trials. Serious hypersensitivity reactions, including angioedema and anaphylaxis, have occurred in patients treated with liraglutide. Thyroid C-cell tumors have been reported in rodents given liraglutide, and the FDA has required a boxed warning about the risk of thyroid C-cell tumors in the package insert. The drug is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in those with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Pregnancy

Saxenda is contraindicated (category X) for use during pregnancy because weight loss is not beneficial for pregnant women and may harm the fetus.

Drug Interactions

Liraglutide delays gastric emptying and may decrease the rate of absorption of other drugs. For patients who are taking an insulin secretagogue concurrently, the dose of the insulin secretagogue should be reduced.

Dosage and Administration

Saxenda is available in packages containing either three or five 18 mg/3 mL pre-filled multi-dose pens that deliver doses of 0.6, 1.2, 1.8, 2.4, or 3 mg. The starting dose for treatment of obesity is 0.6 mg injected subcutaneously in the abdomen, thigh, or upper arm once daily. The dose is titrated in weekly increments of 0.6 mg up to the recommended daily dosage of 3 mg once daily (the recommended daily dose for diabetes is 1.8 mg). If weight loss of $\geq 4\%$ is not achieved within 16 weeks of starting treatment, liraglutide should be discontinued.

Table 2. Some FDA-Approved Drugs for Long-Term Treatment of Obesity^a

Drug	Some Available Formulations	Usual Adult Dosage	Mean Weight Loss ^b	Cost ^c
Sympathomimetic Amine/Antiepileptic Combination				
Phentermine/Topiramate ER - Qsymia (vivus)	7.5/46, 15/92 mg ER caps ^d	7.5/46-15/92 mg once/d	4.1-10.7 kg ^{e-g}	\$170.70
Lipase Inhibitor				
Orlistat - Xenical (Genentech)	120 mg caps	120 mg tid	2.5-3.4 kg ^h	512.10
Alli ⁱ (GSK)	60 mg caps	60 mg tid		44.00
Serotonin Receptor Agonist				
Lorcaserin - Belviq (Eisai)	10 mg tabs	10 mg bid	2.9-3.6 kg ^{j-1}	199.50
Opioid Antagonist/Antidepressant Combination				
Naltrexone/bupropion - Contrave (Orexigen/Takeda)	8/90 mg ER tabs	16/180 mg bid	3.7-5.2 kg ^{g,m-o}	199.50
GLP-1 Receptor Agonist				
Liraglutide - Saxenda (Novo Nordisk)	18 mg/3 mL prefilled pen ^p	3 mg SC once/d	5.8-5.9 kg ^{q,r}	1068.30

ER = extended-release.

^a Weight loss drugs, including over-the-counter medications, are not recommended for use during pregnancy.

^b Placebo-corrected weight loss above diet and lifestyle modifications alone after one year.

^c Approximate WAC for 30 days' treatment with the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. www.fdbhealth.com/policies/drug-pricing-policy. Medicare does not cover weight loss drugs.

^d Also available in 3.75/23 mg and 11.25/69 mg capsules, which are intended for use only during titration.

^e DB Allison et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 2012; 20:330.

^f KM Gadde et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377:1341.

^g The range includes weight loss observed with titration and maintenance dosages.

^h SZ Yanovski and JA Yanovski. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 2014; 311:74.

ⁱ Available over the counter.

^j SR Smith et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; 363:245.

^k MC Fidler et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab* 2011; 96:3067.

^l PM O'Neil et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; 20:1426.

^m FL Greenway et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; 376:595.

ⁿ CM Apovian et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)* 2013; 21:935.

^o TA Wadden et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)* 2011; 19:110.

^p Each pen can deliver doses of 0.6, 1.2, 1.8, 2.4, or 3 mg. Sold in packages containing 3 or 5 multi-dose pens.

^q A Astrup et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2012; 36:843.

^r TA Wadden et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 2013; 37:1443.

Conclusion

Use of the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (Saxenda) as an adjunct to diet and exercise resulted in placebo-corrected weight loss of about 6 kg after one year. As

with other drugs approved for this indication, its effectiveness may wane in the second year and thereafter. Liraglutide must be injected daily, gastrointestinal adverse effects are common, and it is expensive.

ARTICLE INFORMATION

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3. 2 new drugs for weight loss [published correction appears in *Med Lett Drugs Ther*. 2012;54(1399):76]. *Med Lett Drugs Ther*. 2012;54(1398):69-71.

4. Contrave—a combination of bupropion and naltrexone for weight loss. *Med Lett Drugs Ther*. 2014;56(1455):112-114.