Liraglutide for Weight Management (Saxenda)

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This monograph contains information on liraglutide as Saxenda for use as a weight loss drug. Please consult the liraglutide (Victoza) documents for information on its use in the management of diabetes mellitus.

FDA Approval Information	
Description/Mechanism of Action	Liraglutide is glucagon-like peptide (GLP-1) receptor agonist initially approved for the treatment of type 2 diabetes and noted to also produce weight loss. GLP-1 agonists reduce fasting and postprandial glycemia, enhance glucose-dependent insulin secretion, inhibit glucagon secretion and slow gastric emptying. Weight loss is also attributed their increasing satiety and reducing food intake.
Indication(s)	As an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of • 30 kg/m^2 or greater (obese) • 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).
Dosage Form(s) Under Review	Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg (6 mg/mL, 3 mL)
REMS	☒REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy	Category X *See Special Populations for additional information*

Executive Summary	
Efficacy	• Compared to placebo, liraglutide 3mg resulted in significantly greater weight loss, in patients with and without type 2 diabetes, as measured in study primary endpoints of absolute weight loss, percent loss in body weight, and achieving a ≥5% and ≥10% loss in body weight. These effects were maintained 2 years after randomization. • Overweight and obese patients with prediabetes or who are at risk for prediabetes assigned to liraglutide 3 mg had reduced odds of prediabetes compared to placebo. Liraglutide also lowered the odds of patients with prediabetes developing type 2 diabetes.
Safety	• Gastrointestinal complaints, most notably nausea, were the most common reasons for discontinuing treatment. Dehydration can result from nausea, vomiting and diarrhea. Patients who can tolerate liraglutide in the dose titration phase are likely to continue treatment. • Thyroid C-cell tumors (medullary thyroid carcinoma), acute pancreatitis, acute gallbladder disease, acute or worsening of chronic renal failure. • Serious hypoglycemia, particularly if used in combination with a sulfonylurea. Consider lowering the dose of anti-diabetic drugs to reduce the risk of

	hypoglycemia.
Projected Place in Therapy	• Liraglutide's place in therapy is as an adjunct to behavior and lifestyle modifications. In clinical trials liraglutide resulted in more weight loss and prevention of weight regain after up to nearly 2.5 years. Overweight and obese patients with prediabetes or who are at risk for prediabetes may benefit specifically from liraglutide's reduction in prediabetes. Liraglutide also lowered the odds of patients with prediabetes developing type 2 diabetes. • As expected, liraglutide improved measures of glycemic control in patients with type 2 diabetes and may be a rational treatment choice in those not being treated with insulin, DDP-4 inhibitors, meglitinides, or alpha-glucosidase inhibitors who wish to lose weight.

Background

Purpose for review

The FDA approval of liraglutide 3 mg per day (Saxenda) for weight management prompted the need for review. The monograph will review liraglutide's (Saxenda) safety and efficacy in weight management.

Other therapeutic options

Formulary Alternatives	Other Considerations
None	

Non-formulary Alternative (if applicable)	Other Considerations
Orlistat	Does not affect appetite. Requires a low fat diet which may not be consistent with the patient's weight loss diet.
Phentermine/topiramate	REMS requires specialty pharmacy. VA pharmacies can become specialty pharmacy.
Lorcaserin	
Naltrexone/bupropion	To be reviewed.

Efficacy (FDA Approved Indications)[1]

Literature Search Summary

A literature search was performed on PubMed/Medline (2011 to February 2016) using the search terms liraglutide, Saxenda, obesity, overweight, weight loss, and weight management. The search was limited to studies performed in humans and published in the English language. Reference lists of clinical trials and review articles were searched for relevant clinical trials and the FDA Medical Review was also reviewed. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy[1-7]

- The FDA approval of liraglutide (Saxenda) was based on pivotal Phase 3 trials in patients with and without type 2 diabetes who were obese or overweight with weight-related comorbidities.
- The overall quality of the evidence is Moderate. The randomized clinical trials were well designed and sample sizes were adequate. Quality is lowered because weight change is an indirect measure of health outcome, the

use of last observation carried forward for missing data in weight maintenance analysis, and study completion rates of 65% to 75% which was anticipated and comparable to trials with other weight loss medications. Furthermore study subject demographics were not representative of the Veteran population cared for in VHA.

Clinical Trials[2-7]

- European, multicenter, 20-week randomized, double-blind, placebo-controlled study with a 2-year extension.
  - 564 subjects 18-65 years with a BMI of 30-40 kg/m^2 and a fasting plasma glucose <7 mmol/L were enrolled. Persons excluded from the study were those with type 1or 2 diabetes, taking any obesity inducing medication, had used a weight loss medication or participated in a weight control study in the previous 3 months, had bariatric surgery, or had major medical condition.
  - All subjects were instructed to follow a 500-cal deficit low-fat diet at the start of a 2-week, single-blind, placebo run-in period and to monitor their physical activity with a pedometer.
  - Subjects were randomized (1:1:1:1:1:1) to once daily liraglutide 1.2, 1.8, 2.4, 3 mg or placebo subcutaneous injection, or orlistat 120 mg three times a day. The double-blind was maintained for subjects assigned to liraglutide or placebo through Year 1; orlistat was used open-label. The dose of liraglutide and placebo were titrated from 0.6 mg daily to the target dose over 2-4 weeks.
  - The primary endpoint was change in bodyweight over 20 weeks. Secondary outcomes included changes in waist circumference, blood pressure, prevalence of metabolic syndrome, prediabetes status, fasting lipids, cardiovascular markers, glucose metabolism, and homoeostasis model assessment (HOMA) of β-cell function and insulin resistance.
  - Study treatment groups were largely women (75%-77%), with a mean age of 45-47.2 years and mean baseline body weights of 96.0 - 98.4 kg and BMI of 34.1 – 35.0 kg/m^2.
  - At the end of 20 weeks, eligible subjects were invited to continue in a 2-year extension trial. During Year 1 subjects continued on their randomized treatment. At the start of Year 2 subjects originally randomized to liraglutide or placebo were switched to liraglutide 2.4 mg, then to liraglutide 3 mg between Weeks 70-96 (if approved locally).
  - 472 of the 564 subjects randomized completed the 20-week phase (84%).
  - 398 subjects entered the extension trial, 356 completed Year 1 and 268 completed Year 2.

Table 1 Weight loss from randomization to Week 20, and end of Year 1 & 2 extensions

	Randomization to Week 20				Year 1				Year 2		
Intervention	Mean weight loss, kg	Mean difference in weight loss, kg	>5% weight loss, %	>10% weight loss, %	Mean weight loss, kg	Mean difference in weight loss, kg	>5% weight loss, %	>10% weight loss, %	Mean weight loss, kg	>5% weight loss, %	>10% weight loss, %
L1.2 mg	4.8	2.1	52.1	7.4	3.8	1.8	43.0	17.0	-	-	-
L1.8 mg	5.5	2.8	53.3	18.9	5.4	3.4	51.0	26.0	-	-	-
L 2.4 mg	6.3	3.5	60.8	22.8	6.1	4.1	53.0	27.0	-	-	-
L 3 mg	7.2	4.4	76.1	28.3	7.8	5.8	73.0	37.0	5.3	52.0	26.0
Orlistat	4.1	1.3	44.2	9.5	3.9	1.9	44.0	14.0	2.3	29.0	16.0
Placebo	2.8	-	29.6	2.0	2.0	-	28.0	10.0	-	-	-

  - Liraglutide's weight loss effect was dose-related. After 20-weeks the mean difference in weight loss from placebo was significantly greater for all doses of liraglutide as were the proportions of subjects who lost >5% of their baseline (randomization) body weight. Liraglutide 3 mg demonstrated the greatest effect on weight
    - 76% lost >5% body weight vs. 2% with placebo
    - 2% lost no weight or gained weight vs. 22% with placebo
    - 34% moved from obese to overweight (BMI change from ≥30% to <30%) vs. 11% with placebo
  - At the end of Year 1, the weight loss achieved in the 20-week phase was largely maintained. Mean weight loss and the percent of subjects with a >5% or >10% weight loss from baseline were significantly greater with liraglutide 1.8 – 3 mg compared to placebo. Mean placebo-subtracted weight loss was significantly greater in subjects receiving liraglutide 3 mg, 5.8 kg (95% 3.7-8.0).
  - At the end of Year 2, subjects taking liraglutide 2.4/3 mg maintained significantly greater weight loss and proportion of subjects who'd lost >5% and >10% of body weight than those taking orlistat.

- The prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%, respectively, after Year 2 in subjects taking liraglutide 2.4/3 mg.

- SCALE Trials[5-7]
  - Three individual Phase 3 studies (referred to as the SCALE trials) have been conducted: a maintenance trial, a weight management trial in nondiabetics, and a weight management trial in diabetics. All three used a double-blind, placebo-control, parallel group design with a 56-week active treatment phase. Persons with a BMI $\geq$30 mg/m^2 or $\geq$27 mg/m^2 with comorbidities of treated or untreated dyslipidemia and/or treated or untreated hypertension were eligible to participate.
  - Exclusion criteria included type 1 diabetes, type 2 diabetes (2 trials), major depressive disorder or other severe psychiatric illness, treatment with a GLP-1 agonist or other medication that could cause significant weight gain or loss, bariatric surgery, history of idiopathic acute or chronic pancreatitis, or clinically significantly active cardiovascular disease.
  - In each trial liraglutide was titrated over 4 weeks in 0.6 mg per week increments to the target dose.

SCALE MAINTENCE[5]

- The study was designed to test liraglutide's efficacy for maintaining weight loss initially achieved by a low calorie diet.
- To be eligible for randomization, subjects had to achieve a $\geq$5% weight loss over a 4 to 12 week period. Once a $\geq$5% weight loss occurred subjects were randomized to liraglutide 3 mg or placebo once-daily subcutaneous injections stratified by comorbidity status and BMI. Doses were titrated to the target dose over a 4-week period.
- During the randomization phase, subjects were prescribed a 500 kcal/day deficit diet and instructed to continue the physical activity recommended during the initial weight loss phase.
- Liraglutide and placebo were discontinued at Week 56 and subjects participated in monthly visits for 12 weeks.
- The study's 3 co-primary end points were 1) the mean percentage change in body weight 2) the proportion of individuals that maintained the $\geq$5% reduction in body weight achieved with a low calorie diet, and 3) the proportion that lost $\geq$5% of body weight. All 3 were measured from randomization to week 56 and tested hierarchically.
- Secondary end points included physiologic and metabolic measures, and the proportion of subjects achieving >10% weight loss.

Results

Demographics	Liraglutide	Placebo
Mean age at screening (yrs):	45.9 (11.9)	46.5 (11)
Men/Women, %	16/84	21/79
Race		
White	170 (80%)	185 (88%)
Black	32 (15%)	24 (11%)
Asian and other	10 (5%)	1 (1%)
Comorbidities		
Hypertension	71 (33%)	61 (46%)
Dyslipidemia	59 (28%)	65 (31%)

Table 2 SCALE Maintenance: Baseline, Co-primary and Secondary Endpoints at Week 56

Measure	Liraglutide 3 mg	Placebo	Estimated Treatment Difference or Odds Ratio (OR 95% CI) Liraglutide - placebo
Baseline (End of Run-in)	**n = 212**	**n = 206**	
Body weight, kg (s.d.)	100.4 (20.8)	98.7 (21.2)	
BMI, kg/m^2	36.0 (5.9)	35.2 (5.9)	
Waist circumference, cm	109.4 (15.3)	107.8 (15.2)	
Primary Endpoints, week 56	**n = 207**	**n = 206**	
Mean % change from randomization	-6.2 (7.3)	0.2 (7.0)	-6.1 (-7.5 to -4.6)
Maintaining ≥5% weight loss, %	81.4	48.99	OR 4.8 (3.0, 7.7)
Lost ≥5% body weight post randomization, %	50.5	21.8	OR 3.9 (2.4, 6.1)
Secondary Endpoints			
Body weight, kg	-6.0 (7.3)	-0.1 (6.9)	-5.9 (-7.3 to -4.4)
>10% weight loss	26.1%	6.3%	OR 5.3 (2.8, 10.1)
BMI, kg/m^2	-2.1 (2.6)	0.0 (2.3)	-2.1 (-2.5 to -1.6)
Waist circumference, cm	-4.7 (7.4)	-1.2 (6.4)	-3.5 (-4.8 to -2.2)
Physiologic/Metabolic, mean change			
Systolic blood pressure, mmHg	0.2 (12.0)	2.8 (10.4)	-2.7 (-4.7 to -0.8)
Diastolic blood pressure, mmHg	1.4 (8.7)	1.2 (7.7)	-0.3 (-1.7 to 1.1)
Pulse, bpm	3.6 (9.4)	2.4 (8.6)	1.0 (-0.5 to 2.5)
HbA_{1c}, %	-0.1 (0.3)	0.1 (0.3)	-0.3 (-0.3 to -0.2)
Fasting plasma glucose, pmol/L	-0.5 (0.6)	-0.2 (0.7)	-0.4 (-0.5 to -0.3)
Fasting insulin, pmol/L	2.8 (51.2)	16.2 (55.4)	-13.3 (-24.0 to -2.6)
Change from randomization to week 68	**n = 159**	**n = 144**	
Body weight, % change	-4.1 (8.2)	0.3 (7.7)	-4.2 (-6.0 to -2.4)

- Of the 551 persons who entered the low calorie diet run-in phase, 422 lost at least 5% of their body weight and were randomized. Mean weight loss 6% (6.3 kg).
- Of subjects randomized to liraglutide or placebo, 75% (159) and 69.5% (146) completed the 56 week double-blind phase, respectively.
- Liraglutide was superior to placebo in all 3 primary end point measures.
- Liraglutide was superior to placebo in resulting in a >10% weight loss and mean absolute weight loss.
- Significantly greater decreases in BMI and waist circumference occurred with liraglutide than placebo.
- Mean systolic and diastolic blood pressures and pulse fluctuated within the normal range in both treatment groups. At week 56 the mean change in systolic blood pressure was significantly lower in the liraglutide group, while there was no difference in diastolic blood pressure or pulse.
- Changes in glycemic parameters HbA1c, fasting plasma glucose and fasting insulin concentrations favored liraglutide over placebo.
- Changes in lipids were small (data not shown)
- Weight reduction maintenance in the 12 week period after liraglutide and placebo were discontinued was significantly greater in the liraglutide group than placebo.

SCALE Obesity & Prediabetes: Weight Management Trial in Nondiabetics[6]

- Study purpose: To evaluate the efficacy and safety of liraglutide 3 mg as an adjunct to a reduced-calorie diet and increased physical activity (lifestyle modification counseling) for weight management in adults who are overweight or obese without diabetes at baseline.
- An oral glucose tolerance test (OGTT) was administered to all participants at screening to determine prediabetes status. The OGTT was repeated after 56 weeks.
- Randomization 2:1 liraglutide 3 mg or placebo subcutaneously once daily. Subjects were stratified by prediabetes status and BMI (≥30 vs. <30).

- In order to determine if efficacy was maintained after discontinuation, after 56 weeks subjects without prediabetes at screening assigned to liraglutide were randomized (1:1) to continue liraglutide or placebo while those originally assigned to placebo continued placebo for 12 weeks.
- Co-primary end points 1) weight change from baseline, 2) the proportion of subjects who lost ≥5% of their baseline body weight, and 3) the proportion of subjects who lost ≥10% of their baseline body weight.

Results

Demographics	Liraglutide	Placebo
N	2487	1244
Mean age (years):	45.2 (21.3)	45.0 (12.0)
Men/Women, %	21.3/78.7	21.9/78.1
Race		
White	84.7%	85.3%
Black	9.7%	9.2%
Asian	3.6%	3.7%
Other	2.0%	1.8%
Comorbidities		
Hypertension	34.2%	35.9%
Dyslipidemia	29.6%	28.9%
Prediabetes	61.4%	60.9%

Table 3 SCALE Obesity & Prediabetes: Baseline and Change in Primary and Secondary Endpoints

Measure	Liraglutide 3 mg	Placebo	Estimated Treatment Difference or Odds Ratio (95% CI) Liraglutide - placebo
Baseline	**n = 2487**	**n = 1244**	
Body weight, kg (s.d.)	106.2 (21.2)	106.2 (21.7)	
BMI, kg/m^2	38.3 (6.4)	38.3 (6.3)	
Waist circumference, cm	115.0 (14.4)	114.5 (14.3)	
Primary Endpoints, week 56	**n = 2437**	**n = 1225**	
Mean % change in body weight, %	-8.0 (6.7)	-2.6 (5.7)	-5.4 (-5.8 to -5.0)
Mean body weight change, kg	-8.4 (7.3)	-2.8 (6.5)	-5.6 (-6.0 to -5.1)
>5% weight loss, %	63.2	27.1	OR 4.8 (4.1, 5.6)
>10% weight loss, %	33.1	10.6	OR 4.3 (3.5, 5.3)
Secondary Endpoints			
BMI, kg/m^2	-3.0 (2.6)	-1.0 (2.3)	-2.0 (-2.2 to -1.9)
Waist circumference, cm	-8.2 (7.3)	-3.9 (6.6)	-4.2 (-4.7 to -3.7)
Physiologic/Metabolic, mean change			
Systolic blood pressure, mmHg	0.2 (12.0)	2.8 (10.4)	-2.7 (-4.7 to -0.8)
Diastolic blood pressure, mmHg	1.4 (8.7)	1.2 (7.7)	-0.3 (-1.7 to 1.1)
Pulse, bpm	3.6 (9.4)	2.4 (8.6)	1.0 (-0.5 to 2.5)
HbA_{1c}, %	-0.1 (0.3)	0.1 (0.3)	-0.3 (-0.3 to -0.2)
Fasting plasma glucose, pmol/L	-0.5 (0.6)	-0.2 (0.7)	-0.4 (-0.5 to -0.3)
Fasting insulin, pmol/L	2.8 (51.2)	16.2 (55.4)	-13.3 (-24.0 to -2.6)
Re-randomization: Change Week 56 to Week 68 (Prediabetes only)	**Liraglutide/liraglutide n = 351**	**Liraglutide/placebo n = 350**	**Placebo n = 304**
Body weight, % change	0.69 (2.58)	2.91 (3.01)	0.28 (2.39)
Body weight, kg	0.61 (2.42	2.63 (2.71)	0.30 (2.43)

- Mean changes in all primary endpoints were significantly greater in the liraglutide arm than with placebo.
- Mean changes in BMI and waist circumference were significantly greater with liraglutide.
- Differences in mean changes in physiologic and metabolic measures were notable for systolic blood pressure, pulse and fasting insulin concentrations. Small, but statistically significant, improvements in fasting lipid values were noted with liraglutide.

- Following the second OGTT at week 56, the prevalence and odds of prediabetes were significantly lower in the liraglutide group than placebo independent glycemic status at screening: Normoglycemic 7.2% vs. 20.7%; OR 0.30 (95% CI 0.21, 0.42) and prediabetes 30.8% vs. 67.3%; OR 0.20 (0.17, 0.25).
- The odds of a patient developing type 2 diabetes during the trial were 8.1 times greater in the placebo group (95% CI 2.6, 4.7). All but one subject who developed type 2 diabetes had prediabetes at screening.
- Mean changes in overall and individual measures of quality of life scores on Impact of Weight on Quality or Life-Lite version and 36-item Short Form (SF-36) health status survey showed significant improvement with liraglutide compared to placebo after 56 weeks.
- 12-weeks after re-randomization of non-prediabetics at week 56 the mean change in weight, as regain, was greatest in subjects switched from liraglutide to placebo. This same observation was noted for waist circumference, fasting plasma glucose and systolic blood pressure (data not shown).

SCALE Weight Management Trial in Type 2 Diabetes[7]

- Study purpose: To evaluate the efficacy and safety of liraglutide 3 mg as an adjunct to a reduced-calorie diet and increased physical activity (lifestyle modification counseling) for weight management in adults with type 2 diabetes that are overweight or obese.
- Type 2 diabetes was diagnosed by a HbA1c of 7.0% - 10.0% treated with diet and exercise alone or in combination with 1 to 3 oral hypoglycemic agents (metformin, thiazolidione, sulfonylurea). Subjects taking a sulfonylurea were asked to reduce their dose by 50% in an effort to avoid hypoglycemia. Individuals taking insulin were excluded from the study.
- Subjects were randomized 2:1:1 to liraglutide 3 mg, liraglutide 1.8 mg or placebo as a once daily subcutaneous injection.
- Subjects were encouraged to follow a 500 kcal/d deficit diet composed of a maximum of 20% calories from protein, 30% from fat, and 50% from carbohydrates. An exercise program of $\geq$150 min/week of brisk walking or equivalent activity was also prescribed.
- Co-primary end points 1) weight change from baseline, 2) the proportion of subjects who lost $\geq$5% of their baseline body weight, and 3) the proportion of subjects who lost $\geq$10% of their baseline body weight. All 3 were measured from randomization to week 56 and tested hierarchically.

Results

Demographics	Liraglutide 3 mg	Liraglutide 1.8 mg	Placebo
N	423	211	212
Mean age (years):	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)
Men/Women, %	52.0/48.0	51.2/48.8	45.8/54.2
Race			
White	83.5%	83.9%	82.5%
Black	10.4%	12.8%	12.7%
Asian	2.6%	1.9%	1.9%
Other	3.1%	1.4%	2.4%
Comorbidities			
Hypertension	69.3%	70.1%	68.4%
Dyslipidemia	69.7%	67.8%	59.4%
Diabetes Treatment			
Diet + exercise	11.2%	14.2%	9.5%
Metformin	57.5%	54.4%	59.7%
Metformin + Glitazone	5.3%	6.4%	4.7%
Metformin + Sulfonylurea	20.9%	21.6%	22.7%
Metformin + Sulfonylurea + Glitazone	2.4%	2.0%	1.9%
Sulfonylurea	1.7%	1.0%	0.5%
Sulfonylurea + Glitazone	1.0%	0.5%	0.5%

Table 4 SCALE Weight Management in Type 2 Diabetes: Baseline and Change in Primary and Secondary Endpoints

Measure	Liraglutide 3 mg	Liraglutide 1.8 mg	Placebo
Baseline, means (s.d.)	**n = 412**	**n = 204**	**n = 211**
Body weight, kg	105.7 (21.9)	105.8 (21.0)	106.5 (21.3)
BMI, kg/m^2	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)
Waist circumference, cm	118.0 (14.4)	117.5 (14.7)	117.3 (14.0)
Primary Endpoints, week 56			
Mean % change in body weight, %	-6.0	-4.7	-2.0
Mean body weight change, kg	-6.4	-5.0	-2.2
≥5% weight loss, %	54.3	40.4	21.4
≥10% weight loss, %	25.2	15.9	6.7
Secondary Endpoints, change at wk 56			
BMI, kg/m^2	-2.2 (2.1)	-1.7 (2.1)	-0.8 (1.7)
Waist circumference, cm	-6.1 (6.5)	-4.8 (5.6)	-2.7 (5.4)
Physiologic/Metabolic, mean change			
Systolic blood pressure, mmHg	-2.8 (13.5)	-3.5 (12.7)	-0.4 (13.4)
Diastolic blood pressure, mmHg	-0.9 (8.7)	-1.1 (9.4)	-0.5 (9.1)
HbA_{1c}, %	-1.3 (0.9)	-1.1 (1.0)	-0.3 (0.9)
Fasting plasma glucose, mg/dL	-34.3 (38.5)	-26.8 (50.3)	-0.2 (37.0)
Discontinuation: Change Week 56 to Week 68			
Body weight, % change	2.3%	2.0%	-0.1
Body weight, kg	2.1	1.8	-0.2

- Both doses of liraglutide resulted in a significant difference from placebo in all 3 coprimary efficacy end points at week 56.
- A significant difference from placebo was found favoring both doses of liraglutide for the secondary efficacy end points of waist circumference, BMI, HbA_{1c}, fasting plasma glucose, and systolic blood pressure. No difference was found for diastolic blood pressure, or lipids.
- The odds of achieving a target HbA_{1c} < 7% were 8.79 times and 7.71 times greater with liraglutide 3 mg and 1.8 mg, respectively, than placebo.
- Additional evidence of significantly improved glycemic control with liraglutide 3 mg and 1. 8 mg was found in prandial plasma glucose increment, fasting glucagon level, proinsulin level, proinsulin-to-insulin ratio, and HOMA-IR indices (liraglutide 3 mg only).
- A net decrease in medications for diabetes was found for both doses of liraglutide; most notable in subjects taking a sulfonylurea.
- Subjects assigned to liraglutide 3 mg reported significantly improved quality of life on the IEQoL-Lite scale. All subscales except "public distress" demonstrated a "minimally important difference. Improve physical function was the largest driver of improved quality of life.

Potential Off-Label Use

- 3 mg dose for management of type 2 diabetes.

Safety[1]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Risk of thyroid C-cell tumors. Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide (Saxenda) causes thyroid C-cell tumors, including medullary thyroid carcinoma (MCT), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Liraglutide (Saxenda) is contraindicated in patients with a personal or family history of MCT or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for

	early detection of MTC in patients treated with liraglutide (Saxenda).
Contraindications	• See Box Warning • Prior serious hypersensitivity reaction to liraglutide or to any of the product components. • Saxenda and Victoza both contain the same active ingredient, liraglutide, and therefore should not be used together. Liraglutide (Saxenda) should not be used in combination with any other GLP-1 receptor agonist. • Liraglutide (Saxenda) has not been studied in patients taking insulin. Liraglutide (Saxenda) and insulin should not be used together. • The effects of liraglutide (Saxenda) on cardiovascular morbidity and mortality have not been established. • The safety and effectiveness of liraglutide (Saxenda) in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established. • Liraglutide (Saxenda) has not been studied in patients with a history of pancreatitis.
Warnings/Precautions	• Thyroid C-cell Tumors – see Box Warning • Acute Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated. • Serious Hypoglycemia: Can occur when liraglutide is used with an insulin secretagogue (e.g. a sulfonylurea). Consider lowering the dose of anti-diabetic drugs to reduce the risk of hypoglycemia. • Heart Rate Increase: Monitor heart rate at regular intervals consistent with clinical practice. • Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Saxenda® in patients with renal impairment. • Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue Saxenda® and other suspect medications. • Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue liraglutide if symptoms develop.

Safety Considerations[1]

- Gastrointestinal complaints, most notably nausea, were the most common reasons for discontinuing treatment. Dehydration can result from nausea, vomiting and diarrhea. Patients who can tolerate liraglutide in the dose titration phase are likely to continue treatment.
- Thyroid C-cell tumors (medullary thyroid carcinoma), acute pancreatitis, acute gallbladder disease, acute or worsening of chronic renal failure.
- Serious hypoglycemia, particularly if used in combination with a sulfonylurea. Consider lowering the dose of anti-diabetic drugs to reduce the risk of hypoglycemia.

Adverse Reactions[1-7]

Common adverse reactions	• Gastrointestinal disorders were more common in patients assigned to liraglutide (68%) than placebo (39%) most notably nausea (39.3% vs. 13.8%), diarrhea (20.9% vs. 9.9%), constipation (19.4% vs. 8.5%), vomiting (15.7% vs. 3.9%) and dyspepsia (9.6% vs. 2.7%). Nausea most often occurred during the liraglutide titration with the percentage of patients reporting nausea declining by week 10. Most gastrointestinal complaints were mild or moderate and did not lead to discontinuation. • Hypoglycemia, documented symptomatic with plasma glucose $\leq$70 mg/dL, in type 2 diabetics: liraglutide 3 mg 23% (87 events/100 patient-years) vs. placebo 12.7% (31 events per 100 patient-years). Severe hypoglycemia

	(requiring assistance from another person) was reported in 5 persons assigned to liraglutide vs. none with placebo. All 5 persons were taking a sulfonylurea which was found to be a risk factor for hypoglycemia in all treatment groups. • Other commonly reported adverse reactions, liraglutide vs. placebo: decreased appetite (10% vs. 2.3%), injection site erythema (2.5% vs. 0.2%), injection site reaction (2.5% vs. 0.6%), increased lipase (5.3% vs. 2.2%), insomnia (2.4% vs. 1.7%), and anxiety (2.0% vs. 1.6%). • Mean increases in resting heart rate of 2 to 3 beats per minute (bpm) were observed with routine clinical monitoring in liraglutide treated patients compared to placebo. More patients treated with liraglutide, compared with placebo, had changes from baseline at two consecutive visits of more than 10 bpm (34% versus 19%, respectively) and 20 bpm (5% versus 2%, respectively). At least one resting heart rate exceeding 100 bpm was recorded for 6% of liraglutide-treated patients compared with 4% of placebo treated patients, with this occurring at two consecutive study visits for 0.9% and 0.3%, respectively. The clinical significance of the heart rate elevation with liraglutide treatment is unclear, especially for patients with cardiac and cerebrovascular disease as a result of limited exposure in these patients in clinical trials.
Death/Serious adverse reactions	• 4 deaths were reported in the 3 SCALE trials: 2 in patients assigned to liraglutide, neither was attributable to liraglutide (cardiomegaly and hypertensive heart disease, and pulmonary embolism and thromboembolic stroke). The 2 deaths in the placebo arms were due pulmonary fibrosis and cardiorespiratory arrest. • In clinical trials with liraglutide (Saxenda), 6 (0.2%) of 3384 liraglutide-treated patients and none of the 1941 placebo-treated patients reported suicidal ideation; one of these liraglutide-treated patients attempted suicide.
Discontinuations due to adverse reactions	• In clinical trials, 9.8% of patients treated with liraglutide and 4.3% of patients treated with placebo prematurely discontinued treatment as a result of adverse reactions. • The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for liraglutide and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%).

Drug Interactions[1]

Drug-Drug Interactions

- Liraglutide causes a delay in gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with liraglutide.

Risk Evaluation (February 2016)

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	NME Drug Name: Lexi-Comp; First DataBank; ISMP; Clinical Judgment

Liraglutide 18mg/3mL SC Pen Injector	None	None	None	Albiglutide Dulaglutide Linaclotide Teduglutide
Saxenda	None	None	None	Savella

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations[1]

- REMS: The goal of the liraglutide (SAXENDA) REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with SAXENDA® by:
  - Informing healthcare providers about the potential risk of medullary thyroid carcinoma associated with liraglutide (SAXENDA)
  - Informing healthcare providers about the risk of acute pancreatitis (including necrotizing pancreatitis) associated with liraglutide (SAXENDA)
  - Additional information at http://www.accessdata.fda.gov/drugsatfda_docs/rems/Saxenda_2016-02-01_REMS_full.pdf

Dosing and Administration[1]

- Recommended dose of liraglutide (Saxenda) is 3 mg daily. Administer at any time of day, without regard to the timing of meals.
- Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose by 0.6 mg until a dose of 3 mg is reached.
- Inject subcutaneously in the abdomen, thigh or upper arm.
- The injection site and timing can be changed without dose adjustment.
- Discontinue after 16 weeks if weight loss is less than 4% of starting body weight
- See the package insert for detailed information on dosing and administration.

Special Populations (Adults)[1]

	Comments
Elderly	• A dose adjustment based on age is not necessary. • Per the manufacturer, in the liraglutide (Saxenda) clinical trials, 232 (6.9%) of the liraglutide-treated patients were 65 years of age and over, and 17 (0.5%) of the liraglutide-treated patients were 75 years of age and over. No over all differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Pregnancy	• Pregnancy Category X. • Risk Summary - Liraglutide (Saxenda) is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. There are no adequate and well-controlled studies of liraglutide (Saxenda) in pregnant women. Liraglutide (Saxenda) should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with liraglutide (Saxenda) should be discontinued.
Lactation	• It is not known whether liraglutide (Saxenda) is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, a decision should be made whether to discontinue nursing or to discontinue liraglutide, taking into

	account the importance of the drug to the mother. In lactating rats, liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma concentrations. • It is generally recommended that women who are breastfeeding not use weight loss medications.
Renal Impairment	• There is limited experience with liraglutide (Saxenda) in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure with liraglutide, which may sometimes require hemodialysis. • Liraglutide (Saxenda) should be used with caution in this patient population.
Hepatic Impairment	• There is limited experience in patients with mild, moderate, or severe hepatic impairment. Therefore, liraglutide (Saxenda) should be used with caution in this patient population.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- In FY 2014 78.5% of Veterans enrolled in VHA were overweight or obese with a mean BMI of 29.6 kg/m^2. The health consequences of being overweight or obese are well documented. Yet, a 5% to 10% loss in total body improves risk factors for cardiovascular disease including elevated blood glucose, high blood pressure and plasma triglycerides.
- Significant weight loss can be achieved by many persons by dietary, physical activity and behavior therapy. Unfortunately, weight regain of up to 40% is common in the year following weight loss.
- Clinical practice guidelines on weight management, including the VA DoD 2014 update, place pharmacotherapy as adjunct to behavior and lifestyle modifications including diet and increased physical activity. Liraglutide was approved for weight management after the guidelines were updated.
- In clinical trials patients assigned to liraglutide 3 mg per day realized significantly greater absolute weight loss, percent change in body weight, achieved a $\geq$5% and $\geq$10% loss in body weight, and experienced less weight regain compared to placebo. Liraglutide 3 mg has only been compared to orlistat 120 mg three times a day as an open-label arm in a 20 week trial with a 2-year extension. Patients taking liraglutide realized greater absolute weight loss, percent change in body weight, achieved a $\geq$5% and $\geq$10% loss in body weight, and experienced less weight regain than those taking orlistat.
- Liraglutide's place in therapy is as an adjunct to behavior and lifestyle modifications. In clinical trials liraglutide resulted in more weight loss and prevention of weight regain after up to nearly 2.5 years. Overweight and obese patients with prediabetes or who are at risk for prediabetes may benefit specifically from liraglutide's reduction in prediabetes. Liraglutide also lowered the odds of patients with prediabetes developing type 2 diabetes.
- As expected, liraglutide improved measures of glycemic control in patients with type 2 diabetes and may be a rational treatment choice for those not being treated with insulin, DDP-4 inhibitors, meglitinides, or alpha-glucosidase inhibitors who wish to lose weight.
- The overall quality of the evidence is Moderate. The randomized clinical trials were well designed and sample sizes were adequate. Quality is lowered because weight change is an indirect measure of health outcome, the use of last observation carried forward for missing data in weight maintenance analysis, and study completion rates of 65% to 75% which was anticipated and comparable to trials with other weight loss medications. Furthermore study subject demographics were not representative of the Veteran population cared for in VHA.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant | methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.