PREMERA HMO

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PHARMACY POLICY – 5.01.621

Drugs for Weight Management

Effective Date:	Dec. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Nov. 12, 2024	None
Replaces:	N/A	

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Introduction

Excess weight is associated with many health risks such as diabetes, high blood pressure, high cholesterol, and heart disease along with an increased risk of death. Many individuals are able to lose weight by changing their diet and increasing their exercise. The challenge for most people is keeping off the weight they have lost. Initiation of drug therapy in overweight individuals should be made after consideration of the benefits and risks. There are a number of medications approved by the US Food and Drug Administration (FDA), when used in combination with diet and exercise, for the treatment of weight management. This policy describes when drugs for chronic weight management may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Contrave (naltrexone/bupropion)	**Contrave (naltrexone/bupropion) may be considered medically necessary for chronic weight management when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months
	AND
	• Has a body mass index (BMI) of ≥ 30 kg/m^2
	OR
	• Has a BMI of ≥ 27 kg/m^2 and one or more of the following weight-related comorbid conditions:
	  ○ Type 2 diabetes mellitus
	  ○ Hypertension
	  ○ Sleep apnea
	  ○ Hyperlipidemia
	  ○ Cardiovascular disease
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND
	• The dose is limited to four Contrave 8 mg/90 mg tablets per day (taken as two tablets in the morning and two tablets in the evening)
	AND
	• Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Qsymia, Saxenda, Wegovy, Xenical, and Zepbound)
	
	Note: Drugs for weight management are excluded under many benefit plans. Therefore, use of Contrave (naltrexone/bupropion) for weight management may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see **Benefit Application** for further information).

Drug	Medical Necessity

Qsymia (phentermine/topiramate extended-release)	**Qsymia (phentermine/topiramate extended-release) may be considered medically necessary for chronic weight management when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months
	AND
	• Has a body mass index (BMI) of ≥ 30 kg/m^2
	OR
	• Has a BMI of ≥ 27 kg/m^2 and one or more of the following weight-related comorbid conditions:
	  ○ Type 2 diabetes mellitus
	  ○ Hypertension
	  ○ Sleep apnea
	  ○ Hyperlipidemia
	  ○ Cardiovascular disease
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND
	• The dose is limited to one Qsymia 15 mg/92 mg capsule per day
	AND
	• Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Saxenda, Wegovy, Xenical, and Zepbound)
	
	Qsymia (phentermine/topiramate extended-release) may be considered medically necessary for chronic weight management in pediatric individuals when the following criteria are met:
	• The individual is aged between 12 and 17 years
	AND
	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months

Drug	Medical Necessity
	AND • Currently has a BMI ≥ 95th percentile for age and sex (see **Appendix**) **AND** • Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity **AND** • The dose is limited to one Qsymia 15 mg/92 mg capsule per day **AND** • Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Saxenda, Wegovy, Xenical, and Zepbound) **Note:** Drugs for weight management are excluded under many benefit plans. Therefore, use of Qsymia (phentermine/topiramate extended-release) for weight management may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see **Benefit Application** for further information).

Saxenda (liraglutide)	**Saxenda (liraglutide) may be considered medically necessary for chronic weight management in adult individuals when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months
	AND
	• Has a body mass index (BMI) of ≥ 30 kg/m^2
	OR
	• Has a BMI of ≥ 27 kg/m^2 and one or more of the following weight-related comorbid conditions:
	  ○ Type 2 diabetes mellitus
	  ○ Hypertension
	  ○ Sleep apnea
	  ○ Hyperlipidemia
	  ○ Cardiovascular disease

Drug	Medical Necessity
	AND • Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity **AND** • The dose is limited 3 mg per day **AND** • Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Wegovy, Xenical, and Zepbound) **Saxenda (liraglutide) may be considered medically necessary for chronic weight management in pediatric individuals when the following criteria are met:** • The individual is aged between 12 and 17 years **AND** • Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months **AND** • Currently has a BMI ≥ 95th percentile for age and sex (see **Appendix**) **AND** • Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity **AND** • The dose is limited 3 mg per day **AND** • Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Wegovy, Xenical, and Zepbound) **Note:** Drugs for weight management are excluded under many benefit plans. Therefore, use of Saxenda (liraglutide) for weight management may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see **Benefit Application** for further information).

Drug	Medical Necessity

Wegovy (semaglutide)	**Wegovy (semaglutide) may be considered medically necessary for chronic weight management when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months
	AND
	• Has a body mass index (BMI) of ≥ 30 kg/m^2
	OR
	• Has a BMI of ≥ 27 kg/m^2 and one or more of the following weight-related comorbid conditions:
	  ○ Type 2 diabetes mellitus
	  ○ Hypertension
	  ○ Sleep apnea
	  ○ Hyperlipidemia
	  ○ Cardiovascular disease
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND
	• The dose is limited to 2.4 mg once weekly
	AND
	• Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Xenical, and Zepbound)
	
	Wegovy (semaglutide) may be considered medically necessary for chronic weight management in pediatric individuals when the following criteria are met:
	• The individual is aged between 12 and 17 years
	AND
	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months
	AND

Drug	Medical Necessity

	• Currently has a BMI ≥ 95th percentile for age and sex (see **Appendix**)
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND
	• The dose is limited to 2.4 mg once weekly
	AND
	• Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Xenical, and Zepbound)
	
	Wegovy (semaglutide) may be considered medically necessary to reduce the risk of major adverse cardiovascular events (MACE) in adults with established cardiovascular disease when ALL the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Has a body mass index (BMI) of ≥ 27 kg/m^2
	AND
	• Meets one of the following:
	  ○ Has experienced a prior heart attack or stroke
	  ○ Has a history of symptomatic peripheral arterial disease as evidenced by one of the following:
	  ▪ Intermittent claudication with ankle-brachial index <0.85
	  ▪ Peripheral arterial revascularization procedure
	  ▪ Amputation due to atherosclerotic disease
	AND
	• Medication is used in combination with optimized drug therapy for established cardiovascular disease
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND

Drug	Medical Necessity
	• The dose is limited to 2.4 mg once weekly **AND** • Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Xenical, and Zepbound) **Note:** Drugs for weight management are excluded under many benefit plans. Therefore, use of Wegovy (semaglutide) for weight management may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see **Benefit Application** for further information).
Xenical (orlistat), brand orlistat	**Xenical (orlistat) and brand orlistat may be considered medically necessary for chronic weight management in adult individuals when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months **AND** • Has a body mass index (BMI) of ≥ 30 kg/m^2 **OR** • Has a BMI of ≥ 27 kg/m^2 and one or more of the following weight-related comorbid conditions: ○ Type 2 diabetes mellitus ○ Hypertension ○ Sleep apnea ○ Hyperlipidemia ○ Cardiovascular disease **AND** • Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity **AND** • The dose is limited to three 120 mg capsules daily (taken as one capsule three times a day) **AND**

Drug	Medical Necessity
	• Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Wegovy, and Zepbound) **Xenical (orlistat) and brand orlistat may be considered medically necessary for chronic weight management in pediatric individuals when the following criteria are met:** • The individual is aged between 12 and 17 years **AND** • Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months **AND** • Currently has a BMI ≥ 95th percentile for age and sex (see **Appendix**) **AND** • Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity **AND** • The dose is limited to three 120 mg capsules daily (taken as one capsule three times a day) **AND** • Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Wegovy, and Zepbound) **Note:** Drugs for weight management are excluded under many benefit plans. Therefore, use of Xenical (orlistat) or brand orlistat for weight management may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see Benefit Application for further information).
Zepbound (tirzepatide)	**Zepbound (tirzepatide) may be considered medically necessary for chronic weight management when the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity

	• Has engaged in a trial of behavioral modification and dietary restriction for at least 3 months
	AND
	• Has a body mass index (BMI) of ≥ 30 kg/m^2
	OR
	• Has a BMI of ≥ 27 kg/m^2 and one or more of the following weight-related comorbid conditions:
	  ○ Type 2 diabetes mellitus
	  ○ Hypertension
	  ○ Sleep apnea
	  ○ Hyperlipidemia
	  ○ Cardiovascular disease
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND
	• The dose is limited to 15 mg once weekly
	AND
	• Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Xenical, and Wegovy)
	
	Note: Drugs for weight management are excluded under many benefit plans. Therefore, use of Zepbound (tirzepatide) for weight management may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see Benefit Application for further information).

Drug	Investigational
As listed	**All other uses of the medications listed in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Contrave (naltrexone/bupropion) may be approved for 4 months.** **Qsymia (phentermine/topiramate extended-release) may be approved for 6 months.** **Saxenda (liraglutide) may be approved for 4 months.** **Wegovy (semaglutide) and Zepbound (tirzepatide) may be approved for 7 months.** **Xenical (orlistat) and brand orlistat may be approved for 6 months.**
Re-authorization criteria	**Future re-authorization of Contrave (naltrexone/bupropion) may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 5% baseline body weight after 15 weeks of treatment **AND** • The individual continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Qsymia (phentermine/topiramate extended-release) for adults may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 5% baseline body weight after 26 weeks of treatment **AND** • The individual continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Qsymia (phentermine/topiramate extended-release) for pediatric individuals ≥ 12 years of age**

Length of Approval	
Approval	**Criteria**
	and < 18 years of age may be approved for 1 year when clinical benefit/response at the time of re-authorization show: • Weight loss of ≥ 5% baseline BMI after 26 weeks of treatment **AND** • The individual continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Saxenda (liraglutide) for adults may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 4% baseline body weight after 16 weeks of treatment **AND** • The individual is able to tolerate a Saxenda maintenance dose of 3 mg once daily **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Saxenda (liraglutide) for pediatric individuals ≥ 12 years of age and < 18 years of age may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 1% baseline BMI after 16 weeks of treatment **AND** • The individual is able to tolerate a Saxenda maintenance dose of 2.4 mg once daily or 3 mg once daily **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Wegovy (semaglutide) for chronic weight management in adults may be approved for 1 year**

Length of Approval	
Approval	**Criteria**
	when clinical benefit/response at the time of re-authorization show: • Weight loss of ≥ 5% baseline body weight after 7 months of treatment **AND** • Is able to tolerate a Wegovy maintenance dose of 2.4 mg once weekly **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Wegovy (semaglutide) for chronic weight management in pediatric individuals ≥ 12 years of age and < 18 years of age may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 1% baseline BMI after 7 months of treatment **AND** • The individual is able to tolerate a Wegovy maintenance dose of 1.7 mg once weekly or 2.4 mg once weekly **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Wegovy (semaglutide) to reduce the risk of major adverse cardiovascular events (MACE) in adults with established cardiovascular disease may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • The individual is aged 18 years or older **AND** • At baseline prior to treatment with Wegovy (semaglutide), the individual had a body mass index (BMI) of ≥ 27 kg/m^2 **AND** • Meets one of the following:

Length of Approval	
Approval	**Criteria**
	○ Has experienced a prior heart attack or stroke ○ Has a history of symptomatic peripheral arterial disease as evidenced by one of the following: ▪ Intermittent claudication with ankle-brachial index <0.85 ▪ Peripheral arterial revascularization procedure ▪ Amputation due to atherosclerotic disease **AND** • Medication is used in combination with optimized drug therapy for established cardiovascular disease **AND** • Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity **AND** • The dose is limited to 2.4 mg once weekly **AND** • Medication is not being used concurrently with other medications intended for weight loss (e.g., phentermine, benzphetamine, diethylpropion, phendimetrazine, Alli, Contrave, Qsymia, Saxenda, Xenical, and Zepbound) **Future re-authorization of Xenical (orlistat) and brand orlistat for adults may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 5% baseline body weight after 6 months of treatment **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Xenical (orlistat) and brand orlistat for pediatric individuals ≥ 12 years of age and < 18 years of age may be approved for 1 year when clinical benefit/response at the time of re-authorization show:**

Length of Approval	
Approval	**Criteria**
	• Weight loss of ≥ 5% baseline BMI after 6 months of treatment **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity **Future re-authorization of Zepbound (tirzepatide) may be approved for 1 year when clinical benefit/response at the time of re-authorization show:** • Weight loss of ≥ 5% baseline body weight after 7 months of treatment **AND** • The individual is able to tolerate a Zepbound (tirzepatide) maintenance dose of up to 15 mg once weekly **AND** • Continues to adhere to a reduced-calorie diet and increased physical activity

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the individual's baseline body weight, body mass index (BMI), relevant history including any weight-related comorbidities, dietary plan, physical activity plan, and medication dosage

Coding

N/A

Related Information

Consideration of Age

The ages stated in this policy for which Contrave (naltrexone/bupropion), Qsymia (phentermine/topiramate extended-release), Saxenda (liraglutide), Wegovy (semaglutide), Xenical (orlistat), brand orlistat, and Zepbound (tirzepatide) are considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

Many benefit plans exclude drugs for weight management. Please refer to the applicable benefit plan to determine benefit availability and the terms, conditions, and limitations of coverage. For questions about benefit information, providers should contact customer service using the telephone number on the back of the member's identification card.

Evidence Review

Summary of Evidence

Contrave (naltrexone/bupropion)

The effects of Contrave on weight loss in conjunction with reduced caloric intake and increased physical activity was studied in double-blind, placebo-controlled trials (BMI range 27 to 45 kg/m^2) with study durations of 16 to 56 weeks randomized to naltrexone and/or bupropion or placebo.

Four 56-week multicenter, double-blind, placebo-controlled obesity trials (Contrave Obesity Research, or COR-I, COR-II, COR-BMOD, and COR-Diabetes) were conducted to evaluate the effect of Contrave in conjunction with lifestyle modification in 4,536 individuals randomized to Contrave or placebo. The COR-I, COR-II, and COR-BMOD trials enrolled individuals with obesity (BMI 30 kg/m^2 or greater) or overweight (BMI 27 kg/m^2 or greater) and at least one comorbidity (hypertension or dyslipidemia). The COR-Diabetes trial enrolled individuals with BMI greater than 27 kg/m^2 with type 2 diabetes with or without hypertension and/or dyslipidemia.

Treatment was initiated with a three-week dose-escalation period followed by approximately 1 year of continued therapy. Individuals were instructed to take Contrave with food. COR-I and

COR-II included a program consisting of a reduced-calorie diet resulting in an approximate 500 kcal/day decrease in caloric intake, behavioral counseling, and increased physical activity. COR-BMOD included an intensive behavioral modification program consisting of 28 group counseling sessions over 56 weeks as well as a prescribed diet and exercise regimen. COR-Diabetes evaluated individuals with type 2 diabetes not achieving glycemic goal of a HbA1c less than 7% either with oral antidiabetic agents or with diet and exercise alone. Of the overall population from these four trials, 24% had hypertension, 54% had dyslipidemia at study entry, and 10% had type 2 diabetes.

The co-primary endpoints were percent change from baseline body weight and the proportion of individuals achieving at least a 5% reduction in body weight. In the 56-week COR-I trial, the mean change in body weight was -5.4% among individuals assigned to Contrave 32 mg/360 mg compared with -1.3% among individuals assigned to placebo (Intent-To-Treat [ITT] population). In this trial, the achievement of at least a 5% reduction in body weight from baseline occurred more frequently for individuals treated with Contrave 32 mg/360 mg compared with placebo (42% vs 17%). The percentages of individuals who achieved at least 5% or at least 10% body weight loss from baseline were greater among those assigned to Contrave, compared with placebo, in all four obesity trials

Safety

Contrave has a boxed warning regarding suicidal thoughts and behaviors. Contrave contains the antidepressant bupropion and individuals with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. In placebo-controlled clinical trials with Contrave for the treatment of obesity in adult individuals, no suicides or suicide attempts were reported in studies up to 56 weeks duration with Contrave (equivalent to bupropion doses of 360 mg/day). In these same studies, suicidal ideation was reported by 3 (0.20%) of 1,515 individuals treated with placebo compared with 1 (0.03%) of 3,239 treated with Contrave.

In Contrave clinical trials, 24% of subjects receiving Contrave and 12% of subjects receiving placebo discontinued treatment because of an adverse event. The most frequent adverse reactions leading to discontinuation with Contrave were nausea (6.3%), headache (1.7%) and vomiting (1.1%). The top 5 adverse reactions among individuals' treatment with Contrave and more common than placebo are nausea (32.5% vs. 6.7%), constipation (19.2% vs. 7.2%), headache (17.6% vs. 10.4%), vomiting (10.7% vs. 2.9%), and dizziness (9.9% vs. 3.4%).

Qsymia (phentermine/topiramate extended-release)

The effect of Qsymia on weight loss in conjunction with reduced caloric intake and increased physical activity was studied in 2 randomized, double-blind, placebo-controlled studies in obese individuals (Study 1) and in obese and overweight individuals with two or more significant co-morbidities (Study 2). Both studies had a 4-week titration period, followed by 52 weeks of treatment. There were 2 co-primary efficacy outcomes measured after 1 year of treatment (Week 56): 1) the percent weight loss from baseline; and 2) treatment response defined as achieving at least 5% weight loss from baseline.

In Study 1, obese individuals (BMI greater than or equal to 35 kg/m^2) were randomized to receive 1 year of treatment with placebo (N=514), Qsymia 3.75 mg/23 mg (N=241), or Qsymia 15 mg/92 mg (N=512) in a 2:1:2 ratio. Individuals ranged in age from 18-71 years old (mean age 43) and 83% were female. Approximately 80% were Caucasian, 18% were African American, and 15% were Hispanic/Latino. At the beginning of the study the average weight and BMI of individuals was 116 kg and 42 kg/m^2, respectively. Individuals with type 2 diabetes were excluded from participating in Study 1. During the study, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended to all individuals and individuals were offered nutritional and lifestyle modification counseling.

In Study 2, overweight and obese individuals were randomized to receive 1 year of treatment with placebo (N=994), Qsymia 7.5 mg/46 mg (N=498), or Qsymia 15 mg/92 mg (N=995) in a 2:1:2 ratio. Eligible individuals had to have a BMI greater than or equal to 27 kg/m^2 and less than or equal to 45 kg/m^2 (no lower limit on BMI for individuals with type 2 diabetes) and two or more of the following obesity-related co-morbid conditions:

- Elevated blood pressure (greater than or equal to 140/90 mmHg, or greater than or equal to 130/85 mmHg for diabetics) or requirement for greater than or equal to 2 antihypertensive medications;
- Triglycerides greater than 200-400 mg/dL or were receiving treatment with 2 or more lipid-lowering agents;
- Elevated fasting blood glucose (greater than 100 mg/dL) or diabetes; and/or
- Waist circumference greater than or equal to 102 cm for men or greater than or equal to 88 cm for women.

After 1 year of treatment with Qsymia, all dose levels resulted in statistically significant weight loss compared to placebo. A statistically significant greater proportion of the individuals randomized to Qsymia than placebo achieved 5% and 10% weight loss.

The effect of Qsymia on BMI in conjunction with reduced caloric intake and increased physical activity was evaluated in Study 3 (NCT 03922945), a 56-week, randomized, double-blind, placebo-controlled study in pediatric individuals (12 to 17 years of age) with BMI ≥ 95th percentile standardized by age and sex. Individuals were randomized to receive treatment with placebo (N=56), Qsymia 7.5 mg/46 mg (N=54), or Qsymia 15 mg/92 mg (N=113) in a 1:1:2 ratio. During the study, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended to all individuals and individuals were offered a family-based lifestyle modification program for adolescents.

Individuals' mean age was 14 years old, approximately 55% were female, 67% were Caucasian, 26% were African American, and 33% were Hispanic/Latino. At the beginning of the study, the average weight and BMI of individuals was 106 kg and 38 kg/m^2, respectively, with approximately 81% considered severely obese (120% of the 95th percentile or greater for BMI standardized by age and sex). Thirty-eight (38%) of randomized individuals withdrew from the study prior to week 56.

The primary efficacy parameter was mean percent change in BMI. After 56 weeks of treatment with Qsymia, all dose levels resulted in statistically significant reduction in BMI compared to placebo. A greater proportion of individuals randomized to Qsymia than placebo achieved 5%, 10%, and 15% BMI reduction.

Safety

Adverse reactions in adults occurring at a rate of greater than or equal to 5% and at a rate at least 1.5 times placebo include paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Adverse reactions in pediatric individuals occurring at a rate greater than or equal to 4% and higher than placebo include depression, pyrexia, dizziness, arthralgia, influenza, and ligament sprain.

Qsymia is contraindicated in pregnant individuals. The use of Qsymia can cause fetal harm and weight loss offers no clear clinical benefit to a pregnant individual. Available data from a pregnancy registry and epidemiologic studies indicate an increased risk in oral clefts (cleft lip with or without cleft palate) with first trimester exposure to topiramate, a component of Qsymia.

When phentermine and topiramate were co-administered to rats at doses of 3.75 and 25 mg/kg, respectively [approximately 2 times the maximum recommended human dose (MRHD) based on area under the curve (AUC)], or at the same dose to rabbits (approximately 0.1 times and 1 time, respectively, the clinical exposures at the MRHD based on AUC), there were no drug-related malformations. However, structural malformations, including craniofacial defects and reduced fetal weights occurred in offspring of multiple species of pregnant animals administered topiramate at clinically relevant doses.

Saxenda (liraglutide)

The safety and efficacy of Saxenda for chronic weight management in conjunction with reduced caloric intake and increased physical activity were studied in three 56-week, randomized, double-blind, placebo-controlled trials. In all studies, Saxenda was titrated to 3 mg daily during a 4-week period. All individuals received instruction for a reduced calorie diet (approximately 500 kcal/day deficit) and exercise counseling (recommended increase in physical activity of minimum 150 mins/week) that began with the first dose of study medication or placebo and continued throughout the trial.

Study 1 enrolled 3731 individuals with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; individuals with type 2 diabetes mellitus were excluded. Individuals were randomized in a 2:1 ratio to either Saxenda or placebo. Individuals were stratified based on the presence or absence of abnormal blood glucose measurements at randomization. All individuals were treated for up to 56 weeks. Those individuals with abnormal glucose measurements at randomization (2254 of the 3731 individuals) were treated for a total of 160 weeks. At baseline, mean age was 45 years (range 18-78), 79% were women, 85% were Caucasian, 10% were African American, and 11% were Hispanic/Latino. Mean baseline body weight was 106.3 kg and mean BMI was 38.3 kg/m^2.

Study 2 was a 56-week trial that enrolled 635 individuals with type 2 diabetes and with either overweight or obesity (as defined above). Individuals were to have an HbA of 7-10% and be treated with metformin, a sulfonylurea, or a glitazone as single agent or in any combination, or with diet and exercise alone. Individuals were randomized in a 2:1 ratio to receive either Saxenda or placebo. The mean age was 55 years (range 18-82), 50% were women, 83% were Caucasian, 12% were African American, and 10% were Hispanic/Latino. Mean baseline body weight was 105.9 kg and mean BMI was 37.1 kg/m^2.

Study 3 was a 56-week trial that enrolled 422 individuals with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; individuals with type 2 diabetes mellitus were excluded. All individuals were first treated with a diet (total energy intake 1200-1400 kcal/day) in a run-in period lasting up to 12 weeks. Individuals who lost at least 5% of their screening body weight after 4 to 12 weeks during the run-in were then randomized, with equal allocation, to receive either Saxenda or placebo for 56 weeks. The mean age was 46 years (range 18-73), 81% were women, 84% were Caucasian, 13% were African American, and 7% were Hispanic/Latino. Mean baseline body weight was 99.6 kg and mean BMI was 35.6 kg/m^2.

For Study 1 and Study 2, the primary efficacy parameters were mean percent change in body weight and the percentages of individuals achieving greater than or equal to 5% and 10% weight loss from baseline to week 56. For Study 3, the primary efficacy parameters were mean percent change in body weight from randomization to week 56, the percentage of individuals not gaining more than 0.5% body weight from randomization (i.e., after run-in) to week 56, and the percentage of individuals achieving greater than or equal to 5% weight loss from randomization to week 56. Because losing at least 5% of fasting body weight through lifestyle intervention during the 4- to 12-week run-in was a condition for their continued participation in the randomized treatment period, the results may not reflect those expected in the general population.

After 56 weeks, treatment with Saxenda resulted in a statistically significant reduction in weight compared with placebo. Statistically significantly greater proportions of individuals treated with Saxenda achieved 5% and 10% weight loss than those treated with placebo. In Study 3, statistically significantly more individuals randomized to Saxenda than placebo had not gained more than 0.5% of body weight from randomization to week 56.

Safety

Saxenda includes a boxed warning since it causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether Saxenda will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in individuals treated with liraglutide have been reported in the post-marketing period; the data in these reports are insufficient to establish or exclude a causal relationship

between MTC and liraglutide use in humans. Saxenda is contraindicated in individuals with a personal or family history of MTC or in individuals with MEN 2.

In clinical trials, 9.8% of individuals treated with Saxenda and 4.3% of individuals 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 Saxenda and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%). The top 5 adverse reactions among individuals' treatment with Saxenda and more common than placebo are 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 headache (13.6% vs. 12.6%).

Wegovy (semaglutide)

The safety and efficacy of Wegovy for chronic weight management (weight loss and maintenance) in conjunction with a reduced calorie diet and increased physical activity were studied in three 68-week, randomized, double-blind, placebo-controlled trials and one 68-week, randomized, double-blind, placebo withdrawal trial. In Studies 1, 2, and 3, Wegovy or matching placebo was escalated to 2.4 mg subcutaneous weekly during a 16-week period followed by 52 weeks on maintenance dose. In Study 4, Wegovy was escalated during a 20-week run-in period, and individuals who reached Wegovy 2.4 mg after the run-in period were randomized to either continued treatment with Wegovy or placebo for 48 weeks.

In Studies 1, 2 and 4, all individuals received instruction for a reduced calorie meal diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended to a minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial. In Study 3, individuals received an initial 8-week low-calorie diet (total energy intake 1000 to 1200 kcal/day) followed by 60 weeks of a reduced calorie diet (1200-1800 kcal/day) and increased physical activity (100 mins/week with gradual increase to 200 mins/week).

Study 1 was a 68-week trial that enrolled 1961 individuals with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition, such as treated or untreated dyslipidemia or hypertension; individuals with type 2 diabetes mellitus were excluded. Individuals were randomized in a 2:1 ratio to either Wegovy or placebo. At baseline, mean age was 46 years (range 18-86), 74.1% were women, 75.1% were White, 13.3% were Asian and 5.7% were Black or African American. A total of 12.0% were Hispanic or Latino. Mean baseline body weight was 105.3 kg and mean BMI was 37.9 kg/m^2.

Study 2 was a 68-week trial that enrolled 807 individuals with type 2 diabetes and BMI greater than or equal to 27 kg/m^2. Individuals included in the trial had HbA1c 7-10% and were treated with either: diet and exercise alone or 1 to 3 oral anti-diabetic drugs (metformin, sulfonylurea, glitazone or sodium-glucose co-transporter 2 inhibitor). Individuals were randomized in a 1:1 ratio to receive either Wegovy or placebo. At baseline, the mean age was 55 years (range 19-84), 50.9% were women, 62.1% were White, 26.2% were Asian and 8.3% were Black or African American. A total of 12.8% were Hispanic or Latino. Mean baseline body weight was 99.8 kg and mean BMI was 35.7 kg/m^2.

Study 3 was a 68-week trial that enrolled 611 individuals with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; individuals with type 2 diabetes mellitus were excluded. The individuals were randomized in a 2:1 ratio to receive either Wegovy or placebo. At baseline, the mean age was 46 years, 81.0% were women, 76.1% were White, 19.0% were Black or African American and 1.8% were Asian. A total of 19.8% were Hispanic or Latino. Mean baseline body weight was 105.8 kg and mean BMI was 38.0 kg/m^2.

Study 4 was a 68-week trial that enrolled 902 individuals with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; individuals with type 2 diabetes mellitus were excluded. Mean body weight at baseline for the 902 individuals was 106.8 kg and mean BMI was 38.3 kg/m^2. All individuals received Wegovy during the run-in period of 20 weeks that included 16 weeks of dose escalation. Trial product was permanently discontinued before randomization in 99 of 902 individuals (11%); the most common reason was adverse reactions (n=48, 5.3%); 803 individuals reached Wegovy 2.4 mg and were then randomized in a 2:1 ratio to either continue on Wegovy or receive placebo. Among the 803 randomized individuals, the mean age was 46 years, 79% were women, 83.7% were White, 13% were Black or African American, and 2.4% Asian. A total of 7.8% were Hispanic or Latino. Mean body weight at randomization (week 20) was 96.1 kg and mean BMI at randomization (week 20) was 34.4 kg/m^2.

The proportions of individuals who discontinued study drug in Studies 1, 2, and 3 was 16.0% for the Wegovy-treated group and 19.1% for the placebo-treated group, and 6.8% of individuals treated with Wegovy and 3.2% of individuals treated with placebo discontinued treatment due to an adverse reaction. In Study 4, the proportions of individuals who discontinued study drug were 5.8% and 11.6% for Wegovy and placebo, respectively.

For Studies 1, 2 and 3, the primary efficacy parameters were mean percent change in body weight and the percentages of individuals achieving greater than or equal to 5% weight loss from baseline to week 68.

After 68 weeks, treatment with Wegovy resulted in a statistically significant reduction in body weight compared with placebo. Greater proportions of individuals treated with Wegovy achieved 5%, 10% and 15% weight loss than those treated with placebo.

For Study 4, the primary efficacy parameter was mean percent change in body weight from randomization (week 20) to week 68. From randomization (week 20) to week 68, treatment with Wegovy resulted in a statistically significant reduction in body weight compared with placebo. Because individuals who discontinued Wegovy during titration and those who did not reach the 2.4 mg weekly dose were not eligible for the randomized treatment period, the results may not reflect the experience of individuals in the general population who are first starting Wegovy.

A reduction in body weight was observed with Wegovy irrespective of age, sex, race, ethnicity, BMI at baseline, body weight (kg) at baseline, and level of renal function impairment.

The safety and efficacy of Wegovy to reduce the risk of a major adverse cardiovascular event (MACE) was studied in one multicenter, double-blind, placebo-controlled trial, named the SELECT trial. In the SELECT trial, 17,604 patients who were 45 years or older, had an initial BMI greater than 27, and established cardiovascular disease were randomized in a 1:1 ratio to receive once-weekly subcutaneous Wegovy at a dose of 2.4 mg (after a 16-week dose escalation period) or placebo.

At baseline, the mean age was 62 years (range 45-93), 72% were male, 84% were White, 4% were Black or African American, and 8% were Asian, and 10% were Hispanic or Latino. Mean baseline body weight was 97 kg and mean BMI was 33 kg/m^2. At baseline, prior myocardial infarction was reported in 76% of randomized individuals, prior stroke in 23%, and peripheral arterial disease in 9%. Heart failure was reported in 24% of patients. At baseline, cardiovascular disease and risk factors were managed with lipid-lowering therapy (90%), platelet aggregation inhibitors (86%), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (74%), and beta blockers (70%). A total of 10% had moderate renal impairment (eGFR 30 to <60 $mL/min/1.73m^3$) and 0.4% had severe renal impairment of eGFR <30 $mL/min/1.73m^2$.

The median follow-up duration was 41.8 months. The primary efficacy endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Wegovy statistically significantly reduced the risk of MACEs by 20% compared to placebo when added to standard of care.

Safety

Wegovy includes a boxed warning since it causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether Wegovy will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in individuals treated with liraglutide, another GLP-1 receptor agonist, have been reported in the post-marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. Wegovy is contraindicated in individuals with a personal or family history of MTC or in individuals with MEN 2.

In clinical trials, 6.8% of individuals treated with Wegovy and 3.2% of individuals treated with placebo permanently discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (1.8% versus 0.2%), vomiting (1.2% versus 0%), and diarrhea (0.7% versus 0.1%) for Wegovy and placebo, respectively.

The safety profile of Wegovy observed in the SELECT trial was consistent with previously published studies. The most common adverse events (AEs) reported in the Wegovy arm were gastrointestinal in nature, including those that lead to treatment discontinuation. Patients 75 years of age and older reported more fractures of the hip and pelvis on Wegovy than on placebo and reported more serious adverse reactions overall compared to younger adult patients.

Xenical (orlistat)

The effects of Xenical on weight loss, weight maintenance, and weight regain and on a number of comorbidities (e.g., type 2 diabetes, lipids, blood pressure) were assessed in the 4-year XENDOS study and in seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of therapy, the studies of 2-year duration assessed weight loss and weight maintenance. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of Xenical on weight regain. These studies included over 2800 individuals treated with Xenical and 1400 individuals treated with placebo (age range 17-78 years, 80.2% women, 91.0% Caucasians,

5.7% Blacks, 2.3% Hispanics, 0.9% Other). The majority of these individuals had obesity-related risk factors and comorbidities. In the XENDOS study, which included 3304 individuals (age range 30-58 years, 55% women, 99% Caucasians, 1% other), the time to onset of type 2 diabetes was assessed in addition to weight management. In all these studies, treatment with Xenical and placebo designates treatment with Xenical plus diet and placebo plus diet, respectively.

During the weight loss and weight maintenance period, a well-balanced, reduced-calorie diet that was intended to result in an approximate 20% decrease in caloric intake and provide 30% of calories from fat was recommended to all individuals. In addition, all individuals were offered nutritional counseling.

Pooled data from five clinical trials indicated that the overall mean weight loss from randomization to the end of 1 year of treatment in the intent-to-treat population was 13.4 lbs in the individuals treated with Xenical and 5.8 lbs in the placebo-treated individuals. After 1 year of treatment, the mean percent weight loss difference between Xenical-treated individuals and placebo-treated individuals was 3%. One thousand seventy-two (69%) individuals treated with Xenical and 701 (63%) individuals treated with placebo completed 1 year of treatment. Of the individuals who completed 1 year of treatment, 57% of the individuals treated with Xenical (120 mg three times a day) and 31% of the placebo-treated individuals lost at least 5% of their baseline body weight.

Three studies were designed to evaluate the effects of Xenical compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with Xenical (two studies, 14119C and 14185). The diet utilized during the 1-year weight regain portion of the studies was a weight-maintenance diet, rather than a weight-loss diet, and individuals received less nutritional counseling than individuals in weight-loss studies. For studies 14119C and 14185, individuals' previous weight loss was due to 1 year of treatment with Xenical in conjunction with a mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of treatment with Xenical on weight regain in individuals who had lost 8% or more of their body weight in the previous 6 months on diet alone.

In study 14119C, individuals treated with placebo regained 52% of the weight they had previously lost while the individuals treated with Xenical regained 26% of the weight they had previously lost ($p<0.001$). In study 14185, individuals treated with placebo regained 63% of the weight they had previously lost while the individuals treated with Xenical regained 35% of the weight they had lost ($p<0.001$). In study 14302, individuals treated with placebo regained 53% of the weight they had previously lost while the individuals treated with Xenical regained 32% of the weight that they had lost ($p<0.001$).

In the 4-year double-blind, placebo-controlled XENDOS study, the effects of Xenical in delaying the onset of type 2 diabetes and on body weight were compared to placebo in 3304 obese individuals who had either normal or impaired glucose tolerance at baseline. Thirty-four percent of the 1655 individuals who were randomized to the placebo group and 52% of the 1649 individuals who were randomized to the Xenical group completed the 4-year study.

At the end of the study, the mean percent weight loss in the placebo group was -2.75% compared with - 5.17% in the Xenical group ($p<0.001$). Forty-five percent of the placebo individuals and 73% of the Xenical individuals lost ≥5% of their baseline body weight, and 21% of the placebo individuals and 41% of the Xenical individuals lost ≥10% of their baseline body weight following the first year of treatment. Following 4 years of treatment, 28% of the placebo individuals and 45% of the Xenical individuals lost ≥5% of their baseline body weight and 10% of the placebo individuals and 21% of the Xenical individuals lost ≥10% of their baseline body weight. After 4 years of treatment, the mean % difference in weight loss between Xenical treated individuals and placebo was 2.5%.

Safety

Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of Xenical in the seven double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥5% and an incidence in the Xenical 120 mg group that is at least twice that of placebo.) The top 5 adverse events among individuals' treatment with Xenical during year 1 and more common than placebo are oily spotting (26.6% vs. 1.3%), flatus with discharge (23.9% vs. 1.4%), fecal urgency (22.1% vs. 6.7%), fatty/oily stool (20.0% vs. 2.9%), and oil evacuation (11.9% vs. 0.8%). In general, the first occurrence of these events was within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with Xenical treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

Zepbound (tirzepatide)

Zepbound is a dual GLP-1 and GIP receptor agonist approved for chronic weight management. The efficacy of Zepbound for chronic weight management (weight reduction and maintenance) in conjunction with a reduced-calorie diet and increased physical activity was studied in two randomized, double-blind, placebo-controlled trials (Study 1 and Study 2), in which weight

reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose). In Study 1, the dose of Zepbound or matching placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period. In Study 2, the dose of Zepbound or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period.

In Study 2, the dose of Zepbound or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period. In Studies 1 and 2, all individuals received instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended to a minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial.

Study 1 (NCT04184622) was a 72-week trial that enrolled 2539 adult individuals with obesity (BMI ≥30 kg/m2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; individuals with type 2 diabetes mellitus were excluded. Individuals were randomized in a 1:1:1:1 ratio to Zepbound 5 mg, Zepbound 10 mg, Zepbound 15 mg, or placebo once weekly.

Study 2 (NCT04657003) was a 72-week trial that enrolled 938 adult individuals with BMI ≥27 kg/m2 and type 2 diabetes mellitus. Individuals included in the trial had HbA1c 7-10% and were treated with either diet and exercise alone, or any oral anti-hyperglycemic agent except dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists. Individuals who were taking insulin or injectable GLP-1 receptor agonists for type 2 diabetes mellitus were excluded. Individuals were randomized in a 1:1:1 ratio to Zepbound 10 mg, Zepbound 15 mg, or placebo once weekly.

The proportions of individuals who discontinued study drug in Study 1 were 14.3%, 16.4%, and 15.1% for the 5 mg, 10 mg, and 15 mg ZEPBOUND-treated groups, respectively, and 26.4% for the placebo-treated group. The proportions of individuals who discontinued study drug in Study 2 were 9.3% and 13.8% for the 10 mg and 15 mg Zepbound-treated groups, respectively, and 14.9% for the placebo-treated group. For Studies 1 and 2, the primary efficacy parameters were mean percent change in body weight and the percentage of individuals achieving ≥5% weight reduction from baseline to Week 72. After 72 weeks of treatment, Zepbound resulted in a statistically significant reduction in body weight compared with placebo, and greater proportions of individuals treated with Zepbound 5 mg, 10 mg, and 15 mg achieved at least 5% weight reduction compared to placebo. Among individuals treated with Zepbound 10 mg and 15 mg, greater proportions of individuals achieved at least 10%, 15%, and 20% weight reduction

compared to placebo. A reduction in body weight was observed with Zepbound irrespective of age, sex, race, ethnicity, baseline BMI, and glycemic status.

Safety

Zepbound was evaluated for safety in 2 randomized, double-blind, placebo-controlled trials that included 2519 adult individuals with overweight or obesity treated with Zepbound for up to 72 weeks and a 4-week off drug follow-up period. The majority of patients who discontinued Zepbound due to adverse reactions did so during the first few months of treatment due to gastrointestinal adverse reactions. There is a black box warning for the risk of thyroid c-cell tumors. Suicidal behavior and ideation have been reported in clinical trials with other chronic weight management products.

2021 Update

Reviewed prescribing information for all drugs listed in policy and no new evidence was identified that would require changes to the coverage criteria. Added a new FDA-approved drug to policy called Wegovy (semaglutide) for the treatment of chronic weight management.

2022 Update

Reviewed prescribing information for all drugs listed in policy and identified a new pediatric indication for Qsymia (phentermine/topiramate extended-release). Added coverage criteria to Qsymia for chronic weight management in pediatric individuals with a BMI ≥ 95th percentile for age and sex. Added coverage for brand orlistat with the identical coverage criteria as Xenical (orlistat). Added specific re-authorization criteria to Qsymia, Xenical, and brand orlistat for pediatric individuals. Updated the re-authorization criteria for all drugs to specify that for adults the weight loss percent is from baseline body weight and for pediatric individuals the weight loss percent is from baseline BMI.

2023 Update

Reviewed prescribing information for all drugs listed in policy. Minor correction made to the pediatric quantity limit for Wegovy (semaglutide). Added a new FDA-approved drug to the policy called Zepbound (tirzepatide) for the treatment of chronic weight management.

2024 Update

Reviewed prescribing information for all drugs listed in policy. Updated Wegovy (semaglutide) coverage criteria to include use in certain individuals with established cardiovascular disease.

Appendix

Table 1: BMI Cut-offs for Obesity by Sex and Age for Pediatric Individuals Aged 12 Years and Older (CDC Criteria).

Age (years)	Body mass index (kg/m2) at 85th Percentile		Body mass index (kg/m2) at 95th Percentile	
	Males	Females	Males	Females
12	21.0	21.7	24.2	25.2
12.5	21.4	22.1	24.7	25.7
13	21.8	22.5	25.1	26.3
13.5	22.2	23.0	25.6	26.8
14	22.6	23.3	26.0	27.2
14.5	23.0	23.7	26.4	27.7
15	23.4	24.0	26.8	28.1

15.5	23.8	24.3	27.2	28.5
16	24.2	24.6	27.5	28.9
16.5	24.5	24.9	27.9	29.3
17	24.9	25.2	28.2	29.6
17.5	25.3	25.4	28.6	30.0

References

1. Contrave (naltrexone/bupropion) Prescribing Information. Currax Pharmaceuticals LLC, Morristown, NJ. Revised March 2024.
2. Qsymia (phentermine/topiramate extended-release) Prescribing Information. VIVUS, Inc., Campbell, CA. Revised September 2024.
3. Saxenda (liraglutide) Prescribing Information. Novo Nordisk Inc., Plainsboro, NJ. Revised November 2024.
4. Wegovy (semaglutide) Prescribing Information. Novo Nordisk Inc., Plainsboro, NJ. Revised November 2024.
5. Xenical (orlistat) Prescribing Information. H2-Pharma, LLC, Montgomery, AL. Revised November 2022.
6. Zepbound (tirzepatide) Prescribing Information. Eli Lilly and Company, Indianapolis, IL. Revised October 2024.

History

Date	Comments
01/01/21	New policy, approved December 8, 2020, effective for dates of service on or after January 1, 2020. Add to Prescription Drug section. Coverage criteria added for Contrave (naltrexone/bupropion), Qsymia (phentermine/topiramate extended-release), Saxenda (liraglutide), and Xenical (orlistat) for the treatment of chronic weight management.
08/01/21	Annual Review, approved July 22, 2021. Added coverage criteria for Wegovy (semaglutide) for the treatment of chronic weight management.
01/01/22	Interim Review, approved December 14, 2021. Updated the initial authorization criteria for all drugs in policy adding requirement the patient has engaged in a trial of behavioral modification and dietary restriction and changed the weight related comorbid conditions for patients with a BMI ≥ 27 kg/m^2. Added Saxenda (liraglutide)

Date	Comments
	and Xenical (orlistat) specific pediatric coverage criteria for patients ≥ 12 years of age and < 18 years of age. Updated the initial authorization duration for Contrave (naltrexone/bupropion) to 4 months, Saxenda to 4 months, and Wegovy (semaglutide) to 7 months. Updated the re-auth criteria for Contrave to weight loss ≥ 5% after 15 weeks of treatment. Updated the re-auth criteria for Qsymia (phentermine/topiramate extended-release) to weight loss ≥ 5% after 26 weeks of treatment. Updated re-auth criteria for Saxenda to weight loss ≥ 4% after 16 weeks of treatment and patient is able to tolerate the Saxenda maintenance dose. Added re-auth criteria for Saxenda for pediatric patients ≥ 12 years of age and < 18 years of age. Updated re-auth criteria for Wegovy to weight loss ≥ 5% after 7 months of treatment and patient is able to tolerate the Wegovy maintenance dose. Updated re-auth criteria for Xenical to weight loss ≥ 5% after 6 months of treatment.
11/01/22	Annual Review, approved October 11, 2022. Added coverage criteria to Qsymia (phentermine/topiramate extended-release) for chronic weight management in pediatric individuals. Added coverage for brand orlistat with the identical coverage criteria as Xenical (orlistat). Added specific re-authorization criteria to Qsymia, Xenical, and brand orlistat for pediatric individuals. Updated the re-authorization criteria for all drugs to specify that for adults the weight loss percent is from baseline body weight and for pediatric individuals the weight loss percent is from baseline BMI. Changed the wording from "patient" to "individual" throughout the policy for standardization.
03/01/23	Interim Review, approved February 14, 2023. Added coverage criteria to Wegovy (semaglutide) for chronic weight management in pediatric individuals. For pediatric coverage for Qsymia, Saxenda, and Xenical the requirement for a trial of behavioral modification and dietary restriction was shortened from 4 months to 3 months, the requirement regarding current BMI was updated to require the individual has a BMI ≥ 95th percentile for age and sex (obesity), and for re-auth the requirement that the individual currently has BMI > 85th percentile was removed. Updated policy criteria for all drugs restricting concurrent use with other medications intended for weight loss. Added an appendix table for BMI cut-offs for obesity by sex and age for pediatric individuals aged ≥ 12.
06/01/23	Annual Review, approved May 22, 2023. Minor correction made to the pediatric quantity limit for Wegovy (semaglutide).
12/01/23	Interim Review, approved November 14, 2023. Added criteria for Zepbound (tirzepatide) for the treatment of chronic weight management.
12/01/24	Annual Review, approved November 12, 2024. Updated Wegovy (semaglutide) coverage criteria to include use in certain individuals with established cardiovascular disease.

and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

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