Oral Semaglutide (WEGOVY) for Weight Management
National Drug Mini-Monograph

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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION[1]

Description / MOA	Semaglutide is a human glucagon-like peptide-1 (GLP-1) receptor agonist that acts by increasing glucose-dependent insulin secretion, decreasing inappropriate glucagon secretion, and slowing gastric emptying. It also acts in brain regions involved in appetite regulation, leading to decreased calorie intake and weight loss.
Indication Under Review	Oral WEGOVY is indicated as an adjunct to a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity (BMI 30 kg/m²) or overweight (BMI 27 kg/m²) with at least one weight-related comorbid condition. It is also indicated to reduce the risk of major adverse cardiovascular events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
Dosage Regimen	Initial dose: 1.5 mg orally once daily for 30 days. Titration every 30 days to 4 mg, then 9 mg, then 25 mg once daily. WEGOVY tablets are co-formulated with salcaprozate sodium (SNAC) to facilitate the absorption of semaglutide in the stomach.
Dosage Forms Under Review	Tablets are available in strengths of 1.5 mg, 4 mg, 9 mg, and 25 mg

EFFICACY CONSIDERATIONS

Trial **OASIS 1[2]**

Design Randomized, double-blind, placebo-controlled, phase 3 superiority trial lasting 68 weeks.

Population 667 adults (BMI 30 kg/m² or 27 kg/m² with weight-related complications) without type 2 diabetes. Less than 10% of the study's population had a BMI less than 30 kg/m². It should be noted that other bodyweight-lowering therapies (bariatric surgery or pharmacotherapy) were allowed during the trial. One patient in the oral semaglutide group and 17 patients in the placebo group used another bodyweight-lowering therapy.

Intervention Oral semaglutide titrated to 50 mg once daily plus lifestyle intervention.

Comparator Placebo once daily plus lifestyle intervention.

Results While only 287 participants were still taking semaglutide and 259 were still taking placebo at week 68, a total of 612 (317 oral semaglutide and 295 placebo) participants from the original group provided weight data at week 68 to be included in the primary efficacy analysis.
Oral semaglutide plus lifestyle intervention resulted in statistically and clinically significant (>5%) weight loss after 68 weeks of therapy. **These results should be taken in context of the labelled maximum dose of oral semaglutide is half (25 mg daily) of what was administered in this clinical trial.**

	Outcome	Oral Semaglutide 50 mg (n with observation at week 68 = 317)	Placebo (n with observation at week 68 = 295)	Treatment Difference (95% CI)	p value
Co-primary Endpoints	Mean BW change (%)	-15.1	-2.4	-12.7 (-14.2, -11.3)	p<0.0001
	Participants with ≥ 5% BW reduction	269 (85%)	76 (26%)	OR 12.6 (8.5, 18.7)	p<0.0001
Select Secondary Endpoints	Participants with ≥ 10% BW reduction	220 (69%)	35 (12%)	OR 14.7 (9.6, 22.6)	p<0.0001
	Participants with ≥ 15% BW reduction	170 (54%)	17 (6%)	OR 17.9 (10.4, 30.7)	p<0.0001

BW: bodyweight

Trial **OASIS 2[3]**

Design Multicenter, double-blind, placebo-controlled, phase 3a trial lasting 68 weeks.

Population 201 East Asian adults. Although the Japanese Society for the Study of Obesity (JASSO) and the Korean Society for the Study of Obesity (KSSO) define obesity as a BMI of 25 or greater, the inclusion criteria of this trial was BMI 27 with 2+ complications or 35 with 1+ complication with or without type 2 diabetes. 37% of the study's population had a BMI less than 30 kg/m², which is a much larger proportion compared to OASIS 1 and OASIS 4.

Intervention Oral semaglutide titrated to 50 mg once daily plus lifestyle recommendations.

Comparator Placebo once daily plus lifestyle recommendations.

Results While only 118 participants were still taking semaglutide at week 68, a total of 127 participants in the oral semaglutide group provided weight data at week 68 to be included in the primary efficacy analysis. The 64 patients in the placebo group were all still taking placebo at week 68.
Oral semaglutide plus lifestyle intervention resulted in statistically and clinically significant (>5%) weight loss after 68 weeks of therapy. **These results should be taken in context of the labelled maximum dose of oral semaglutide is half (25 mg daily) of what was administered in this clinical trial.**
Though the indirect comparison of results does appear to be similar to that seen in the study population without type 2 diabetes (OASIS 1 and OASIS 4), it should be noted that OASIS 2 was a much smaller trial; hence the confidence intervals are much wider than those seen in OASIS 1 and OASIS 4.

	Outcome	Oral Semaglutide 50 mg (n with observation at week 68 = 127)	Placebo (n with observation at week 68 = 64)	Treatment Difference (95% CI)	p value
Co-primary Endpoints	Mean BW change (%)	-14.3	-1.3	-13.07 (-15.61, -10.52)	p<0.001
	Participants with ≥ 5% BW reduction	107 (84.3%)	11 (17.2%)	OR 23 (10.28, 51.42)	p<0.001
Select Secondary Endpoints	Participants with ≥ 10% BW reduction	83 (65.4%)	6 (9.4%)	OR 19.76 (7.74, 50.42)	p<0.001
	Participants with ≥ 15% BW reduction	60 (47.2%)	0	OR 121.21 (7.25, 2027.55)	p<0.001

Trial **OASIS 4[4]**

Design	Double-blind, randomized, placebo-controlled phase 3 trial conducted over 64 weeks.
Population	307 adults without diabetes (BMI 30 or 27 with 1+ obesity-related complication). Less than 10% of the study's population had a BMI less than 30 kg/m². Other obesity medications were not permitted during this trial.
Intervention	Oral semaglutide titrated to 25 mg once daily plus lifestyle interventions.
Comparator	Placebo once daily plus lifestyle recommendations.
Results	Oral semaglutide plus lifestyle intervention resulted in statistically and clinically significant (>5%) weight loss after 64 weeks of therapy. **This is the only published phase 3 that titrated to the labelled maximum dose of oral semaglutide (25 mg daily).**

	Outcome	Oral Semaglutide 25 mg (n with observation at week 64 = 192)	Placebo (n with observation at week 64 = 90)	Treatment Difference (95% CI)	p value
Co-primary Endpoints	Mean BW change (%)	-13.6	-2.2	-11.4 (-13.9, -9)	p<0.001
	Participants with ≥ 5% BW reduction	152 (79.2%)	28 (31.1%)	OR 7.3 (4.2, 12.8)	p<0.001
Select Secondary Endpoints	Participants with ≥ 10% BW reduction	121 (63%)	13 (14.4%)	OR 9.1 (4.7, 17.3)	p<0.001
	Participants with ≥ 15% BW reduction	96 (50%)	5 (5.6%)	OR 15.7 (6.2, 40.2)	p<0.001

SAFETY CONSIDERATIONS[1,2]

Boxed Warnings	Risk of Thyroid C-cell Tumors: contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
Contraindications	In addition to above contraindications; also patients with a known hypersensitivity to semaglutide or its excipients.
Other Warnings	Warnings include acute pancreatitis, acute gallbladder disease (cholelithiasis and cholecystitis), and hypoglycemia when used with insulin or insulin secretagogues. Additional warnings involve acute kidney injury due to volume depletion, severe gastrointestinal reactions, complications from diabetic retinopathy in patients with type 2 diabetes, heart rate increase, suicidal behavior and ideation, and risk of pulmonary aspiration during general anesthesia.
Top 5 AEs	Based on the OASIS 1 clinical trial, the most common adverse events for oral semaglutide were: nausea (52%), COVID-19 (36%), constipation (28%), diarrhea (27%), and vomiting (24%).
Drug Interactions	Because semaglutide delays gastric emptying, it may impact the absorption of other oral medications. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or require clinical monitoring.
Pregnancy	Treatment with oral semaglutide may cause fetal harm. It should be discontinued when pregnancy is recognized. Patients of reproductive potential should discontinue treatment at least 2 months prior to a planned pregnancy due to the long half-life of semaglutide.
Lactation	Breastfeeding is not recommended during treatment with semaglutide tablets because of the potential for serious adverse reactions in infants from the possible accumulation of the absorption enhancer SNAC.
Trial Safety Results	Adverse events were reported in 91%-93.1% of semaglutide patients across trials. Permanent treatment discontinuation due to adverse events occurred in 4.5% to 6.9% of semaglutide patients compared to 0% to 5.9% in placebo groups. Gastrointestinal disorders were the most frequent adverse events leading to discontinuation. No deaths occurred during the clinical trial periods.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	CFU	FDA Approved Indications	% Weight Loss	≥ 5% Weight Loss (OR)	≥ 10% Weight Loss (OR)
Semaglutide (WEGOVY) tablets[1,4]	TBD		- Weight loss/maintenance - CV event risk reduction in established CV disease and overweight or obesity	-11.4%	7.3	9.1
Semaglutide (WEGOVY) injection[1,5]	No	Yes	- Weight loss/maintenance - CV event risk reduction in established CV disease and overweight or obesity - MASH	-11.4%	9.82	13.32
Tirzepatide (ZEPBOUND)[6,7]	No	Yes	- Weight loss/maintenance - Moderate to severe OSA in obesity	-18.73%	19.28	18.99
Liraglutide (SAXENDA)[7,8]	No	No	- Weight loss/maintenance	-4.67%	4.91	4.8
Phentermine/Topiramate[7,9]	PA-F	Yes	- Weight loss/maintenance	-7.98%	8.02	9.74
Bupropion/Naltrexone[7,10]	PA-F	Yes	- Weight loss/maintenance	-4.11%	5.04	5.19
Orlistat[7,11]	PA-F	Yes	- Weight loss/maintenance	-3.06%	2.73	2.43

Weight loss outcomes are vs placebo. CV: cardiovascular; OSA: obstructive sleep apnea; MASH: noncirrhotic metabolic dysfunction-associated steatohepatit

POTENTIAL PLACE IN THERAPY

1. Overweight (BMI 25 to 29.9 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) is of significant concern for the U.S. healthcare system due to high prevalence in the population and the association with an increased risk of related health conditions (including type 2 DM, hypertension, dyslipidemia, metabolic syndrome, osteoarthritis, obstructive sleep apnea, noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH)) and all-cause mortality. As noted in the 2025 VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity[12], obesity prevalence ranged from 28% to 49% across 140 VHA facilities in 2017. Veterans are 12% more likely to have overweight or obesity per data from 2003- 2019.
2. In clinical trials, oral semaglutide with diet and exercise produced clinically significant weight loss over diet and exercise alone. In addition to a significant reduction in weight, results from OASIS trials have noted an improvement in surrogate endpoints (e.g., blood pressure, A1C, cholesterol) of select chronic conditions. The 2025 VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity recommends semaglutide or tirzepatide be offered to patients with a BMI $\geq$ 30 kg/m^2 and to those with a BMI $\geq$ 27 kg/m^2 who also have obesity associated conditions, as an adjunct to comprehensive lifestyle intervention.
3. There are currently no direct comparison trials of oral semaglutide to other pharmacotherapies at doses used for weight management. Indirect comparison of OASIS 4 (the only clinical trial that utilized the FDA-labelled maximum dose of 25 mg daily) outcomes to metanalysis data of injected semaglutide seems to show a similar average weight loss, though slightly lower odds ratios of achieving 5, 10, and 15% weight loss.
4. Oral semaglutide does have an indication to prevent major cardiovascular events in those with pre-existing cardiovascular disease and overweight or obesity. The direct evidence of this benefit is less certain than with injected semaglutide.[13] The only cardiovascular event outcome trials for oral semaglutide have been done at lower doses in the type 2 diabetes population[14,15]. Oral semaglutide does not have an indication for the treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH).
5. When selecting a weight management medication, a number of factors should be considered including each drug's efficacy, side effects, warnings and precautions, the patient's comorbidities, as well as the cost of the medication. Specifically, oral semaglutide's administration instructions including: taking with no more than 4 ounces of water and waiting at least 30 minutes before eating, drinking, or taking any other medications may impact choice to use this medication. As noted previously, treatment with a weight management medication should be in conjunction with comprehensive lifestyle intervention.

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