Orforglipron (FOUNDAYO) for Chronic Weight Management
National Drug Monograph

May 2026

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee 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	Orforglipron is a small-molecule glucagon-like peptide-1 receptor agonist (GLP-1 RA) 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	In combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.
Dosage Regimen	Initial dose: 0.8 mg orally daily for at least 30 days. Titration every 30 days to 2.5 mg, then 5.5 mg, then 9 mg, then 14.5 mg, then 17.2 mg once daily. Doses of 5.5mg – 17.2mg daily are considered maintenance doses. Tablets should be swallowed whole and can be taken with or without food.
Dosage Forms Under Review	Oral tablet (0.8 mg, 2.5 mg, 5.5 mg, 9 mg, 14.5 mg, 17.2 mg)

EFFICACY CONSIDERATIONS

*** Important Note: Lilly attested to the FDA that the capsule strengths used in clinical trials were equivalent to the following marketed tablet strengths: 6mg study capsule = 5.5mg tablet ; 12 mg study capsule = 9 mg tablet ; 36 mg study capsule = 17.2 mg tablet ***

Trial	**ATTAIN-1[2]**
Design	A phase 3, multinational, randomized, double-blind, placebo-controlled trial conducted over 72 weeks.
Population	3,127 adults with a body-mass index (BMI) of at least 30, or a BMI between 27 and 30 with at least one obesity-related complication (e.g., hypertension, dyslipidemia), without diabetes mellitus.
Intervention	Patients were randomly assigned 3:3:3:4 to receive once daily orforglipron (6 mg, 12 mg, or 36 mg) or placebo.
Comparator	Placebo
Results	The primary endpoint was mean bodyweight change at week 72. Orforglipron had a treatment difference of -5.5% (-6.5, -4.5) for 6 mg, -6.3% (-7.3, -5.4) for 12 mg, and -9.1% (-10.1, -8.1) for 36 mg ($p<0.001$ for all). This demonstrates both statistically and clinically significant weight loss for all maintenance doses studied. For the 36 mg dose versus placebo, key secondary weight loss targets achieved were 5% loss: 71.8% vs. 26.8%; 10% loss: 54.6% vs. 12.9%; 15% loss: 36% vs. 5.9%; and 20% loss: 18.4% vs. 2.8%. Improvements were also noted in waist circumference, blood pressure, and lipid levels.
Trial	**ATTAIN-2[3]**
Design	A phase 3, double-blind, randomized, multicenter, placebo-controlled trial lasting 72 weeks.
Population	1,613 adults with type 2 diabetes (T2D) and a BMI 27 or higher. Baseline A1C was 7-10% and other T2D therapies needed to be stable for at least 90 days prior to starting the trial. During the trial, sulfonylurea dose was halved or discontinued (if at lowest dose) at randomization. Other T2D pharmacotherapy could be started or adjusted (except for GLP-1 RAs, DPP-4 inhibitors, or amylin analogues or agonists).
Intervention	Participants were randomly assigned 1:1:1:2 to receive daily doses of orforglipron (6 mg, 12 mg, or 36 mg) or placebo
Results	The primary endpoint was mean bodyweight change at week 72. Orforglipron had a treatment difference of -2.7% (-3.7, -1.6) for 6 mg, -4.5% (-5.5, -3.6) for 12 mg, and -7.1% (-8.2, -6.1) for 36 mg ($p<0.001$ for all). This demonstrates statistically but not a clinically significant weight loss for all maintenance doses studied, except for 36 mg which was clinically significant. For the 36 mg dose versus placebo, key secondary weight loss targets achieved were 5% loss: 67.2% vs. 26.6%; 10% loss: 45.6% vs. 9%; 15% loss: 26% vs. 3%. Additionally, HbA1c treatment difference ranged from -0.76 to -1.2%.

SAFETY CONSIDERATIONS[1-3]

Boxed Warnings	Risk of Thyroid C-cell Tumors: GLP-1 receptor agonists have caused thyroid C-cell tumors in rodents. While orforglipron did not produce tumors in rodents, the human relevance of rodent thyroid C-cell tumors for this class has not been determined. FOUNDAYO is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
Contraindications	History of MTC or MEN 2; known serious hypersensitivity to orforglipron or its excipients.
Other Warnings	Warnings include acute pancreatitis, severe gastrointestinal reactions, acute kidney injury due to volume depletion, and hypoglycemia when used with insulin or secretagogues. Additional precautions involve serious hypersensitivity reactions,

	complications of diabetic retinopathy, acute gallbladder disease, and risk of pulmonary aspiration during general anesthesia.
Top 5 AEs	Based on the maintenance dose of 36 mg in clinical trials (17.2 mg marketed tablet), the most common adverse events were: nausea (35%), diarrhea (25%), vomiting (24%), constipation (24%), and abdominal pain (14%).
Drug Interactions	Strong CYP3A4 inhibitors increase exposure; the maximum FOUNDAYO dosage is 9 mg when co-administered with a strong CYP3A4 inhibitor. Avoid strong CYP3A4 inhibitors that also inhibit OATP1B (e.g., ritonavir, clarithromycin). Avoid strong CYP3A4 inducers. Simvastatin dosage should not exceed 20 mg once daily due to orforglipron's effect on simvastatin's active metabolite. Due to delayed gastric emptying, orforglipron may impact the absorption of other oral medications, including oral contraceptives.
Pregnancy	Orforglipron may cause fetal harm and should be discontinued when pregnancy is known.
Lactation	Breastfeeding is not recommended.
Trial Safety Results	Treatment discontinuation due to adverse events, primarily gastrointestinal, occurred in 5.3% to 10.3% of orforglipron patients in ATTAIN-1 and 6.1% to 10.6% in ATTAIN-2. In ATTAIN-1, five adjudication-confirmed mild pancreatitis cases occurred in the orforglipron groups.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

Medication for Weight Loss	Route of Administration	Formulary Status	CFU	FDA Approved Indications	% Weight Loss vs Baseline: treatment difference vs placebo
Orlistat [4]	Oral	PA-F	Yes	- Weight loss/maintenance	-3.06%
Naltrexone/bupropion[4]	Oral	PA-F	Yes	- Weight loss/maintenance	-4.11%
Liraglutide [4]	Subcutaneous	Nonformulary	No	- Weight loss/maintenance	-4.67%
Phentermine/topiramate[4]	Oral	PA-F	Yes	- Weight loss/maintenance	-7.98%
Orforglipron [5,2]	Oral	TBD	TBD	- Weight loss/maintenance	-4.8% to -9.1%
Semaglutide tablet[6]	Oral	Nonformulary	Yes	- Weight loss/maintenance - CV event risk reduction in established CV disease and overweight or obesity	-11.4%
Semaglutide inj [4, 7]	Subcutaneous	Nonformulary	Yes	- Weight loss/maintenance - CV event risk reduction in established CV disease and overweight or obesity - MASH	-11.4% 7.2 mg (STEP UP): -18.7%
Tirzepatide[8]	Subcutaneous	Nonformulary	Yes	- Weight loss/maintenance - Moderate to severe OSA in obesity	-18.73%

POTENTIAL PLACE IN THERAPY OF ORFORGLIPRON

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 T2D, 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[9], 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, orforglipron with diet and exercise produced clinically significant weight loss over diet and exercise alone. In addition to a significant reduction in weight, results from ATTAIN 1 and 2 have noted an improvement in surrogate endpoints (e.g., blood pressure, A1C, cholesterol) of select chronic conditions. Similar to other GLP-1 RAs, average weight loss is lower in people with T2D. Based on ATTAIN-2, orforglipron may not show clinically meaningful weight loss over diet and exercise alone in people with T2D unless the dose can be titrated to the highest maintenance dose (17.2 mg daily).
3. There are currently no direct comparison trials of orforglipron to other pharmacotherapies at doses used for weight management. Indirect comparison of clinical trial and meta-analysis outcomes to meta-analysis and clinical trial data of other weight management medications (see above) shows that orforglipron may result in less weight loss than other GLP-1 RAs.
4. Orforglipron is the second oral GLP-1 RA. Different from oral semaglutide, orforglipron can be taken with or without food. Orforglipron has more drug-drug interactions to consider than oral semaglutide (see above Safety Considerations).
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, administration considerations, as well as the cost of the medication. As noted previously, treatment with a weight management medication should be in conjunction with comprehensive lifestyle intervention.

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