



INDIAN HEALTH SERVICE

National Pharmacy and Therapeutics Committee

Formulary Brief: Long-term Pharmacotherapy for the Patient with Overweight or Obesity



-August 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of anti-obesity agents. Obesity disproportionately affects American Indian and Alaska Native (AI/IN) patients and is associated with increased risk for many comorbid conditions including coronary heart disease, type 2 diabetes, disability, and death.^{1,2} Following review and analysis, the NPTC voted to **remove phentermine** and **add phentermine/topiramate extended-release (ER)** to the National Core Formulary (NCF).

Discussion:

Obesity is a non-communicable chronic disease. Although behavioral interventions and pharmacotherapy have been proven to be effective for weight loss, weight re-gain is common after therapy is discontinued. Clinical guidelines agree that long-term management is required for successful treatment of obesity and that pharmacotherapy should be offered for patients with overweight and weight-related comorbidities, or with obesity.³⁻⁶ Clinical guidelines support those anti-obesity therapies which are approved by the U.S. Food and Drug Administration (FDA) for long-term/chronic weight management; phentermine is approved only for short term use (<3 months) and was removed from the NCF.

Five medications are currently FDA-approved for the long-term management of patients with overweight (body mass index (BMI) of ≥ 27 + at least 1 weight-related comorbidity) or obesity (BMI ≥ 30). The FDA defines effective therapy for obesity as treatment that produces at least 5% total body weight loss (greater than placebo and with a statistically significant difference) over a one-year treatment period. Each of these approved medications are recommended for use in combination with a reduced-calorie diet and increased physical activity.

Medication	Dosage	REMS	Controlled Substance	Boxed Warning	Administration	Contraindication	Adverse Events
Phentermine/topiramate ER	15/92 mg	Yes [Teratogenic risk]	CIV	No	Once daily Oral capsule	Pregnancy, glaucoma, hyperthyroidism, MAOI use	Constipation, paresthesia, dry mouth, dysgeusia, insomnia, dizziness
Orlistat	120 mg	No	No	No	Three times daily Oral capsule	Pregnancy, chronic malabsorption syndrome, cholestasis	Flatus with discharge, fecal urgency, fecal incontinence, malabsorption, hepatotoxicity, cholelithiasis, nephrolithiasis
Naltrexone/bupropion ER	8/90 mg (per day)	No	No	Yes [suicidal thoughts and behaviors]	Twice daily Two oral tablets	Hypertension, seizures, bulimia or anorexia, opioid use or withdrawal, MAOI use	Seizures, increased blood pressure and heart rate, hepatotoxicity, glaucoma, hypoglycemia
Liraglutide	3.0 mg	No	No	Yes [thyroid c-cell tumors]	Once daily Subcutaneous injection	Pregnancy, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2	Nausea, constipation, diarrhea, hypoglycemia, pancreatitis, suicidal behavior and ideation
Semaglutide	2.4 mg	No	No	Yes [thyroid c-cell tumors]	Once weekly Subcutaneous injection	Pregnancy, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2	Nausea, constipation, diarrhea, pancreatitis, hypoglycemia, suicidal behavior and ideation, acute kidney injury, retinopathy

A 2022 [network meta-analysis](#) reviewed 143 trials with ~49,000 patients and concluded that phentermine/topiramate ER and glucagon-like peptide 1 receptor agonist (GLP-1 RA) medications were the best drugs for weight reduction (% body weight change from baseline, mean difference from placebo; **phentermine/topiramate -7.79**, 95% CI: -9.28 to -6.66, **GLP-1 RA -5.76**, 95% CI: -6.30 to -5.21). A post-hoc analysis clarified that semaglutide had a larger effect than the other GLP-1 RAs (**semaglutide -11.41**, 95% CI: -12.54 to -10.27, **liraglutide -4.68**, 95% CI: -5.30 to -4.06). In this study, naltrexone/bupropion and orlistat did not produce $\geq 5\%$ average body weight reduction.⁷

In August 2022, the [Institute for Clinical and Economic Review](#) released an [evidence report](#) comparing treatments for overweight and obesity. This included a network meta-analysis which also indicated superior efficacy of semaglutide, followed by phentermine/topiramate (% body weight change from baseline, mean difference from placebo; **semaglutide -13.7**, 95% CI: -12.6 to -15.1, **phentermine/topiramate ER -9.1**, 95% CI: -7.1 to -11, **liraglutide -5.0**, 95% CI: -3.9 to -6.1, naltrexone/bupropion -4.6, 95% CI: -3.0 to -6.0). Discontinuation rates were similar among all interventions. The authors created a model analysis which predicted that phentermine/topiramate would provide the greatest value per quality-adjusted life year gained.²

**medications bolded above are currently named to the National Core Formulary*

The SEQUEL trial was designed to study extended use of phentermine/topiramate ER for a total of 108 weeks. Patients who continued the medication maintained significant weight loss (% body weight change from baseline, mean difference from placebo; -8.7, 95% CI: -10 to -7.9) with reduced rates of adverse events occurring between weeks 56-108 compared to weeks 0-56.⁸ Likewise, the STEP 5 trial was designed to study extended use of semaglutide for a total of 108 weeks. The treatment group sustained significant weight loss (% body weight change from baseline, mean difference from placebo; -12.6, 95% CI: -15.3 to -9.8) with rates of adverse events similar to the first year of treatment.⁹

There are numerous clinical trials underway designed specifically to examine the long-term effects of GLP-1 RAs on obesity and obesity-related comorbidities including heart disease, stroke, heart failure, and type 2 diabetes. Additionally, there are several investigational drugs within this class that are currently in early phase trials. Another medication, tirzepatide, combines a GLP-1 RA with a glucose-dependent insulinotropic polypeptide and has been approved for treatment of type 2 diabetes. This combination also produces weight loss, and is under investigation for the treatment of overweight and obesity.¹⁰

Findings:

Each of the five FDA-approved medications for long-term treatment of overweight and obesity may have a role in select patient populations given the differing mechanisms of action and contraindications as well as efficacy, safety, and tolerability profiles. Semaglutide has the best overall efficacy and tolerability; however, high economic burden limits its wide-spread use for treatment of overweight and obesity. Phentermine/topiramate ER is efficacious, well tolerated, and at a lower price point, offering the best overall value for long-term management of overweight and obesity. In consideration of these factors, the NPTC voted to add phentermine/topiramate extended-release (ER) to the National Core Formulary (NCF). Notably, there is a [Risk Evaluation and Mitigation Strategy \(REMS\) program](#) in place for this medication due to the risk of teratogenicity during pregnancy. In 2022, the prescriber training element of the REMS program was removed, requiring application only from the dispensing pharmacies and distributors.¹¹ The IHS National Supply Service Center has worked directly with the manufacturer to ensure access to the medication is available for all I/T/U pharmacies.

REMS required documents: (Please review [this webpage](#) for pharmacy requirements)

- (1) [Pharmacy Training Program](#)
- (2) [Pharmacy Enrollment Form – Independent Pharmacy](#)
- (3) All contents (downloadable and printable) for the [Qsymia REMS Pharmacy Training Program](#)
- (4) Fax all documents to the manufacturer REMS program at 1-855-302-6699

Key Message(s):

- Overweight and obesity are disease states with important impacts on overall patient health.
- Long-term management of overweight and obesity offers significant health benefits for patients.
- Pharmacotherapy has an important role in treatment of overweight and obesity.
- There are several medications that are safe and effective for management of overweight and obesity.
- Semaglutide and Phentermine/topiramate offer the greatest impact on weight management.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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