



**Indian Health Service**  
**IHS National Pharmacy and Therapeutics Committee**  
**Antiobesity Medications**  
**February 2014**



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**Background:**

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults along with the antiobesity medications lorcaserin, phentermine/topiramate ER combination, and orlistat for long-term use and the noradrenergic sympathomimetic drugs phentermine, diethylpropion, phendimetrazine, and benzphetamine for short-term use in weight loss. The discussion included clinical, utilization and procurement data for this class of medications. This discussion did not lead to a formulary modification; however, it was felt that a formulary brief would benefit IHS providers.

**Discussion:**

The 2013 AHA/ACC/TOS guidelines recommend pharmacotherapy as an adjunct to comprehensive lifestyle intervention in patients with a BMI  $\geq 30$  or a BMI  $\geq 27$  with comorbidity.<sup>1</sup> The principal components of an effective high-intensity, on-site comprehensive lifestyle intervention include: 1) a moderately-reduced calorie diet; 2) a program of increased physical activity; 3) the use of behavioral strategies to facilitate adherence to diet and activity recommendations. Pharmacotherapy should only be used as a potential adjunct to lifestyle interventions. Medications should be FDA-approved, and clinicians should be knowledgeable about the product label. The guidelines did not fully address the various aspects of pharmacotherapy since there was only 1 approved medication for long-term weight loss at the time of their development. New long-term use medications, phentermine/topiramate (ER) and lorcaserin have been released, along with orlistat, giving IHS clinicians the ability to further individualize long-term weight loss pharmacotherapy for patients based on side-effect profiles, efficacy, contraindications, cost, and patient specifics. There are no head-to-head studies that show a definite advantage of one agent over the other.

Orlistat inhibits pancreatic lipase, thus reducing the absorption of dietary fat. Orlistat has a favorable safety profile, but can still cause fearful gastrointestinal side effects, including oily spotting, flatus with discharge, fecal urgency, fatty/oily stools, among others.<sup>2,3</sup> Orlistat should be avoided in pregnancy, in patients with a chronic malabsorption syndrome, or liver disease as severe liver injury has been reported. In the largest long-term orlistat study, XENDOS, 3,305 patients were enrolled in a diabetes prevention program and were randomized to either placebo or orlistat. At the end of the 4-year period, both groups achieved and maintained significant weight loss with an average weight reduction of 2.7 kg in the placebo group and 5.8 kg in the orlistat group ( $P < 0.001$ ).<sup>4</sup> Earlier trials with orlistat show a 3.3 kg weight loss with 120 mg TID and 2.5 kg loss with 60mg TID after two years.

Lorcaserin is a selective serotonin 2C receptor agonist and works by stimulating serotonin receptors resulting in satiety and decreased food intake. The serotonin receptor specificity greatly reduces the risk of valvulopathy associated with previous nonselective serotonin agonists such as fenfluramine. Lorcaserin is contraindicated in pregnancy and warnings for the drug include co-administration with other serotonergic or antidopaminergic agents and its use in valvular heart disease patients. Most common adverse reactions include headache, hypoglycemia, decreased lymphocytes, back pain, and upper respiratory tract infection/nasopharyngitis.<sup>9</sup> In three major placebo controlled RCTs, BLOOM, BLOSSOM, and BLOOM-DM, lorcaserin reduced body weight in patients by approximately 3.2 kg more than placebo (mean weight loss between 4.5 and 5.8%) and significantly more patients treated with lorcaserin 10mg BID vs. placebo lost at least 5% (BLOOM [47% vs 20%], BLOSSOM [47% vs 25%], BLOOM-DM [37% vs 16%]) or at least 10% (BLOOM [23% vs 8%], BLOSSOM [23% vs 10%], BLOOM-DM [16% vs 4%]) of their initial weight.<sup>10-12</sup>

Phentermine plus topiramate extended-release (ER) fixed combination is designed to combine the appetite-depressing sympathomimetic effect of phentermine with the satiety-prolonging properties of topiramate. When used together, dosing of the individual drugs can be reduced, and the two drugs also mitigate each other's side effects. The medication is administered as a once-daily capsule with 4 fixed dose combinations and the dosage is titrated to the top dose if weight loss is inadequate. The contraindications for the combination are similar to those of phentermine alone: pregnancy, glaucoma, hyperthyroidism and MOAI use. Warnings for the combination are concern for fetal toxicity, increased heart rate, metabolic acidosis, elevated creatinine and hypoglycemia as well as cognitive impairment and mood disorders, including risk of suicidal behavior and ideation present with topiramate use.<sup>13</sup> In two phase 3 placebo-controlled clinical trials (EQUIP and CONQUER), phentermine/topiramate ER has shown a mean weight loss between 10.9% and 9.8% of initial body weight at the higher 15/92 mg dose. In the CONQUER trial the one-year mean weight loss was 8.1 kg from baseline at the 7.5/46 mg dose and 10.2 kg (9.8% of total body weight) with the 15/92 mg dose vs. 1.4 kg with placebo.<sup>14,15</sup> In an extension to the CONQUER trial, the SEQUEL trial, followed patients for a total of 108 weeks and patients had a sustained weight loss of 9.3% of their total body weight at the 7.5/46 mg dose and 10.5% at the 15/92 mg dose.<sup>16</sup>

## Findings:

Current antiobesity agents induce moderate but significant weight loss compared to placebo as an adjunct to lifestyle modification. Head-to-head comparison trials are not available at this time. Obesity medications approved for long-term use, when prescribed with lifestyle interventions, produce additional weight loss relative to placebo ranging from approximately 3% to 5% of initial weight for orlistat and lorcaserin to 10% for top-dose (15/92 mg) phentermine plus topiramate ER at 1 year. The proportion of patients achieving clinically meaningful (at least 5%) weight loss ranges from 37% to 47% for lorcaserin, 35% to 73% for orlistat, and 67% to 70% for top-dose phentermine plus topiramate–extended release.<sup>17</sup> All 3 medications produce greater improvements in many cardiometabolic risk factors than placebo, but no obesity medication has been shown to reduce cardiovascular morbidity or mortality. Further studies are needed to determine the long-term health effects of obesity medications. **Pharmacotherapy for obesity should be viewed as an adjunct to, not substitutes for, changes in lifestyle.** Without sustainable changes in diet, exercise, and behavior patients are unlikely to receive sufficient reductions from drug therapy alone. Even more important is addressing American Indian youth who are affected disproportionately by the epidemic of obesity and its comorbidities through integrating culturally appropriate healthy diets and increased activity at an early age. This may be accomplished through the use of programs such as the Diabetes Prevention Demonstration Project's best practices.

If you have any questions regarding this document, please contact the NPTC at [nptc1@ihs.gov](mailto:nptc1@ihs.gov).

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