Background:
The National Pharmacy and Therapeutics Committee (NPTC) reviewed the pharmacological treatment of obesity at its Summer 2018 meeting. This topic was last reviewed by the NPTC in February 2014 and no medications were added to the National Core Formulary (NCF) at that time. Although the NCF currently contained no approved medications for obesity treatment, several medications on the NCF have a role in weight management. Following extensive discussion, the NPTC added phentermine to the NCF.

Discussion:
Obesity, defined as a body mass index (BMI) of ≥30 kg/m², is a complex, chronic disease that is highly prevalent in U.S. adults, affecting nearly 40% of adults in 2015-2016. Lifetime risk of significant health conditions including heart disease, stroke, diabetes, and certain types of cancers is increased by obesity. American Indians and Alaskan Natives (AI/AN) have similar rates of patients classified as overweight (BMI ≥ 25 kg/m²) as other races/ethnicities but are 50% more likely to have obesity than non-Hispanic whites. Additionally, AI/AN adolescents are 30% more likely to have obesity when compared with non-Hispanic white counterparts. Medical costs for patients with obesity are substantially higher per patient ($1429 more reported) than in those at normal weight.

The goals for treatment of individuals with overweight and/or obesity are to reduce body weight and improve overall health. Treatment of obesity is multifaceted, requiring a variety of interventions and healthcare providers to be successful and sustainable. Modest to moderate weight loss can result in significant health benefits and life-long, chronic treatment is indicated as weight re-gain commonly occurs following medication discontinuation. The cornerstone to the treatment of obesity is comprehensive lifestyle intervention, which includes dietary enhancement, physical activity, sleep, stress and behavioral modification. Review of the patient’s medication list (Table 2) for drugs contributing to weight gain is also strongly encouraged. Obesity medications are frequently used as ancillary to these lifestyle modification and are recommended in patients with either (1) BMI ≥ 30 kg/m² or (2) BMI ≥ 27 kg/m² with at least one co-morbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes). Medications should be re-evaluated following 12-16 weeks of use (adherence and efficacy) to determine if continuation, discontinuation or dose titration is indicated. Loss of 3-5% total body weight at 3 months is used to define initial success.

Several, older sympathomimetic medications indicated for short-term weight management (e.g., phentermine, phendimetrazine, diethylpropion) have been used for decades and have demonstrated positive results despite little available literature on long-term safety and efficacy. Since 1999 however, five new anti-obesity medications received FDA approval for chronic weight management (i.e., >12 weeks), namely liraglutide, lorcaserin, orlistat and the drug combinations of bupropion-naltrexone and phentermine-topiramate. Profiles for the chronic anti-obesity medications along with phentermine are detailed below according to their approval date. Clinicians are encouraged to review individual medication profiles and tailor pharmacotherapeutic selection according to patient characteristics and expectations, outcomes and probability of sustained success.

Phentermine (Adipex-P®, Lomaira®)
Phentermine was originally approved for use in weight management in 1959 and remains the most commonly prescribed anti-obesity medication today, both within the IHS and the United States. It has pharmacologic properties similar to amphetamines and acts via the sympathomimetic pathway to reduce appetite. Advantages of phentermine include its long history of availability and use in millions of patients, minimal adverse event profile, low cost due to multiple generics and flexible dosing. Limitations for phentermine use include its scheduled status as a C-IV drug, modest weight loss, contraindication in patients with uncontrolled HTN or CVD and short-term approved indication (<12 weeks). Long-term use of phentermine, albeit off-label, is common, has demonstrated no potential for abuse/addiction, and is supported in guidelines, provided clinicians review and follow suggested guidance.
Orlistat (Xenical®, Alli® [OTC])<sup>6,4</sup>

Orlistat was originally approved for obesity treatment in 1990 but became available over-the-counter in 2007. As a lipase inhibitor, orlistat works to reduce intestinal absorption of dietary fats by approximately 30%. Orlistat offers clinicians the benefit of OTC availability and lower cost, availability of long-term data, modestly reduced incidence of diabetes in hyperglycemic patients and lowered blood cholesterol levels. Limitations to orlistat use include minimal weight loss comparatively and notable adverse events including flatulence (with discharge) and steatorrhea, which contribute to its high discontinuation rate (~30%).

Lorcaserin (Belviq®)<sup>3,4</sup>

Lorcaserin was approved in 2012 and is the only anti-obesity medication to activate serotonin 5-HT2c receptors, which results in satiety and decreased food intake. Benefits to lorcaserin use include a mild side effect profile, reduction of total cholesterol and triglycerides (although no benefit of LDL or HDL) and safe use in patients with obesity and CVD, HTN or diabetes. Higher drug costs, modest weight reduction, drug scheduling (C-IV) and potentially increased risk (animal studies only) of certain malignancies (e.g., breast) limit broad use of lorcaserin.

Phentermine/Topiramate ER (Qsymia®)<sup>4,5,8</sup>

The inclusion of extended-release topiramate with phentermine was approved in 2012 despite the pathway by which topiramate exerts its weight-lowering effects remains uncertain. Due to topiramate’s known teratogenicity, the FDA maintains a Risk Evaluation Mitigation Strategy (REMS) for the combination product. Prescriber enrollment is encouraged however pharmacies are required to certify prior to drug dispensation. Of note, in patients of childbearing age, monthly pregnancy tests are suggested. Despite the REMS requirements, phentermine-topiramate provides arguably the greatest weight loss of the obesity drugs with a more favorable adverse effect profile. Moreover, it has positive benefits on total, HDL and LDL cholesterol. Drawbacks include drug scheduling (C-IV), higher reported rates of depression and anxiety (4-7 times higher) and potentially reduced ethinyl estradiol levels. Of note, the individual components of Qsymia®, used alone or in combination, are now available on the NCF.

Naltrexone/Bupropion SR (Contrave®)<sup>4,5,8</sup>

Approved in 2014, naltrexone/bupropion is the second combination medication product for chronic weight management. Bupropion is well known to reduce cravings for both nicotine and food although the overall benefit from the synergism is not completely understood. Naltrexone/bupropion has mid-to-high efficacy for weight reduction, minimal adverse events and positive benefits on all major lipoproteins. Additionally, the combination is not a controlled substance but its use is contraindicated in patients receiving opioids. Transient increases in heart rate and blood pressure are common in the initial 3 months of therapy, precluding its use in uncontrolled HTN. A boxed warning of suicide risk in depression is also listed on the product label, although patients ≥24 years showed no increased risk of suicidal thoughts of behaviors. Of note, the individual components of Contrave®, used alone or in combination, are available on the NCF.

Liraglutide (Saxenda®)<sup>4,5,8</sup>

Liraglutide, a GLP-1 receptor inhibitor, is more commonly known for its role in the management of Type 2 diabetes mellitus. Branded differently as a weight loss medication, liraglutide (Saxenda®) is a weekly injectable medication and its dosing (3 mg per week) is higher than that used for diabetes. Owing to its effect on insulin release, hypoglycemia is a major concern and caution is advised in patients receiving other anti-diabetic medications. Furthermore, a boxed warning on thyroid cancer risk remains a concern (although only observed in animal studies) while use is contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia. A Saxenda® REMS is in place.

**“Guidelines & Comparative Reviews”**

Three contemporary guidelines from professional organizations on obesity management are available for review including those from the American Heart Association, American College of Cardiology and The Obesity Society (2013), The Endocrine Society (2015) and the American Academy of Clinical Endocrinologists (2016). A recent 2018 review of the aforementioned clinical guidelines is also available which succinctly details similarities and differences. Regarding initial pharmacotherapeutic preference in obesity treatment, the guidelines collectively make no recommendations towards any specific medication but rather emphasize the adjunctive role of pharmacotherapy (to proven lifestyle interventions) in the global effort to address and manage overweight/obesity. Lastly, a 2014 VA/DoD clinical practice guideline is available for review and is notable due to its pharmacotherapeutic preference recommendations.
Methodologically sound reviews of anti-obesity medications comparing active and placebo controls are rare. A 2016 meta-analysis compared safety and efficacy data from the five long-term indicated anti-obesity medications. All data was derived from 28 randomized, controlled trials comprised of 29,018 patients receiving anti-obesity medication for at least 1 year. Researchers reported that 23% of placebo patients achieved a predefined 5% weight loss while 75% patients on phentermine-topiramate met the 5% weight loss metric; as did 63% taking liraglutide; 55% taking naltrexone-bupropion, 49% taking topiramate and 44% taking orlistat. Weight loss at 1 year for each agent is as follows: 8.8 kg for phentermine-topiramate ER (95% CI: -10.20 to -7.42 kg); 5.3 kg for liraglutide (95% CI: -6.06 to -4.52 kg); 5.0 kg for naltrexone-bupropion (95% CI: -5.94 to -3.96 kg); 3.2 kg for topiramate (95% CI: -3.97 to -2.46 kg); and 2.5 kg for orlistat (95% CI: -3.04 to -2.16 kg). Conversely, the odds of discontinuing the medication due to adverse events were highest for liraglutide (OR: 2.95; 95% CI: 2.11-4.23); followed by naltrexone-bupropion (OR: 2.64; 95% CI: 2.10-3.35). Lorcaserin was associated the lowest odds of discontinuation, comparatively.

Off-label medications
Several common non-FDA approved medications have been used in weight management for years including bupropion, exenatide, metformin, topiramate, and zonisamide. Prescribers choosing to utilize off-label medications for weight loss are encouraged to (1) advise patients of their lack of FDA approval, (2) detail the risks and benefits of this treatment approach with the patient and (3) document all reviewed topics with the patient in the patient’s medical record. Not surprisingly, little published information is available on the safety and efficacy of these off-label medications for obesity treatment.

Findings:
With the recent addition of phentermine to the National Core Formulary, there are now several medications available that have a role in the current treatment of obesity. To date, no anti-obesity medication has been shown to directly reduce cardiovascular morbidity or mortality, with the exception of liraglutide for the treatment of patients with Type 2 diabetes. Pharmacotherapy offers patients receiving guideline-recommended lifestyle interventions the added benefit of improved long-term weight maintenance, ameliorated co-morbidities and enhanced adherence to behavioral modifications.

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: