INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***GLP1 and GLP1/GIP RAs in DM2 and Obesity***
-October 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of the glucagon-like peptide-1 receptor agonists (GLP1-RA) and GLP1/glucose-dependent insulinotropic peptide receptor agonists (GIP-RA) agents. Prior to this review, the IHS National Core Formulary (NCF) included "semaglutide or liraglutide" for the treatment of type 2 diabetes mellitus (DM2). For treatment of obesity, the NCF included extended-release phentermine/topiramate. Following review and analysis, the NPTC voted to (1) **ADD semaglutide (Wegovy®) with recommended local adoption of criteria for use**, (2) **REMOVE extended-release phentermine/topiramate**, and (3) **REMOVE liraglutide** from the NCF.

Discussion:

Obesity is a complex disease defined as weight greater than what is considered healthy for a given height. Body mass index (BMI) is used as a screening and monitoring tool. Obesity affects 1 in 5 children and 1 in 3 adults in the United States (US). An estimated $147 billion is spent on obesity-related healthcare per year[1]. In 2022, 48% of American Indian and Alaska Native (AI/AN) people carried a diagnosis of obesity compared to 31% of non-Hispanic white people, with higher risk in women, people living in communities ≥30-minute drive from primary care, and those living in communities with high poverty rates[2]. Prevalence of obesity among AI/AN children and adolescents was the highest in the country at 18.4% in 2020[3]. Health consequences of obesity include increased risk of endocrine disease, malignancy, osteoarthritis, respiratory disorders, infectious complications, reproductive challenges, dementia, and impaired mental health[4]. DM2 is the most common obesity-related morbidity, with DM2 risk increasing as BMI increases[4]. A 2010 study of AI children whose BMI was in the highest quartile found them to be two times more likely to die from endogenous causes than children in the lowest BMI quartile[4]. Causes of obesity include genetic factors, environmental factors, social determinants of health and more. Treatment always includes lifestyle modification interventions with the addition of pharmacologic agents and even referral for surgical intervention (when indicated for higher-risk persons) if behavioral changes fail. As little as 3-7% total body weight (TBW) loss reduces risk of obesity-related complications and >10% TBW loss is known to improve DM2 and long term cardiovascular (CV) outcomes[20].

Weight stigma refers to social devaluation of individuals because of excess body weight and can lead to negative attitudes, stereotypes, prejudice, discrimination, and poor health outcomes[5,6]. Treatment of patients with obesity should use patient-first language, motivational interviewing, and focus on healthy behaviors rather than weight[6]. Resources about weight bias and stigma can be found on the UConn Rudd Center for Food Policy and Health[7].

Type 2 Diabetes Mellitus (DM2) risk increases as obesity increases. Population studies show that up to 53% of new DM2 cases are attributable to development of obesity[8]. AI/AN adults are 3 times more likely than non-Hispanic white adults to be diagnosed with DM2 and 2.3 times more likely to die from DM2[9]. AI/AN patients have compounded risk with high rates of obesity and high rates of diabetes and will benefit from therapies that address both disease states.

Role of GLP1-RAs and GLP1/GIP-RAs in the treatment of DM2 and obesity. Semaglutide, liraglutide (GLP1-RAs) and tirzepatide (GLP1/GIP RA) were reviewed. Semaglutide and liraglutide are approved for use in treatment of DM2 (Ozempic®, Victoza®) and obesity (Wegovy®, Saxenda®), respectively. Tirzepatide (Mounjaro®) is FDA approved for treatment of DM2. These medications have similar side effect profiles, including a black box warning for risk of thyroid C-cell tumors and are contraindicated for patients with multiple endocrine neoplasia, type 2 (MEN2); increased risk of GI side effects (pancreatitis, gall stone and biliary disease) and acute kidney injury (AKI)[9-11]. Semaglutide and tirzepatide have been associated with increased rates of diabetic retinopathy (DR)[9,11]. Semaglutide is approved for use in patients ≥12 years of age (yoa), while liraglutide is approved for use in ≥10yoa, and tirzepatide is approved for use in ≥18yoa[9-11].

Liraglutide (once daily subcutaneous injection) has been compared to once weekly semaglutide for the treatment of DM2 and obesity. SUSTAIN-10, a head-to-head randomized trial (RCT) found semaglutide 1mg weekly was superior to liraglutide 1.2mg daily in all end points: target A1C of <7.0% and ≤6.5%, weight loss of ≥5% and ≥10%, and a composite endpoint of HbA_{1c} <7.0% without severe hypoglycemia and no weight gain (all $p<0.0001$)[13]. In 2022, the STEP-8 trial compared semaglutide 2.4mg weekly to liraglutide 3.0mg daily, showing liraglutide inferiority for TBW change (-15.8% vs. -6.4%; $p<0.001$) and higher rates of discontinuation with liraglutide[14]. These data helped support the decision to *remove liraglutide from the NCF* due to better efficacy and value with semaglutide, which is currently listed on the NCF.

Semaglutide and Tirzepatide for use in DM2: Large phase 3, manufacturer-funded RCTs evaluating semaglutide (SUSTAIN trials) and tirzepatide (SURPASS trials) have demonstrated superiority of both drugs against placebo and

active comparators for the treatment of DM2. SUSTAIN trials 1-5 and 7 demonstrated superiority of semaglutide compared to placebo, sitagliptin, exenatide, glargine, metformin, and dulagtuide[15]. The SURPASS trials demonstrated superiority of tirzepatide over placebo and active comparators. SURPASS-2 is a head-to-head comparison of semaglutide (1mg weekly) versus tirzepatide (5mg, 10mg and 15mg) including 1879 patients with an average A1C of 8.28%, mean age of 56 years and mean weight of 93.7kg[22]. AI/AN participants accounted for 11% of the study group and patients with history of DR were excluded. Tirzepatide (all strengths) showed statistically significant superiority in A1C control compared to semaglutide 1mg, with an absolute decrease in A1C of 0.44% with max dose tirzepatide (15mg). Named to the NCF in 2019, semaglutide continues to provide excellent efficacy and value. A1C improvement with tirzepatide is marginal; *no change was made with regard to GLP1/GIP-RAs for treatment of DM2*.

Clinical practice guidelines regarding use of GLP1-RAs and GLP1/GIP-RAs for treatment of diabetes do not mention specific agents. GLP1-RAs are recommended as first line DM2 therapy in patients who are high risk for or have atherosclerotic cardiovascular disease (ASCVD) and should be considered in patients with DM2 associated kidney disease if SGLT2 inhibitors are contraindicated[17].

Treatment of Obesity: At the time of this clinical review, semaglutide and liraglutide both carry an FDA indication for treatment of obesity while tirzepatide does not. The SURMOUNT-1 trial was a large, industry-funded RCT that enrolled 2538 patients with a BMI of ≥30 or ≥27 with obesity related comorbidities and compared placebo to tirzepatide (5mg, 10mg, 15mg) for 72 weeks with a 20-week dose escalation period[21]. Primary outcomes were percentage of TBW loss from baseline and TBW reduction of ≥5%. Secondary outcomes included TBW loss of ≥10%, ≥15% and ≥20%. Results demonstrated superiority of tirzepatide (all strengths) in both primary outcomes, with an average of 20.9% TBW loss in the 15mg group. Metabolic markers (lipids, blood pressure) and physical function scores also improved. Notably, 35% of patients in the placebo arm met both primary outcomes with their only intervention being regular, professional lifestyle counselling regarding healthy diets, calorie deficits and physical exercise goals.

Prior NPTC reviews evaluated the efficacy of semaglutide for treatment of obesity including a comprehensive review in 2022 of the STEP trials demonstrating superiority of semaglutide over placebo and active comparators. Semaglutide 2.4mg weekly was felt to be the most clinically effective pharmacologic therapy, however potential economic burden and high utilization was of concern and thus was not added to the NCF. Extended-release phentermine/topiramate was added to the NCF after review of clinical efficacy and value. Barriers to use of extended-release phentermine/ topiramate including REMS certification and challenging drug acquisition significantly limited its use in the agency, highlighted during the ongoing NPTC Formulary Alignment project. For these reasons, *phentermine/topiramate was removed from the NCF*.

Wegovy® pricing recently met the $50,000/QALY cutoff set by many value-based analyses including a recent Institute for Clinical and Economic Review report[23]. Given improvement in the value per QALY of Wegovy®, good clinical efficacy, and high burden of obesity and related comorbidities in the AI/AN population, the NPTC *added semaglutide (Wegovy®) for the treatment of obesity with recommended local adoption of criteria for use*.

Recommendations for implementing local Criteria for Use: Criteria for use (CFU) is a set of clinical criteria that must be met for eligibility for use of specific therapy. The VA P&T committee develops CFUs based on efficacy and value. Access to VA CFUs for non-formulary or prior authorization-formulary drugs can be found on the VA Formulary Advisor website. In the IHS, CFU enforcement should occur at the local level due to heterogeneity of populations, clinic types and pharmacy size. The VA's CFU for Wegovy® can be accessed here and are encouraged as a potential model for adaptation by IHS local P&T committees, when indicated and following appropriate deliberation, suitable to the needs of the local service population. Criteria are summarized below.

VA Exclusion criteria include: Pregnancy; breastfeeding; type 1 diabetes; personal or family history of medullary thyroid carcinoma or with MEN2; severe gastrointestinal dysmotility, including gastroparesis, history of pancreatitis (except in patients for whom the cause of pancreatitis is known and no longer presents a risk); a history of suicidal attempts or active suicidal ideation (unless mental health consultation supports benefits); concurrent use of another medication FDA approved for weight loss; known proliferative diabetic retinopathy (PDR), severe non-PDR, clinically significant macular edema (ME), or diabetic ME (unless risks/benefits have been discussed with the patient, documented in EHR, and monitoring plans/follow-up exist with an eye specialist who is informed at the time of the initiation).

VA Inclusion criteria include (must meet all three initial criteria): Verifiable participation in a comprehensive lifestyle intervention targeting diet, physical activity, and behavioral changes; BMI ≥30 OR BMI ≥27 with at least one weight-related comorbidity and medications associated with weight gain discontinued when appropriate PLUS one or more of the following: Failure of ≥2 agents for chronic weight management with documented intolerance, inadequate (e.g., <5%) reduction TBW, or are medically inadvisable; BMI ≥40 -OR- BMI ≥35 with a significant or difficult to manage weight-related condition -OR- is unable to achieve weight loss goals required for surgery -OR- has DM2 treated with semaglutide AND requires additional weight loss to achieve ≥5% reduction in TBW[25].

Findings:

Obesity is common and disproportionately affects AI/AN patients as do obesity-related adverse outcomes including DM2. Death from obesity and DM2 is greater in AI/AN children and adults. Obesity and diabetes are inextricably linked and effective treatment options are rapidly emerging. GLP1-RAs are highly effective for the treatment of obesity and diabetes. Semaglutide for treatment of DM2 is on the NCF and provides excellent clinical efficacy and value. Liraglutide had been shown to be less effective for treatment of both obesity and DM2 and has been removed from the IHS NCF. Tirzepatide is the first in a new class of GLP1-GIP RAs and is effective for the treatment of DM2, the only indication it currently carries as of the time of this clinical review. Compared to semaglutide, tirzepatide had superior, but marginal efficacy difference in A1C control. Based on value, semaglutide was retained as the only GLP1-RA and/or GLP1-GIP RA agent on the NCF.

Treatment of obesity is an agency priority given its prevalence and risk to AI/AN health. The efficacy and value of semaglutide (Wegovy®) meet the highest standards for treatment of obesity and was added to the NCF to improve access to the pharmacy benefit and improve health outcomes for all AI/AN patients. Pending anticipated approval of additional products in these drug classes, subsequent NPTC review is planned.

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.

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