Clinical Bulletin

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Additional Therapy Approved for Chronic Weight Management

On June 4, 2021, the FDA approved Novo Nordisk's Wegovy™ (semaglutide), as an addition to diet and exercise for chronic weight management in adults with obesity or who are overweight with at least one weight-related condition like high blood pressure, type 2 diabetes, or high cholesterol. It is the first approved drug for chronic weight management in adults since 2014. Wegovy is a glucagon-like peptide-1 (GLP-1) receptor agonist and works by mimicking GLP-1 to stimulate insulin production, decrease appetite, and increase feelings of fullness. Wegovy is available in pre-filled, single dose pens and the dosing is titrated over 17 weeks to a subcutaneous 2.4mg weekly dose.

Semaglutide has been FDA approved under the trade name Ozempic ® since 2017. Originally it was indicated with diet and exercise to improve blood sugar in adults with type 2 diabetes. In early 2020, Ozempic received an additional indication to reduce the risk of major cardiovascular events such as heart attack, stroke, or death in adults with type 2 diabetes and heart disease. It is available as a single patient use pen that delivers 0.25, 0.5 mg, or 1 mg per injection. The dosing frequency is once weekly. An oral form of semaglutide was approved by the FDA in 2019 under the trade name Rybelsus®. It was the first oral GLP-1 receptor protein treatment approved to control blood sugar in adult patients with type 2 diabetes. It is available as a 3, 7, and 14 mg tablet. The recommended dosing frequency is once daily.

Approximately 74% of American adults are considered obese or overweight. Body Mass Index (BMI) estimates body fat based on height and weight and is a useful measure of overweight and obesity. A BMI between 25 and 29.9 is considered overweight. A BMI greater than 30 is considered obese. Being obese or overweight is a serious health issue associated with some leading causes of death, including heart disease, stroke, and diabetes, and is linked to an increased risk of breast cancer, colon cancer and leukemia. Obesity also has been identified as a major risk factor for developing severe complications from COVID-19 for people of all ages, including children. Losing 5% to 10% of body weight through diet and exercise has been associated with a reduced risk of cardiovascular disease in adult patients with obesity or who are overweight. In the late 1970s, obesity rates among adults in the United States were around 15% according to the Centers for Disease Control and Prevention (CDC). Based on 2018 data from the CDC, these rates have almost tripled to over 42%.

Wegovy's safety and efficacy were studied in four 68-week STEP trials. Three were randomized, double-blind, placebo-controlled trials. Baseline characteristics of study participants included a mean age of 48 years, 71% women, 72% White, 42% with hypertension, 19% with type 2 diabetes, 43% with dyslipidemia, 28% with a BMI greater than 40 kg/m2, and 4% with cardiovascular disease. Patient inclusion criteria did not require participants to have previously failed diet and exercise programs. One study was a double-blind, placebo-controlled, randomized withdrawal trial in which patients receiving Wegovy either continued with the treatment or switched to a placebo. More than 2,600 patients received

Wegovy for up to 68 weeks in these four studies and more than 1,500 patients received placebo. All participants met with the study staff to discuss healthy food choices, how to be more physically active, and what else the participant can do to lose weight.

The largest placebo-controlled trial enrolled adults without diabetes. The average age at the start of the trial was 46 years and 74% of patients were female. The average body weight was 231 pounds (105 kg) and average BMI was 38 kg/m^2. Individuals who received Wegovy lost an average of 12.4% of their initial body weight compared to individuals who received placebo. Another trial enrolled adults with type 2 diabetes. The average age was 55 years and 51% were female. The average body weight was 220 pounds (100 kg) and average BMI was 36 kg/m^2. In this trial, individuals who received Wegovy lost 6.2% of their initial body weight compared to those who received placebo. Unpublished data from a new trial study called STEP 5 showed treatment with Wegovy over almost two years led to an average weight loss of 17%, with 40% of patients losing 20% or more of body weight. Those who took Wegovy lost weight steadily for 16 months before plateauing.

The most common side effects of Wegovy include nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, belching, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease. Episodes of hypoglycemia have been reported with GLP-1 receptor agonists in patients without type 2 diabetes mellitus. However in the Wegovy clinical trials, hypoglycemia was not a reported adverse reaction in patients without type 2 diabetes mellitus. Reported side effects typically resolved on their own. Less than 7 percent of participants discontinued treatment due to an adverse reaction.

Wegovy is the fifth FDA approved medication for chronic weight management. Saxenda® (liraglutide), is another injectable GLP-1 agonist. There are also three oral therapies: Contrave® (bupropion/naltrexone), Qysmia ® (phentermine/topiramate), and Xenical® (orlistat). Contrave and Qsymia work to improve appetite regulation, while Xenical inhibits the absorption of dietary fats. Saxenda has roughly 85% of sales in the category has been shown to help patients lose 5% of their body weight on average. Although not compared head-to-head, the clinical data from the clinical trials may indicate that Wegovy may have an improved efficacy profile as compared to Saxenda.

Novo is already planning for more convenient dosing for Wegovy. Later this year, they plan to begin a 1,000-subject phase 3a trial to assess the safety and efficacy of oral semaglutide 50 mg versus placebo in patients who are obese or overweight with comorbidities. While Rybelsus (semaglutide) is not a weight loss medication, research has shown that after 26 weeks, patients on Rybelsus 7mg lost an average of 5 pounds while patients on 14mg lost just over 8 pounds.

Novo Nordisk launched Wegovy on June 10th and it should be available by June 18. It has a flat price of $337.25 per injection which equates to a monthly cost of $1,349. As expected, Wegovy is comparably priced to Saxenda, Novo's previously approved weight loss drug.

Reimbursement and patient access will determine the magnitude of Wegovy utilization. Insurers have historically been reluctant to pay for weight loss drugs, which many classify as lifestyle meds such as smoking cessation and hair loss treatments. Lifestyle interventions are typically recommended first-line for weight loss, and can include dietary modifications, exercise, and behavioral therapy. The role of GLP-1 agonists in weight management still needs to be determined. Clinical trial data suggests that Wegovy may work better for treating obesity than any other previously approved drugs, but this needs to be demonstrated through direct head-to-head clinical trials. If Wegovy mitigates long-term medical complications of obesity with a manageable safety profile including impact on glucose metabolism, payers may consider its reimbursement as medically necessary for obese patients who have failed conventional approaches.

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New Ulcerative Colitis Indication for Zeposia

On May 27, 2021, the FDA approved Zeposia ® (ozanimod) for the treatment of adults with moderately to severely active ulcerative colitis (UC). Zeposia is an oral medication taken once daily and the first sphingosine 1-phosphate (S1P) receptor modulator approved for patients with ulcerative colitis. It was originally approved in March of 2020 for relapsing forms of multiple sclerosis (MS). The mechanism by which Zeposia exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into the intestines. It is thought that by targeting S1P receptors on lymphocytes, a type of immune system cell, Zeposia reduces the number of lymphocytes in peripheral blood.

Ulcerative colitis is a chronic inflammatory bowel disease that causes inflammation and ulcers (sores) in the mucosa (lining) of the large intestine (colon) or rectum. The exact cause of ulcerative colitis is unknown but appears to be an immune system malfunction. When the immune system tries to fight off

an invading virus or bacterium, an abnormal immune response causes the immune system to attack the cells of the digestive tract. It is estimated that about 1 million people in the United States have UC.

The approval of Zeposia for UC is based on data from True North, a pivotal Phase 3, multicenter, randomized, double blind, placebo-controlled clinical trial that assessed the efficacy and safety of Zeposia 0.92 mg once daily in patients with moderately to severely active UC who had an inadequate response or were intolerant to any of the following: oral aminosalicylates, corticosteroids, immunomodulators, or a biologic. The True North study comprised 2 periods: a 10-week induction period and a 52-week maintenance period.

Patients were required to be on oral aminosalicylates (Colazal®, Canasa®, Asacol®) and/or corticosteroids prior to and during the induction period. A total of 30% of patients had previously failed or were intolerant to TNF blockers. Of these patients, 63% received at least two biologics, including TNF blockers (e.g. Humira®, Simponi®).

The trial met its primary endpoint of clinical remission during induction at week 10, as well as secondary endpoints including clinical response, endoscopic improvement, and endoscopic-histologic mucosal improvement as compared to placebo. During maintenance at week 52, Zeposia also improved clinical remission and met the same key secondary endpoints as the induction phase. In addition, decreases in rectal bleeding and stool frequency subscores were observed as early as week 2 in patients treated with Zeposia. At this time, Zeposia has not been studied head-to-head against other biologics like TNF inhibitors.

Injectable anti–tumor necrosis factor (TNF) drugs like infliximab (Remicade®), Humira® (adalimumab), and Simponi®(golimumab) lead the UC category in market share. Each one either currently has a less expensive biosimilar competition already or will in the near future. Stelara® (ustekinumab), an interleukin (IL)-12/23 antibody. Entyvio® (vedolizumab), an integrin blocker, and Xeljanz® (tofacitinib), an oral janus kinase (JAK) inhibitor, have each captured increased UC market share in recent years as well.

Novartis' Gilenya® (fingolimod) and Mayzent® (siponimod) are also S1P receptor modulators indicated for MS but neither is pursuing an inflammatory bowel disease indication. However, S1P products may hold a potential advantage compared to the oral JAK inhibitors due to their safety profile. Zeposia also has the advantage of oral administration compared with anti–tumor necrosis factor (TNF) drugs, Entyvio, and Stelara, which are infused or injected.

Despite its good safety profile and oral formulation, Zeposia is not cost advantageous. At a cost of $89,870 per year, Zeposia is a high-priced UC therapy compared with its competitors. The annual cost for Entyvio is $47,298, Humira is $77,586, Simponi is $68,466, Avsola (infliximab biosimilar) is $21,125, and Xeljanz is $59,988. Only Stelara has a higher annual cost at $157,000.

Ulcerative colitis is already a crowded category and is set to gain more competition. There are 7 additional UC products in Phase 3 clinical trials, including 3 interleukin-23 (IL-23) inhibitors, 2 Janus kinase (JAK) inhibitors, and one additional S1P product. Estrasimod, an oral, highly selective S1P receptor modulator, completed enrollment in its phase 3 ELEVATE UC 52 trial and expects top-line data in the first quarter of 2022. Other notable products that hope to gain an indication for UC include Skyrizi®, an IL-23 inhibitor, Rinvoq™, a JAK inhibitor, and deucravacitinib, a tyrosine kinase 2 (TYK2) inhibitor.

As the first S1P receptor modulator for UC, Zeposia provides another treatment alternative, especially for many patients who do not respond or have an inadequate response to currently available therapies. It remains to be seen where Zeposia will fall in the ulcerative colitis treatment algorithm.

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