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EMERGINGTHERAPEUTICS

Pharmacological Interventions for Obesity
Issues Document

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Summary

Obesity is a chronic health condition that should be managed long-term. Over the past few decades, obesity has steadily increased in the U.S. and it continues to be a health concern for children, adolescents and adults. Increased weight is a risk factor for many conditions including diabetes, high cholesterol and high blood pressure. Studies have shown that even a moderate weight loss (5% to 10% from baseline) can decrease the severity of these obesity-associated conditions when it is sustained. Historically, weight-management drugs and supplements have been plagued by low effectiveness, rebounding weight gain, undesirable side effects and/or safety concerns. However, some recent FDA approved and near-term pipeline agents will challenge this narrative and require a closer look. This document provides an overview of currently available obesity drugs and highlights therapies under development that could enter this market over the next several years.

Take-Aways

- The obesity epidemic continues to grow in the U.S. Current estimates are that 42.5% of U.S. adults age 20 years and older were obese in 2018 and 31.1% more were overweight, with no significant difference seen between genders. Also, for children and adolescents between two years and 19 years of age, approximately 19.3% were obese and another 16.1% were overweight.
- Obesity is a chronic disease, which commonly, incorrectly and insensitively is stigmatized. Actually, underlying causes can include genetic, social, economic and environmental circumstances.
- Obesity is a risk factor for many conditions, including diabetes, high cholesterol and high blood pressure. When sustained, just a moderate weight loss of 5% to 10% of the starting weight can result in a significant reduction in obesity-related conditions.
- Guidelines recommend assessing patient readiness to make lifestyle changes to accomplish weight loss, determine goals and comprehensive lifestyle intervention strategies with a goal of achieving 5% to 10% of weight loss and adequate improvement in any health targets.
- Current therapies are limited and, even combined with dieting and exercise, they result in only modest weight loss of approximately 5% as compared to those using diet and exercise alone.
- Due to the limited number of effective therapeutic options, the worsening obesity epidemic leaves prescribers with few drug options to help their patients manage weight.
- Glucagon-like peptide-1 (GLP-1) analogs and an amylin receptor agonist are emerging classes of weight-management drugs that could be used for much larger groups of patients.
- Incivree, a melanocortin-4 receptor (MC4R) agonist, was recently approved for chronic weight management in obese patients with rare genetic conditions caused by impaired signaling along the melanocortin-4-receptor pathway. Imcrivee should only be used in this specific subset of patients.
- Direct-to-consumer (DTC) advertising that is expected to accompany the approvals of pipeline weight-management drugs with broader indications, is likely to increase patient demand.
- Express Scripts supports plan sponsors with a number of strategies (e.g., benefit exclusions, prior authorization, and Care Value Programs) to help manage the appropriate utilization of weight-loss medications.

Background

Obesity is defined as having a body mass index (BMI) score of 30kg/m^2 or greater, whereas overweight is a BMI of 25kg/m^2 to 29.9kg/m^2. BMI is calculated from a person's weight and height. According to the Centers for Disease Control and Prevention (CDC), obesity affected approximately 42.5% of U.S. adults aged 20 years and over in 2018 -- a significant increase from the 26.0% obesity rate reported in 2008. Additionally, another 31.1% of adults in the same age range met the clinical definition for being overweight. Obesity is a chronic disease. Although blaming obesity and overweight on laziness and/or gross overeating is common, many factors contribute to body weight. Genetic, social, economic environmental and other circumstances all can influence it. Weight gain also is associated with having some medical conditions and using several classes of medication such as antidepressants, antipsychotics, antiepileptics, hormonal agents, glucocorticoids and antihyperglycemics. Obesity-related diseases, such as diabetes, heart disease, obstructive sleep apnea (OSA) and certain cancers, are estimated to account for $190.2 billion in annual healthcare costs. Medications for treating obesity-related conditions make up several of the top therapy classes including inflammatory conditions, diabetes, oncology and high blood pressure/heart disease and mental/neurological disorders in Evernorth's 2020 Drug Trend Report. For commercial plans, diabetes alone accounted for $145.24 billion, or 19.2% of commercial plan sponsor's total drug spend in 2020. To review the full Evernorth 2020 Drug Trend report see here.

Tainted Safety History for Weight Loss Drugs

While the need for effective weight loss medications currently is unmet, several drugs and drug classes have been tried. However, the history of weight loss medications has been dominated by safety concerns and market withdrawals. In 1979, amphetamines were banned from use in diet pills due to addiction risks, heart rate increase and high blood pressure. The next weight-loss drug removed from the market was Redux® (dexfenfluramine), a component found in the infamous Fen-Phen combination. Despite effective weight loss (attaining 10-20% reductions for up to 2 years), fenfluramine was pulled off of the market in 1997 due to an association with adverse cardiovascular events (e.g., valvular heart disease). Other market withdrawals include phelypropanolamine (PPA), ephendra and Meridia® (sibutramine) in 2000, 2004 and 2010, respectively, following concerns over unacceptable adverse health outcomes, including heart attacks and/or strokes. The latest weight-loss drug removed from the market is Belviq®/XR® (lorcaserin), in 2020, due to an unexpected increased risk in developing certain cancers.

Obesity Management Guidelines

In 2013, the Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society updated their guidelines to recommend the screening of overweight individuals who have risk factors and those considered to be obese. The guidelines recommend assessing patient readiness to make lifestyle changes aimed at accomplishing weight loss and managing any obesity-related health conditions. In June 2017, the U.S. Preventive Services Task Force (USPSTF) updated its recommendations on screening for obesity in children and adolescents. The recommendations advise clinicians to screen for weight issues in patients age six years and older. Overweight and obese pediatric patients should be offered or referred to comprehensive, intensive behavioral interventions that promote improvements in weight status. In September 2018, updated USPSTF recommendation on screening for and management of obesity in adults gave similar advice to offer or refer adults with a body mass index (BMI) of 30 or higher to intensive, multicomponent behavioral interventions.

Lifestyle Modifications

Lifestyle modifications, the foundation of every obesity management program, include behavioral therapy (counseling), diet restrictions and increased physical activity. Although in-person, high-intensity weight-loss coaching sessions from a trained interventionist is the most effective way to reinforce changes in diet and physical activity, few patients can afford the time and effort needed. Commercial programs such as WW and Noom help many patients adjust behaviors. Others develop their own ways to manage food intake and physical activity. Lifestyle modifications should be maintained for at least six months and should include 14 or more counseling sessions before adding pharmacotherapy is considered.

Drug Therapy

Patients considered appropriate for treatment with weight-management medications have a BMI of at least 30kg/m^2 or 27kg/m^2 with concomitant obesity-related risk factors or diseases. As mentioned above, all weight loss medications should be FDA-approved and used in conjunction with comprehensive lifestyle interventions. A weight loss of an additional 5% to 10% above diet and exercise alone (i.e. placebo-adjusted weight loss) is considered clinically important by FDA. Another measure FDA looks at in clinical study data is the total percentage of patients who lose at least 5% of their weight when they began the study, with a minimum goal of 35% of study patients, which should be at least double the percentage of patients in the control (placebo) group who achieve a comparable weight loss.

Current Weight-Loss Medications

Appetite Suppressants and Lipase Inhibitors

Modestly effective therapies, such as the appetite suppressants and lipase inhibitors, have been available for many years. The appetite suppressants, used since the 1960's, include benzphetamine, diethylpropion, phendimetrazine and phentermine. These therapies are indicated for short-term adjunctive use only. The lipase inhibitor, Xenical® (orlistat 120mg capsules), was approved in 1999 and is now also available with an OTC counterpart Alli® (orlistat 60mg capsules). The lipase inhibitors work works by blocking the absorption of dietary fats. When used in combination with a low calorie diet, these products can result in about a 3-5% placebo-adjusted weight loss.

Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist

At a recommended daily dose of 3mg, Saxenda® (liraglutide [rDNA origin] injection - Novo Nordisk) is an FDA-approved, subcutaneously (SC) injected glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults and children 12 years of age and older. Originally approved as Victoza®, smaller doses of liraglutide are used once a day to manage type 2 diabetes. Saxanda has demonstrated about a 4.5% placebo-adjusted weight loss after one year of therapy.

Combinations

Drugs containing two different medications that work in distinct ways to promote weight loss are Vivus' Qsymia® (phentermine/topiramate) extended-release capsules and Currax Pharmaceuticals' Contrave® (naltrexone/bupropion) extended-release tablets. Both are used in combination with a reduced-calorie diet and increased exercise for chronic weight management. Contrave has demonstrated about a 4.1% weight loss, compared to placebo, after one year of therapy. Qsymia is currently the most effective FDA-approved weight loss drug available, with patients achieving 7.5-10% placebo-adjusted weight loss after a year of therapy.

Obesity drugs: Approved Drugs

Product	Manufacturer	Route	Controlled substance Schedule	Placebo-Adjusted Weight Loss (Timeframe)	Comments
phentermine	Generics	Oral (daily)	CIV	3% to 5% (3 to 6 months)	Weight may increase after 6 months despite dosage changes. This product is approved for short-term use only.
Xenical/Alli (orlistat)	Roche	Oral (three times daily)	N/A	2.9% (1 year)	Reversible inhibitor of gastrointestinal lipases to help prevent absorption of fat from food. Orlistat can be used for weight loss and weight maintenance. Alli was approved for over-the-counter use in 2007.
Qsymia (phentermine/ topiramate)	Vivus	Oral (daily)	CIV	7.5% to 10% (1 year)	Qsymia has a REMS program due to an increased risk of fetal harm in females of reproductive potential. It is approved for both weight loss and weight maintenance.
Contrave (bupropion/naltrexone)	Currax Pharmaceuticals	Oral (twice daily)	N/A	4.1% (1 year)	Contrave has a boxed warning for an increased risk of suicidal thoughts and behavior in children, adolescents and young adults during initial treatment. It is approved for use as chronic weight management.
Saxenda (liraglutide [rDNA origin] injection)	Novo Nordisk	Oral (once daily)	N/A	4.5% (1 year)	Saxenda, like most GLP-1 analogs, has a boxed warning for the risk of thyroid C-cell tumors. It is approved for use as chronic weight management.

Treatment for a Rare Genetic Disorder of Obesity

In November 2020, Rhythm Pharmaceuticals received FDA approval for Imcivree™ (setmelanotide) to treat obesity caused by deficiencies of proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR). These disorders result from defects in specific genes, involving the brain's melanocortin-4 (MC4) receptors, which regulate hunger and energy use. By activating MC4 receptors, Imcivree helps reduce appetite, promote the feeling of fullness and increase energy output. Patients who have obesity caused by POMC, PCSK1 or LEPR deficiency experience continual hunger despite eating large quantities of food. These conditions are very rare with only about 150 cases reported in medical literature for all three, combined. In the second half of 2021, Rhythm Pharmaceuticals is expected to file for supplementary Imcivree indications to treat additional rare genetic forms of obesity, including ciliopathy disorders, Bardet-Biedl syndrome (BBS) and Alström syndromes (AS). Indications to manage these conditions would make an estimated 2,000 to 3,000 U.S. patients eligible for Imcivree treatment. Express Scripts does offer a prior authorization program to ensure this product is prescribed appropriately.

Pipeline Medications

Despite the availability of several weight-loss medications, their modest effectiveness leaves much room for the introduction of more safe and effective therapies for sustained weight management.

The next medication likely to gain FDA approval for weight loss is Novo Nordisk's semaglutide injection, a once-weekly GLP-1 analog. Semaglutide is already approved in a lower strength as Ozempic®, which is indicated in addition to diet and exercise to improve glycemic control for patients who have type 2 diabetes and to reduce the risk of major CV events in adults who have type 2 diabetes along with established CV disease. For chronic weight management, semaglutide is under Priority Review for a new 2.4mg, once-weekly dose. Its Prescription Drug User Fee Act (PDUFA) date is set for June 4, 2021. If approved, it probably will be launched with a new brand name, similar to what we have seen with Victoza and Saxenda.

Eli Lilly's tirzepatide is both a GLP-1 receptor agonist and the first in a new class of drugs -- a glucose-dependent insulinotropic polypeptide (GIP). The once-weekly SC medication is being evaluated in the Phase III SURMOUNT-1 study vs. placebo. Clinical trial results from SURMOUNT-1 are expected in 2024. Of note, tirzepatide is also in Phase III development for diabetes

In phase II clinical studies, Novo Nordisk is evaluating AM833, which is a long-acting, once-weekly, amylin analog intended as a treatment for obesity, both as monotherapy and in combination with semaglutide. After 20 weeks, those receiving the highest dose of AM833 saw an average weight loss of 7.8% as monotherapy and 17.1% in combination with semaglutide.

Obesity Drugs: Near Term Pipeline

Product	Manufacturer	Route	Controlled substance Schedule	Placebo-Adjusted Weight Loss (Timeframe)	Expected Approval	Comments
semaglutide injection (new brand name TBD)	Novo Nordisk	SC (weekly)	N/A	14.8% (48 weeks); 88.7% (47.6%) achieved ≥5% weight loss (placebo)	**2021** PDUFA date of 06/04/2021	A priority review voucher was applied, granting a more rapid FDA review. Once approved, Novo Nordisk will likely launch this product with a unique brand name to differentiate it from the company's diabetes drug, Ozempic.
tirzepatide	Eli Lilly	SC (Weekly)	N/A	8.5% to 13.1% vs. 6.7% (semaglutide 1mg) (40 weeks)	**2023** (Phase 3 for obesity)	The lead indication for tirzepatide is for the treatment of type 2 diabetes. Approval for this use will likely occur in 2023. However, it is also in phase 3 development for chronic weight management. Approval for this use will likely follow.
AM833	Novo Nordisk	SC (Weekly)	N/A	7.8% (26 weeks)	**2024+** (Phase 2 for obesity)	A once-weekly amylin analog in phase 2 development for use as monotherapy, and in combination with semaglutide, for chronic weight management.

Surgery

Although bariatric (obesity-treating) surgery and other invasive procedures can result in profound weight loss, these options generally are reserved for carefully selected patients who have clinically severe obesity (BMIs of at least 40kg/m^2 or 35kg/m^2 with comorbid conditions) when less invasive methods of weight loss have failed and the patient is at high risk for obesity-associated morbidity or mortality. Currently, bariatric surgery is considered to be the most effective option for patients with severe obesity and obesity-related comorbidities.

Summary

More than 70% of adults in the U.S. are overweight or obese, which significantly increases the prevalence of CV disease, diabetes, other conditions and related mortality. Overweight and obese children and teens are developing weight-related conditions at younger ages than previous generations. Historically, weight-loss drugs have been associated with low effectiveness, rebounding weight, undesirable side effects and/or safety concerns. However, newer therapies in the near-term pipeline, along with intensive coaching and lifestyle management, offer the promise of sustained long-term weight loss. Coupled with an increase in direct-to-consumer advertising following approval, newer treatments will spark patient interest and increase demand for new weight-loss products. Coverage of weight-loss medications is a plan sponsor's decision. The landscape is expected to change, though, as physicians gain experience with newer medications and patients demand more effective therapies. As evolving evidence supporting the beneficial effects of weight-loss medications begins to accumulate, management strategies for the obesity drugs may have to be re-evaluated.

Express Scripts' Stance

Express Scripts supports the development of new pharmaceutical therapies for difficult-to-treat conditions associated with obesity and weight management. Our external Pharmacy and Therapeutics (P&T) Committee reviews all newly FDA-approved drugs and determines appropriate formulary placement. In addition, Express Scripts offers a number of proven effective utilization and formulary management solutions that promote use

of clinically appropriate and cost-effective medications. Historically, weight loss agents demonstrated a modest impact on weight over time. However, the new therapies, including the combination drugs, the GLP-1 analogs, and near-term pipeline agents, have demonstrated a more pronounced impact on overall weight loss and maintenance of weight loss, and may warrant at least re-evaluating coverage decisions. Of course, coverage of weight-loss medications depends on a plan sponsor's overall benefit philosophy and may not be a one-size fits all solution. The coverage solution needs to align across pharmacy and medical coverage decisions and may need to change over time to respond to the evolving market. Express Scripts supports plan sponsors with a number of strategies (e.g., benefit exclusions, prior authorization, and Care Value Programs) to help manage the appropriate utilization of weight-loss medications. If you have any questions, please reach out to your account team for more details.

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