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Imcivree® (setmelanotide): A Small Injection Leading to Big Weight Loss

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Obesity, diagnosed using the Body Mass Index (BMI), continues to be an epidemic the United States healthcare system faces today and adds to the risk of many medical diseases. For a person to be considered obese, their BMI must be 30 kg/m^2 or higher.[1] Obesity is further subdivided into three additional categories of class I (30.0-34.9 kg/m2), class II (35.0-39.9 kg/m2), and class III, sometimes defined as "severe" or "extreme" obesity, (BMI 40 or greater).[1,2] Between the years 1999-2000 and 2017-2018, the prevalence of obesity in the United states has increased from 30.5% to 42.4%.2 The National Health and Nutrition Examination survey (NHANES) from 2015-2016 estimates 39.8% of U.S. adults ages 20 and over are obese, including 7.6% with severe obesity and another 31.8% overweight (BMI 25-29.9 kg/m^2).[3] The medical expenditures associated in treating obesity, along with other obesity-related conditions, continues to grow. One of the first analysis of data from the Medical Expenditure Panel Survey (MEPS) concluded that across all payers, obese patients had a per capita medical spending that was between $600 to $1,429 greater than non-obese beneficiaries.[4] In more recent analysis between 2010 through 2015, adults with a BMI of 40 kg/m^2 or higher were faced with $7,800 in annual medical expenditures on average, which was 76% more than non-obese adults.[5] Today, the cost of obesity in the U.S. still ranges in the billons.[4] In addition, inaccurate cost estimates has result in underestimates for government interventions to reduce obesity-related externalities.[5,6] Misallocation of aid has caused delays in treatment and additional obesity-related conditions, such as myocardial infarction, type 2 diabetes, osteoarthritis, asthma, depression, and cancer, to continue to place a burden in medical cost today.[6] Obese patients are twice as likely to be prescribed cardiovascular agents, four times likely to end up on antidiabetic therapies, and nearly 10% end up hospitalized annually.[5] It is clear to see how obesity has become a major risk factor for many comorbid conditions, increase medical expenses, and why research behind the physiology and pathways of obesity to create pharmaceuticals has expanded.

Despite the prevalence of obesity increasing nationwide, certain groups at high risk include non-blacks (49.6%), Hispanics (44.8%), non-Hispanic whites (42.2%) and non-Hispanic Asians (17.4%).[2,7] Within age groups, 40.3% ages 20-39, 46.4% in ages 40 -59, and 42.8% among adults ages 60 and over had higher incidents of obesity in 2017-2018.[2] Obesity occurs when there is an imbalance between energy intake and energy expenditure over time.[8] Factors such as genetics, environment, and other medical conditions may also contribute to its etiology, and have become prime targets in treating obesity through non-pharmacological and pharmacological interventions. These imbalances occur within the neuronal network involving the hypothalamus, limbic system, brainstem, hippocampus, and additional elements of the cortex, which are quickly becoming pharmacotherapy hotspots for further investigation.[8] According to the guidelines released by the American Heart Association (AHA), the American College of Cardiology (ACC), and The Obesity Society (TOS), the recommended initial weight loss goal for adults is between 5-10% of the baseline weight over a six month period.[9] The cornerstone of achieving desired weight loss goals is through the incorporation of multiple factors, such as lifestyle modifications in diet, physical activity and behavioral modifications.[8,9] Choice in pharmacological therapy options depends on other comorbidities, such as choosing therapies that will promote weight loss while benefitting additional conditions like diabetes or cardiovascular disease.[8,9] The AHA/ACC/TOS guidelines do not recommend adding medications to weight-loss plans until the patient has a BMI of 30 kg/m^2 or above, and has failed to achieve weight loss goals with lifestyle changes alone. In the U.S. there are five approved medications used to treat chronic management of obesity: lipase inhibitor orlistat, serotonin 2C receptor agonist lorcaserin, a combination product phentermine-topiramate extended-release, the combination product naltrexone-bupropion extended-release, and the glucagon-like peptide-1 receptor agonist (GLP-1 RA), liraglutide.[8,9]

A small number of cases of obesity may be linked to deficiencies in either the proopiomelanocortin (POMC) and proprotein convertase subtilisin/kexin type 1 (PCSK1) or Leptin receptor (LEPR) sites. In 2007, less than ten patients were reported to have POMC deficiencies.[10] POMC deficiency results from homozygous or compound heterozygous loss of function mutation in the POMC gene (Chromosome 2p23.3). Proopiomelanocortin is

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regulated by leptin and is cleaved by prohormone convertase to produce the melanocortin receptor (MC-R) ligand adrenocorticotropin (ACTH) and melanocyte-stimulating hormones (MSH) alpha, beta, and gamma. Proopiomelanocortin deficiency is a monogenic disorder with early-onset obesity, adrenal insufficiency, red hair, and decreased skin pigmentation. Hyperphagia, cholestasis, exponential weight gain, and adrenal insufficiency are typically observed during the first months of life and in other children it might be established later.[10] In 2007, LEPR deficiency estimate prevalence in the U.S. was described in less than 30 patients, but according to a statement from the Endocrine Society's Annual Meeting and Expo in 2018, their data suggest that more than 12,800 people have LEPR deficiencies that have gone undiagnosed.[11,12] On November 25, 2020, Imcivree® (setmelanotide) was approved by the Food and Drug administration to treat obesity by controlling hunger associated with deficiencies found in the melanocortin-4 (MC4) pathway.[11,12]

Clinical Pharmacology

Mechanism of Action

Setmelanotide is an MC4 agonist with 20-fold less activity at melanocortin-3 (MC3) and melanocortin-1 (MC1) receptors, which re-establishes the MC4 receptor pathway to reduce hunger, decrease caloric intake which promotes weight loss, and increases energy expenditure.[13] Hunger, satiety, and energy expenditure is regulated by melanocortin-4 receptors (MC4R) located in the brain. In patients with POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiencies, obesity results due to insufficient activation of MC4 receptors.

Pharmacokinetics

Maximum plasma concentrations of 37.9ng/mL at steady state are achieved eight hours after dosing.[13] For a 3 mg dose, area under the curve (AUC) and trough concentrations are 495 h*ng/mL and 6.77 ng/mL, respectively. Plasma protein binding is 79.1% with a volume of distribution of 48.7 L. In the body, setmelanotide is metabolized into small peptides by catabolic pathways with a half-life (T1/2) of approximately 11 hours. Steady-state clearance rate was reported to be 4.86 mL/h. Approximately 39% of setmelanotide was excreted unchanged in the urine during, while the remaining 61% goes through catabolic pathways.13 There is an increase of about 19% in AUC among patients with mild renal impairments (estimated glomerular filtration rate (eGFR) of 60-89 mL/min/1.73 m2). Children ages six to 11 years had an AUC and maximum plasma concentrations that were 100% and 92% higher, respectively, when compared to patients over the age of 16. Pediatric patients ages 12 to 17 had AUC and plasma concentrations 44% and 37% higher.13 Other special populations, such as geriatrics, have yet established pharmacokinetic data.[13] **Table 1** will summarize the pharmacokinetics of setmelanotide.

Pharmacodynamics

In 12 healthy obese patients, short-term administration of setmelanotide increased energy expenditure and shifted substrate oxidation to fat.[13] Melanocortin-4 receptor (MC4R) agonists are linked to an increase in sympathetic tone, which directly translates to increases in both heart rate and mean arterial blood pressure, posing challenges in developing MC4R agonist for the treatment of obesity.[14,15] Under the FDA label, setmelanotide reported no clinically significant increase in blood pressure or heart rate when administered to healthy obese patients or patients with monogenic obesity.[13]

Table 1 | Select Remdesivir and Active Metabolites Pharmacokinetics[10,11]

	Remdesivir GS-441524
Absorption	
T_{max}[a] (hours)	8 hours
C_{max}[b]	37.9 ng/mL
AUC[c]	495 h*ng/mL
C_{trough}[d]	6.77 ng/mL
Distribution	
V_d[e]	48.7 L
Protein Binding	79.1%
Metabolism	
Metabolized into small peptides by catabolic pathways	
Elimination	
$T_{1/2}$[f] (hours)	11 hours
Cl_{ss}[g]	4.86 L/h
Urinary Excretion	39%

[a]Time to maximum concentration; [b]Maximum plasma concentration; [c]Area under the curve; [d]Trough concentration; [e]Volume of Distribution; [f]Half-life; [g]steady-state clearance

Clinical Trials

The FDA approval of setmelanotide was based on two identically designed phase III clinical trials (study 1: NCT02896192, study 2: NCT03287960) conducted by Rhythm Pharmaceuticals, Inc.[16] The purpose of these trials were to evaluate the safety and efficacy of setmelanotide for chronic weight management in participants with obesity due to POMC, PCSK1, and LEPR deficiencies.[16] Both trials were one year, single-arm, open-label, multicenter clinical trials, each with an eight week, double-blinded withdrawal period. Both trials confirmed local genetic deficiency results using Sanger sequencing and excluded participants with double heterozygous variants. The participants enrolled either had homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or variants of uncertain significance for either POMC (Study 1) or LEPR (Study 2). The investigators defined POMC and LEPR deficiencies as homozygous or compound heterozygous variants in POMC, PCSK1, or LEPR, and a BMI of at least 30 kg/m^2 for participants 18 years or older. Pediatric participants, between ages six years old through 17, had to have bodyweight more than the 95th percentile compared to growth charts within their age range to be included in the trial. Their BMI was reported as BMI Z score, also called BMI standard deviation (SD) scores. BMI Z scores are measures of relative weight adjusted for child age and sex. Additional key exclusion criteria included exercise and diet regimens within two months of trial, previous gastric bypass surgery resulting in >10% weight loss from baseline weight with no evidence of weight gain, current clinically significant pulmonary, cardiac, or oncological diseases, history of liver disease or abnormal liver function test, impaired renal function, hypersensitivity to drug studied, and inability to comply to daily injections. Since there is low prevalence of these diseases, and the investigators planned to use a small sample size,

a one-sided alpha level of 0.05 was chosen as the primary approach for statistical testing for both POMC and LEPR deficiency trials to establish superiority over placebo. The results were compared with the proportion of responses from historical data in the target population, where it is expected to see 5% of participants in the population of interest achieve 10% weight loss. The following section will highlight the results of the two phase III clinical trials, used for the approval of setmelanotide, as well as the results of a phase 1b trial evaluating the effects of setmelanotide on mutant MC4 receptors in cells and the weight loss response of setmelanotide administration in a rodent model and human clinical trial.17 The results from study 1 and study 2 will be summarized in **Tables 2 and 3.**

Study 1: NCT02896192

The purpose of study 1 was to determine the effect of setmelanotide on weight and hunger in participants with confirmed POMC deficiencies due to a rare biallelic loss-of function POMC or PCSK1 genetic mutations.[16] Study 1 initially enrolled ten participants between February 14, 2017 through September 7, 2018 and was conducted in ten hospitals across Canada, the U.S., Belgium, France, Germany, the Netherlands, and the United Kingdom.16 Participants ages six years old and above, who had confirmed POMC deficiencies leading to obesity, were recruited by study investigators from site databases and any genetic obesity registries to which the investigators had access to.

All ten participants enrolled began with an open-label dose titration phase where setmelanotide was injected at starting doses of 1 mg for participants ages 18 and older and 0.5 mg for ages between six and 17. The mean age of participants was 18.4 years (SD 6.2); two participants were aged younger than 12 years. The mean BMI at baseline was 40.4 kg/m^2 (SD 9.0). For the six participants aged younger than 18 years, the mean BMI Z score was 3.4 (SD 0.6). Doses were titrated up every two weeks by 0.5 mg until an individualized therapeutic dose was achieved. Therapeutic dose was established when the participants lost about two to three kilograms per week for adults and one to two kilograms for pediatrics. Therapeutic dose was 2.5 mg in three participants, 2.0 mg in one participant, and 1.5 mg in six participants. The max dose for both groups was 3 mg. The duration of dose titrations varied between two to 12 weeks, where the final two weeks were at therapeutic doses. Once individualized therapeutic doses were established, participants entered a ten-week open-label treatment phase for a total of 12 weeks of therapeutic dose exposure. Participants who achieved weight loss of at least five kilograms (or weight loss of 5% for participants weighing less than 100 kgs at baseline) entered an eight-week double-blind, placebo-controlled withdrawal sequence. In that sequence, setmelanotide was given first for four weeks followed by four weeks of placebo intervention. Upon completion of the eight-week sequence, participants then resumed 32 weeks of open-label active treatment at the previously established individualized therapeutic dose.[16]

The primary endpoint was measured as the proportion of participants who achieved at least 10% weight loss compared to baseline after one year of treatment. All participants who received at least one dose of study medication and had a baseline assessment were included. Safety and tolerability were assessed concurrently by assessing participant's vitals (heart rate and blood pressure). Key secondary endpoints that were assessed included mean percent change in body weight and mean percent change in hunger score within one year of treatment. The hunger score the investigators chose to utilize was based on the 11-point Likert-type scale in participants ages 12 and over, where a score of zero indicated not hungry at all and a maximum score of ten indicated hungriest possible. The proportion of participants that achieved at least 25% reduction in hunger score at approximately one year of treatment dose were said to have met one of the secondary endpoints. Additional secondary endpoints evaluated included the waist circumference, metabolic parameters, proportion of participants achieving 5%, 15%, 20%, 25%, 30%, 35%, and 40% of weight loss thresholds, as well as percent change in body fat mass after one year of treatment. Weight loss thresholds were chosen as secondary endpoints to help characterize the effects of setmelanotide in the event that the primary endpoint was met, and statistically meaningful weight loss was demonstrated.

Of the ten participants identified with POMC deficiencies, 80% met the primary endpoint of at least 10% weight loss compared with baseline at one year. Of the eight participants who met the 10% weight loss threshold, all met the 20% threshold, seven met the 25%, three met the 30%, and one met the 35% threshold. The authors did not comment on the 15% threshold. The percent change in body weight compared to baseline was statistically significant: -25.6% (SD 9.9; 90% CI -28.8 to -22.0; p<0.0001). The mean most hunger score at baseline was 8.0 (SD 0.8). Waist circumference decreased from 118.9 cm (SD 17.6) at baseline to 100.5 cm (SD 12.4) after one year of therapy. Mean change in BMI ages 18 and older was reported statistically significant as -9.3 kg/m2 (SD 6.9; 90% CI -17.4 to -1.2; p=0.073; n=4). Investigators noted that setmelanotide showed statistical significance in reducing fasting glucose and triglycerides, as well as HDL cholesterol (-17.2% (18.8) 90% CI -28.1 to -6.3; p= 0.018; -36.6% (30.4); 90% CI -54.2 to -19.0; p= 0.0041; 45.0% (43.8); 90% CI 19.6 to

Table 2 | Primary Endpoints from Setmelanotide Phase III Trials[16]

Trial	Trial Design	Primary Outcome	Intervention	Results*
NCT02896192	Phase III, single-arm, open -label, multicenter clinical study	% Achieving ≥ 10% of weight loss in participants with POMC[a] deficiencies	Setmelanotide subcutaneous injection once daily (Individualized therapeutic doses)	80% (p<0.0001)
NCT03287960	Phase III, single-arm, open -label, multicenter clinical study	% Achieving ≥ 10% of weight in participants with LEPR[b] deficiencies	Setmelanotide subcutaneous injection once daily (Individualized therapeutic doses)	45% (p<0.0001)

[a]Proopiomelanocortin; [b]Leptin Receptor;
*All primary endpoints were reported as proportion of participants in the full analysis set (defined as all participants who received at least one dose of study medication and had baseline assessment) who demonstrated at least 10% weight loss at approximately 1 year.

70.3; p=0.010 respectively). However, participants in the study were being treated for their other diseases using additional medications such as hydrocortisone, levothyroxine, ibuprofen, ferrous sulfate, insulin glargine, metformin, ramipril, insulin aspart, insulin lispro, and vitamin D, which could have also led to these changes.

Adverse events most reported included injection site reaction and hyperpigmentation, nausea, and vomiting. It was noted that no emergent adverse event from treatment lead to study drug withdrawal. Study 1 reported no cardiovascular adverse events, such as high blood pressure or heart rate.

Study 2: NCT03287960

The purpose of study 2 was to determine the effects of setmelanotide on weight and hunger in participants six years or older with obesity affected by LEPR deficiencies due to genetic mutations.[16] Study 2 had a study design that was identical to study 1, except that investigators recruited participants with confirmed LEPR deficiencies through databases accessible to them. The inclusion and exclusion criteria and primary and secondary endpoints also remained the same as study 1. The mean age of participants was 23.7 years (SD 8.4). Of the 11 subjects enrolled in the trial, 45% of the participants achieved at least 10% weight loss during the one-year trial. Similar to study 1, study 2 also used a one-sided alpha level of 0.05 to statistically test the primary endpoint and establish superiority over placebo. The mean percentage change of hunger score was -43.7% (n=7; -54.8 to -29.1; p<0.0001). The mean BMI at baseline was 48.2 kg/m2 (SD 10.4). Among the three participants aged younger than 18 years, the mean baseline BMI Z score was 3.5 (SD 0.4). The mean most hunger score at baseline was 7.1 (SD 1.0). The therapeutic dose was 3 mg in two participants, 2.5 mg in six participants, 2.0 mg in two participants, and 1.5 mg in one participant. Of participants, 64% met the threshold during the initial 12 week open-label study. Investigators noted that setmelanotide in the setting of LEPR deficiencies demonstrated significant improvement in HDL cholesterol (19.6% (24.0); 90% CI 4.8 to 3.4; p=0.040). Once more, participants were allowed treatment of any other diseases using various medications, which may also affect these values. Of the five participants who met the 10% weight loss threshold, all met the 15% threshold, two met the 20% threshold, and none met the 25% threshold.

Adverse events commonly reported in the LEPR trial included injection site reaction, skin discoloration, and nausea which resolved without sequelae. It was noted that treatment-related grade 1 spontaneous priapism was reported in one participant in this trial but resolved without sequelae and did not cause discontinuation from the trial. Study 2 reported no cardiovascular adverse events, such as high blood pressure or heart rate.

Adverse Effects and Drug Interactions

Currently, there are no clinical studies evaluating the drug-drug interactions of setmelanotide with no adverse effects due to drug interactions reported in the trials. Of note, 61% of setmelanotide undergoes catabolic pathways, but is still unclear if it has effects on CYP enzymes or PG-proteins. Participants with a history of renal and liver impairments, clinically significant pulmonary dysfunction, cardiac comorbidities, or oncological diseases were not studied which may prevent establishing safety data in this population. The most common treatment related adverse effect observed in both trials was injection site reaction (96%), skin hyperpigmentation (78%), nausea (56%), headache (41%), and diarrhea (37%).[19] In contrast to first-generation MC4R agonist, which have been shown to activate the sympathetic nervous system, setmelanotide did not lead to increases in heart rate or blood pressure.[19] **Table 4** lists the most common adverse effects observed from both trials.

Dosage and Administration

The starting dose of setmelanotide in adults is 2 mg (0.2 mL) injection subcutaneously daily for two weeks.[16] Based on the clinical trials, 2 mg was shown to be the lowest dose where participants experienced weight loss of approximately 2-3 kgs per week for adults and 1-2 kgs per week for pediatric patients ages six through 17 years, up to a maximum of 3 mg. Patients should be monitored for gastrointestinal upset and adverse reactions. If the starting dose is not tolerated, patients should reduce the dose to a minimum of 1 mg (0.1 mL) daily. If the 1 mg daily dose is tolerated and additional weight loss is desired, patients may titrate up between 2 mg (0.2 mL) to a maximum of 3 mg (0.3 mL) daily. When dosing pediatric patients less than 12 years old, the package insert recommends a starting dose of 1 mg (0.1 mL) injected subcutaneously once daily for two weeks. Like the adult dosing, monitoring patients for GI adverse effects will indicate if further doses need to be titrated up or down. For instance, if the 1 mg starting

Table 2 | Secondary Endpoints from Setmelanotide Phase III Trials[16]

Trial	Intervention	Secondary Outcomes	Results (CI[a])	P-value
NCT02896192	Setmelanotide subcutaneous injection once daily (Individualized therapeutic doses)	% Change in Bodyweight	-25.6% (-28.8 to –22.0)	<0.0001
		Change in waist circumference	-18.4 cm (-)	-
		Mean % change in hunger score*	-27.1% (-40.6 to –15.0)	0.0005
NCT03287960	Setmelanotide subcutaneous injection once daily (Individualized therapeutic doses)	% Change in Bodyweight	-12.5% (-16.1 to –8.8)	<0.0001
		Change in waist circumference	-15.1cm (-)	-
		Mean % change in hunger score*	-43.7% (-54.8 to –29.1)	<0.0001

[A]90% Confidence Interval
*11-point Likert-type scale in ages 12 or older within 1-year timeframe

dose is not tolerated, a reduction to 0.5 mg (0.05 mL) daily may be necessary to tolerate. Once the 0.5 mg daily dose is tolerated and additional weight loss is desired, the dose may be increased to 1 mg (0.1 mL) once daily. Titrate the dose to a maximum of 3 mg (0.3 mL) once daily for desired weight loss.

Setmelanotide injections are supplied as 10 mg/mL, clear to slightly opalescent, colorless to slightly yellow solution in a 1 mL multiple-dose vial.[16] Setmelanotide should be free of particulate matter or discoloration. Unopened setmelanotide is to be kept refrigerated between 2°C to 8°C (36°F to 46°F). After removal from refrigerator, vials may be kept at temperatures ranging from refrigerated to room temperature (2°C to 25°C (36°F to 77°F)) for up to 30 days. Discard after 30 days since the vial was first removed from the refrigerator. Discard if setmelanotide was kept above 86°F (30°C). Remove from refrigerator approximately 15 minutes prior to administration. Patients can warm setmelanotide vials by rolling the vial gently between palms of the hands for 60 seconds. Patients must use a 1-mL syringe with a 28 to 29-gauge needle appropriate for subcutaneous injections to draw up dose from multi-dose vial. The most optimal time to administer is at the beginning of the day with or without food. Injection sites include the abdomen, thighs, or back of arm, making sure to rotate the sites each day. Setmelanotide should not be administered as an intramuscular or intravenous injection. If a dose is missed, patients can resume the once daily dose as prescribed with the next scheduled dose.[16]

Special Populations

Setmelanotide has only been approved by the FDA specifically for patients ages six and older with confirmed or suspected deficiencies in POMC or LEPR. Both trials excluded patients with double heterozygous variants with two different genes. At this point in time, the FDA has not approved or cleared specific tests to confirm these genetic deficiencies.

Pregnancy/Lactation

There are no trials to support the safety of setmelanotide in pregnancy. If a patient suspects or confirms they are pregnant, discontinue setmelanotide unless the benefit of therapy outweighs the potential risk to the fetus.[16] As per the package insert, setmelanotide contains the preservative benzyl alcohol. In pregnant women, benzyl alcohol is rapidly metabolized and exposure to the fetus is unlikely. However, there are existing adverse reactions in premature neonates where low birth weight was reported in infants who received intravenous administered benzyl alcohol-containing drugs. Currently, there are no available data in pregnant women to inform of potential drug-associated risk for major birth defect, miscarriage, or adverse maternal or fetal outcomes.[16] Treatment with setmelanotide is not recommended while breastfeeding due to the lack of clinical data.

Pediatrics

The safety and effectiveness of setmelanotide for obesity due to POMC, PCSK1, or LEPR deficiency have been established in pediatric patients aged six years and older.[16] Use of setmelanotide for this indication is supported by evidence from two open-label studies that included nine pediatric patients. The safety and effectiveness of setmelanotide have not been established in pediatric patients younger than six years old. Setmelanotide is not approved for use in neonates or infants.

Table 4 | Common Adverse Effects[16]

Adverse Effect	Incidence
Injection site reaction	96%
Skin hyperpigmentation	78%
Nausea	56%
Headache	41%
Diarrhea	37%
Back pain	33%
Abdominal pain	33%
Vomiting	30%
Fatigue	30%
Depression	26%
Priapism	23%
Suicidal ideation	11%
Muscle cramps	11%

Geriatrics

Both clinical trials that granted setmelanotide FDA approval did not include patients aged 65 and over. There is no established data to show whether geriatric patients will respond differently from younger patients.[16]

Renal Impairment

Population pharmacokinetic analysis suggests decreased clearance in patients with renal impairment. Most participants in the clinical studies had normal renal function. No dose adjustments for patients with mild renal impairment (estimated glomerular filtration rate (eGFR) of 60-89 mL/min/1.73 m^2) are needed. IMCIVREE is not recommended for use in patients with moderate (eGFR 30-59 mL/min/1.73 m^2) and severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) and end stage renal disease (eGFR less than 15 mL/min/1.73 m^2).[16]

Cost and Availability

Imcivree® (setmelanotide) is currently not commercially available at the time of writing in the United States and no additional data is available through online resources, such as the FDA website or GoodRx. Rhythms Pharmaceuticals has yet to release a retail price in their recent press conference but is striving to launch the brand name drug, along with new approved indications, by late 2021.[14,15]

Clinical Implications

Both studies that granted approval of setmelanotide were multicentered trials that took place across ten hospitals in both North America (Canada and USA) and Europe (Belgium, France, Germany, the Netherlands, and the UK) to establish efficacy in patients with POMC, PCSK1, or LEPR deficiencies leading to obesity. The investigators of the trials interpreted their results to support setmelanotide as a treatment for these specific MC4R deficiencies, but many details within the trails are flawed. The investigative team was aware of the rarity of this diseases and planned on using a small sample size for each trial. Unfortunately, the inevitable choice to use a small sample size may have intro-

duced the potential for bias, including type I errors, and confounding. In a statement released back in March 2018 by Rhythms Pharmaceuticals, the drug company that developed setmelanotide claimed that their data identified more than 12,000 people in the U.S. living with rare genetic disorders of obesity, but in their own trial were only able to identify a total of 21 patients with POMC or LEPR deficiencies to include in their findings. In addition, Rhythms Pharmaceuticals funded both trials, potentially introducing conflicts of interest. It is also worth noting that the power estimation of the trial is limited due to the small sample size, in which case the investigative team chose to use a one-sided alpha level of 0.05 with 90% confidence interval to provide 94.5% power to detect a difference if one existed. Although this may not be a flaw within the design of the trial, since the one-tailed test provides more power to detect an effect of superiority over placebo in one direction, there is still question on whether the design missed detecting effect on the other end of the spectrum.

Another main flaw in the study design was in the exclusion and inclusion criteria. The investigators chose to exclude patients with cardiovascular conditions as well as patients who had begun dieting and exercise regimens. Diet and exercise play a huge role in the management of obesity. As per the AHA/ACC/TOS guideline for the management of overweight and obesity in adults, pharmacotherapy is not introduced until a patient has failed to achieve or sustain weight loss of 5% with lifestyle alone, has a BMI of more than or equal to 30 kg/m^2, and at least one risk factor such as hypertension, dyslipidemia, coronary heart disease (CHD), type 2 diabetes, or sleep apnea. Having the trial exclude these participants does not allow the investigators to see how effective setmelanotide is within place of therapy or establish safety of the medication while the patient incorporates dieting and exercise. Excluding diet and exercise from the algorithm omits a large population that represents obese patients, therefore is not an accurate representation of how patients are managed in real practice settings. Finally, the exclusion criteria prevent investigators from identifying potential drug-drug or drug-condition interactions and specific adverse effects within those interactions. The trials establish some efficacy in healthy patients, but it is paramount to see how setmelanotide plays a role in obese patients with additional comorbidities. These important details may make finding the appropriate place in therapy for setmelanotide difficult within the next few years, especially since it has only been studied in an ultrarare form among the large spectrum of obesity. For now, setmelanotide has not yet received a recommendation in the AHA/ACC/TOS guidelines for appropriate place in therapy.

Recruitment of participants for the trial was limited to whatever databases the investigators had access to. It is not clearly stated in the discussion section of the clinical trials which databases these were, limiting patient identification, and could have potentially affected the pool of participants they were able to recruit. Thus, this might not be an accurate representation of the obese population. Each trial population recruited for testing matched what was being studied by confirming through genetic testing POMC or LEPR deficiency, but both deficiencies are ultrarare diseases. The authors do make the argument that these deficiencies might be underdiagnosed due to lack of awareness of the disorders among health-care professionals, clinical features that might overlap with other forms of obesity, and not considering genetic testing for determining causes of obesity.

There are no other head-to-head trials comparing setmelanotide to other MC4R agonists in the treatment setting of obesity. The two trials that approved setmelanotide by the FDA compare it to four weeks of placebo during an eight-week placebo-controlled withdrawal sequence. Within the eight-week withdrawal sequence, four-weeks included blinded setmelanotide treatment. When comparing the length in time between treatment and placebo, placebo had a significant shorter amount of time. There is question whether that is sufficient length. Although, some of the participants were reported to be on various forms of insulins or metformin during the study, there are yet to be trials on the safety and efficacy of using both agents concurrently or clearly delineates where in therapy setmelanotide may be placed, such as before or after liraglutide, which is a common pharmacological choice for weight loss in diabetics. For now, the guidelines orbit around the idea of pharmacologically treating other comorbidities first and using diet and exercise to control obesity until the patient is no longer able to adequately control their weight. Injectable medications, especially when still under patent, have historically cost more than established medications that have already been on the market. If setmelanotide is used as an add-on medication, this may not be favorable for patients with multiple comorbidities, in which they can use one drug for both indications, such as liraglutide. In addition to the rare indication, these factors could quickly become barriers for the drug to succeed in market and limit access to patients. Finally, in the trials, therapeutic doses were individualized and established when individuals achieved either 2-3 kgs of weight loss in adults and 1-2 kgs weight loss in pediatrics. This varied the therapeutic doses among participants and is unclear which is the target dose patients should use outside of trials. If the investigators would have given all their participants 3 mg dose (max dose of setmelanotide), more evidence on the target dose could have been established. In addition, the trial failed to mention time of day when participants administered daily doses of setmelanotide, but in the package insert it is specified that it must be administered at the beginning of the day with or without meals.

NCT02896192 and NCT03287960 only aimed to evaluate safety and efficacy of setmelanotide for reducing bodyweight and hunger with POMC or LEPR deficiencies and compared it to placebo on the same patient and was the first trial to do so. Earlier trials by Collet et al. demonstrated that setmelanotide showed significantly more potency at the MCR4 receptor than endogenous ligand alpha-melanocyte stimulating hormones and can disproportionally rescue signaling by a subset of severely impaired MC4R mutants.[20] Wild-type rodents appear more sensitive to setmelanotide when compared to MC4R heterozygous deficient mice, while MC4R knockout mice fail to respond. In a 28-day Phase 1b clinical trial, setmelanotide led to weight loss in obese MC4R variant carriers. Patients with POMC defects upstream of MC4R show significantly more weight loss with setmelanotide than MC4R deficient patients or obese controls.[20]

Since both trials had small sample sizes, due to how rare these diseases are, it was not feasible to study larger populations. Both trials were funded by Rhythm Pharmaceuticals, who manually determined the treatment sequence and supplied all study drugs. Rhythms Pharmaceuticals intended that for the withdrawal sequence, mentioned earlier, all participants would start with setmelanotide to maximize weight loss before starting placebo. This poses potential confounding because the placebo sequence was not long enough compared to the length of treatment, and neither trial administered placebo first before the treatment during the withdrawal sequence. There is no design in the trial where placebo was given first to patients during the withdrawal period to compare with giving treatment first. The trials were essentially measuring superiority over placebo and having a short placebo sequence

may not fully establish that superiority. Finally, the secondary endpoint used (Hunger score via Likert-type hunger scale) has not been validated, especially in the setting of POMC and LEPR deficiencies. Using this score may potentially not hold true clinical value.

Despite the limitations of the trials, the study did demonstrate the safety and efficacy profile of setmelanotide to support its long-term use in early-onset severe obesity and hyperphagia caused by POMC and LEPR deficiencies. Setmelanotide may potentially be used in long-term early-onset obesity and hyperphagia, but additional evaluation is still warranted in other MC4R disorders that disrupts its activation and pathway. Since it was not compared to the standard of care described in the guidelines, the trials did not clarify whether setmelanotide can be used as monotherapy or in conjunction with other pharmacological and non-pharmacological therapies.

Setmelanotide is a first in class drug. As of November 2020, it has only been approved for obesity caused specifically by POMC, PCSK1, or LEPR deficiencies that must be confirmed with genetic testing prior to using for weight loss. Other drug therapies for obesity, such as liraglutide, have been established in the setting of obesity as effective therapies. GLP-1 receptor agonists also have other effects as an incretin, which facilitates the release of insulin by pancreatic beta cells in response to meal-related glucose, but it is still unclear if addition of setmelanotide will increase weight loss effectiveness along with glucose control. 8 Many obese patients develop diabetes and other cardiovascular conditions simultaneously, so it may be questionable whether it is worth adding a new costly agent that may only control one condition as oppose to an established agent, such as liraglutide, that has been proven to control diabetes, obesity, and offer cardiac protection.

The most common side effect experienced by almost all participants in the trials are injection site reaction, hyperpigmentation (setmelanotide may also work in the MC1R pathway which causes hyperpigmentation), and some gastrointestinal upset. Currently, setmelanotide is not in the market for commercial use. Patients might need prior authorization, like other weight loss therapies such as phentermine, for insurance approval.

Conclusion

Imcivree® (setmelanotide) is first in class MC4R agonist that achieved FDA approval on November 27, 2020 for the treatment of chronic weight management of patients with obesity due to POMC or LEPR deficiencies confirmed by genetic testing. Setmelanotide has not been given a definitive place in therapy but may be considered given its efficacy and safety profile as a long-term treatment for obesity once it becomes available. Further evaluation is warranted in other disorders, such as Bardet-Biedl and Alström Syndrome, resulting from variants in the central melanocortin pathway that causes MC4R activation. Rhythms Pharmaceuticals is currently working on extending indications for setmelanotide to improve its overall utility in the market.

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Personalized Medicine Corner

Using the FDA Table of Pharmacogenetic Associations

Benish Alam, PharmD

Background

Implementations of clinical pharmacogenomics are supported by a large body of primary evidence. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines with drug and dosing recommendations for those gene-drug pairs with significant data or importance.[1] Many of these recommendations are based upon pharmacokinetic and pharmacodynamic parameters affecting drug toxicity, effectiveness, and therapy outcomes. Key examples of drugs with high level of pharmacogenetic evidence and guidelines from CPIC include CYP2C19-clopidogrel, CYP2D6-opioids and TPMT/NUDT15-thiopurines.

Beyond the current guidelines, the pharmacogenomics field continues to grow as new genetic variants affecting pharmacokinetic and pharmacodynamic parameters are discovered, new medications become available, and consequential relationships are established. While various pharmacogenetic resources are available to clinicians to help them assess the impact of pharmacogenetic variants on their patients' medication regimens, it can be difficult to correlate new data with old drug package inserts, and pharmacogenomic and society guidelines.

In February 2020, the Food and Drug Administration (FDA) published their Table of Pharmacogenetic Associations for public use.[2] This table is meant to be a tool for providers and educators to quickly identify medications that may be affected by pharmacogenetic variants their patients may have. The table includes associations that the FDA considers to have sufficient evidence of altered parameters of drug metabolism, risk of adverse events, or even differences in efficacy, depending on pharmacogenetic results. While there is overlap between the FDA table and other pharmacogenomic references such as CPIC and PharmGKB, the threshold of evidence strength for inclusion may be different between these resources.[3]

The table is split into three sections, based upon supporting data and possible clinical applications of the association.

Section 1: Pharmacogenetic associations for which the data support therapeutic management recommendations

In this section, the FDA lists fifty-one gene-drug associations with data to support dosing and regimen modifications, or stricter clinical monitoring, may prevent adverse events (AE) or therapeutic failures. Some of these associations may already have existing CPIC guidelines, such as CYP2C19-clopidogrel, but many do not. Others may have some information in the drug's individual package insert.[4] This section does include recommended actions. Associations in this section include the following examples:

- Aripiprazole-CYP2D6 poor metabolizers: "Higher systemic concentrations, use half the usual dose."
- Dronabinol-CYP2C9 intermediate or poor metabolizers: "Higher systemic concentrations and increased risk of AE, monitor."
- Vortioxetine-CYP2D6 poor metabolizers: "Higher systemic concentrations. Max dose of 10 mg/day."

Section 2: Pharmacogenetic associations for which the data indicate a potential impact on safety or response

The second section of the table lists nineteen associations with data to support pharmacogenetic results may affect the risk for developing AEs with certain medications. It also includes associations that may result in therapeutic failure, and should be considered for patients, but does not list a recommendation if true. Associations in this section include the following examples:

- Allopurinol-HLA-B *58:01 allele positive: "Increased risk of adverse skin reactions."
- Codeine-CYP2D6 poor metabolizers: "Lower systemic active metabolite, resulting in reduced efficacy."
- Nilotinib-UGT1A1 poor metabolizers: "Increased risk of adverse events, such as hyperbilirubinemia."

Section 3: Pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only

Lastly, the FDA lists thirty-seven associations which the data show pharmacogenetic results may impact the metabolism (and thus exposure) of certain drugs. While these associations are less robust for clini-

-cal outcomes, the FDA includes them so that providers may be aware of potential impact on their patient's therapy, but no recommendations are made. Associations in this section include the following examples:

- Diazepam-CYP219 poor metabolizers: "May affect systemic concentrations."
- Dolutegravir-UGT1A1 poor metabolizers: "Higher systemic concentrations."
- Metoprolol-CYP2D6 poor metabolizers: "Higher systemic concentrations."

Conclusion:

The FDA table of Pharmacogenetic Associations does not describe the detailed pharmacokinetic or pharmacodynamic evidence behind associations, nor does it provide detailed dosing recommendations for all listed associations. However, it does include a comprehensive roster of medications on the market that may be affected by a patient's pharmacogenetics. The table's three sections can help a clinician to identify (1) what action or recommendation is made, if any, (2) what potential outcomes to monitor for or prevent (3) potential effects on a patient's metabolism of the drug. It serves as a good starting point for clinicians and educators to identify the potential impact of pharmacogenetics on their patient's health. However, recommendations and actions will need to be patient and scenario specific, with further guidelines or resources reviewed. For example, the CPIC guidelines recommend for CYP2D6 poor metabolizers to avoid codeine use, and if opioid use is warranted, consider a non-tramadol opioid. The guidelines and other resources such as PharmGKB can provide guidance and evidence in greater detail as required for pharmacogenetic informed care.

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