Pharmacy Policy Bulletin

Title:	Setmelanotide (Imcivree®)
Policy #:	Rx.01.244

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **Setmelanotide (Imcivree®)** as provided under the member's prescription drug benefit.

Description:

In a very small percentage of individuals, obesity may occur due to changes in a single gene. The most commonly implicated gene encodes melanocortin 4 (MC4) receptors (the MC4R gene).

Melanocortins are a family of melanocyte stimulating hormones (MSHs), some of which regulate hunger, caloric intake, energy expenditure, and bodyweight primarily thorough the MC4 receptor. Impairment in the MC4 receptor pathway leads to hyperphagia and early-onset severe obesity.

In normal physiology, leptin receptors (LEPRs) are expressed on proopiomelanocortin (POMC) neurons in the brain. The hormone leptin (from adipose tissue in the periphery) activates the LEPRs causing the POMC neurons to release MSH. The proprotein convertase subtilisin/kexin type 1 (PCSK1) gene codes for enzymes that also generate MSH from POMC-producing neurons. MSH binds to and activates MC4 receptors on MC4 receptor-expressing neurons. This binding stimulates a cascade of neurological signaling that ultimately leads to suppression of hunger, decreased food intake, and increased energy expenditure (FDA clinical review 2020, FDA summary review 2020).

Obesity due to POMC, PCSK1, or LEPR deficiency is due to variants in the POMC, PCSK1, or LEPR genes. These are very rare causes of obesity, with approximately 150 reported cases in medical literature for all three causes combined. A defect to one or more of these genes affects hunger levels, satiety, and energy output (metabolism). Individuals are usually a normal weight at birth but hyperphagia leads to progressive weight gain and early-onset obesity, which causes early-onset insulin resistance, hyperlipidemia, cardiovascular disease and other obesity-associated comorbidities. Patients with POMC, PCSK1, or LEPR deficiencies have progressive weight gain, which occurs at an average of 7 to 10 kg per year (Clement et al 2020, FDA press release 2020, FDA clinical review 2020).

Obesity in individuals can also be caused by Bardet-Biedl syndrome (BBS). BBS is an autosomal recessive disorder characterized by obesity and several other abnormalities, including microorchidism in men, intellectual disability, retinal dystrophy, polydactyly, renal malformations (particularly calyceal abnormalities), and polyuria and polydipsia. Mutations in at least 15 genes have been described in patients with this syndrome.

Setmelanotide (Imcivree™) is a melanocortin 4 (MC4) receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS), and Bardet-Biedl syndrome (BBS).

Guidelines for general obesity have not yet been updated to include setmelanotide or treatment algorithms for genetic causes of obesity. There is no data to support traditional therapies for obesity would work in these patients such as FDA approved medications, bariatric surgery, or standard-of-care diet and exercise, since the cause of their obesity is genetic.

Policy:

INITIAL CRITERIA: Setmelanotide (Imcivree™) is approved when ALL of the following are met:

A. Diagnosis of proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome; and
B. Other causes or types of obesity have been ruled out (e.g., obesity due to suspected POMC, PCSK1 or LEPR deficiency with POMC, PCSK1 or LEPR variants classified as benign or likely benign; obesity associated with other genetic syndromes; polygenic obesity; obesity due to Bardet-Biedl syndrome); and
C. Member is obese as defined by BMI of ≥30kg/m2 in adults or ≥95th percentile in pediatric patients using growth chart assessments; and
D. For proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency only: Prescriber submits medical chart note showing the diagnosis was confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, or of uncertain significance (VUS); and
E. Prescribed by or in consultation with ONE of the following:
    1. Endocrinologist; or
    2. Medical geneticist; or
    3. Specialist in the diagnosis and treatment of obesity; and
    4. Member is 6 years of age or older

Initial authorization duration: 6 months

REAUTHORIZATION CRITERIA: Setmelanotide (Imcivree™) is reapproved with documentation of positive clinical response to therapy (e.g., 5% weight loss based on baseline body weight or BMI)

Reauthorization duration: 12 months

Black Box Warning as shown in the drug Prescribing Information:

N/A

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Setmelanotide (Imcivree) [prescribing information]. Rhythm Pharmaceuticals, Inc. June 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213793s000lbl.pdf. Accessed October 17, 2022.

Food and Drug Administration (FDA). Clinical Review: Imcivree. 2020. Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213793Orig1s000MedR.pdf. Accessed October 17, 2022.

Clement K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicenter, phase 3 trials. Lancet Diabetes and Endocrinol. 2020;8(12):960-970.

Perreault, L. Obesity: Genetic contribution and pathophysiology. In: UpToDate. Available from: https://www.uptodate.com/contents/obesity-genetic-contribution-and-pathophysiology?search=imcivree&source=search_result&selectedTitle=1~2&usage_type=default&display_rank=1#H2744130704. Accessed October 17, 2022.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Imcivree™	Setmelanotide

Cross References:

Rx.01.33 Off Label Use

Policy Version Number:	2.00
P&T Approval Date:	September 15, 2022
Policy Effective Date:	January 01, 2023
Next Required Review Date:	September 15, 2023