PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/20/2021
LAST REVIEW DATE:
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ARCHIVE DATE:

Imcivree (setmelanotide)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Imcivree (setmelanotide)

Criteria:

- **Criteria for initial therapy:** Imcivree (setmelanotide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Weight Loss Specialist, Cardiologist, Endocrinologist, or Geneticist

  2. Individual is 6 years of age or older

  3. A confirmed diagnosis of obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency to be used for chronic weight management

  4. Individual does not have **ANY** of the following:
     a. Obesity due to suspected POMC-, PCSK1-, or LEPR-deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign

     b. Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity

     c. Double heterozygous variants in two different genes

     d. Prior gastric bypass surgery resulting in greater than 10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain

     e. Intensive diet and/or exercise regimen with or without the use of other weight loss agents including herbal medications, that has resulted in weight loss or weight stabilization

  5. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Genetic tests demonstrating bi-allelic homozygous or compound heterozygous variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) (See Definition section)

     b. **ONE** of the following:
        i. Adult has body mass index (BMI) of greater than or equal to 30 kg/m^2
        ii. Weight in pediatric patient is greater than or equal to 95^{th} percentile for age on growth chart assessment

     c. Full body skin examination

  6. Individual's estimated glomerular filtration rate (eGFR) is greater than or equal to 60 mL/min/1.73 m^2

Initial approval duration: 4 months

Imcivree (setmelanotide)

Will NOT be renewed if: individual has not lost at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential

- **Criteria for continuation of coverage (renewal request):** Imcivree (setmelanotide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Weight Loss Specialist, Cardiologist, Endocrinologist, or Geneticist

  2. Individual's condition has responded while on therapy
     a. Response is defined as **ONE** of the following:
        i. On first renewal request:
           1. Has lost at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential
        ii. On second renewal request:
           1. Achieved and maintains a ≥10% weight loss

  3. Individual has been adherent with the medication

  4. Individual has not developed any significant adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:
        i. Suicidal thoughts or behaviors
        ii. New onset or worsening depression
        iii. Penile erections lasting longer than 4-hours

  5. There are no significant interacting drugs

  6. Individual's estimated glomerular filtration rate (eGFR) is greater than or equal to 60 mL/min/1.73 m^2

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Imcivree (setmelanotide)

Description:

Imcivree (setmelanotide) is 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 receptors (LEPRs) deficiency **confirmed** by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or a variant of uncertain significance (VUS). Patients with POMC, PCSK1, or LEPR deficiencies have progressive weight gain, which occurs at an average of 7-10 kg per year.

Setmelanotide is **not indicated for** the treatment of patients with obesity due to **suspected** POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign or with other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity, as setmelanotide would not be expected to be effective.

Weight loss should be evaluated after 12-16 weeks of treatment. If a patient has not lost ≥ 5% of baseline bodyweight, or 5% of baseline BMI for patients with continued growth potential, setmelanotide should be discontinued.

Certain genes play a role in controlling energy balance and weight. In most obese individuals, the cause is attributed to interactions among multiple genes and environmental factors that remain poorly understood. A defect to one or more of these genes affects hunger levels, satiety, and energy output (metabolism). 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), however, other genes have been implicated in obesity.

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, LEPRs are expressed on 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 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.

Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In patients with obesity due to POMC, PCSK1, and LEPR deficiency associated with insufficient activation of the MC4 receptor, setmelanotide may re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure. Nonclinical evidence shows that MC4 receptors are important for setmelanotide-regulated appetite and weight loss. The MC1 receptor is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light.

Imcivree (setmelanotide)

There are no obesity treatment guidelines that are specific to obesity caused by POMC, PCSK1, or LEPR deficiencies. Additionally, there were no approved treatments or pharmacologic therapy for obesity caused by POMC, PCSK1, or LEPR deficiency. Bariatric surgery (i.e., gastric or intestinal banding or bypass surgery) is not effective in these patients due to the extreme hunger caused by POMC, PCSK1, or LEPR deficiency that still exists post-surgery. There are no clinical data to show that drugs approved for general obesity would result in weight reduction for these cases of genetic-linked obesity. Non-syndromic obese and overweight patients have shown that standard-of-care diet and exercise programs result in a mean weight loss of 1.2-2.5% at 1 year. Lifestyle modification is rarely successful in the short-term and almost never effective in the long term in these patients due to the intense drive to eat caused by the absence of satiety signals.

Definitions:

Bi-allelic Homozygous:
- Same gene mutation/variant on each allele of the same gene

Bi-allelic Compound Heterozygous:
- Different gene mutation/variant on each allele of the same gene

Double Heterozygous:
- Gene mutations/variants in two different genes

Pathogenic mutation/variant:
- Mutation/variant that is certain to disrupt gene function or certain to cause disease

Likely pathogenic mutation/variant:
- Mutation/variant that could affect gene function or has the potential to cause disease

Mutation/variant uncertain significance (VUS):
- Mutation/variant with unknown significance to gene function or unknown potential to cause disease, usually due to lack of knowledge

Likely benign mutation/variant:
- Mutation/variant with no reason to suspect significance to gene function or potential to cause disease

Benign mutation/variant:
- Mutation/variant does not cause disease

Resources:

Imcivree (setmelanotide) product information, revised by Rhythm Pharmaceuticals, Inc. 11-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on March 05, 2021.

Imcivree (setmelanotide)

Imcivree (setmelanotide) FDA Review. Drugs@FDA: FDA-Approved Drugs. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=213793. Accessed March 11, 2021.

Perreault L, Rosenbaum M. Obesity: Genetic contribution and pathophysiology. In: UpToDate, Pi-Sunyer FX, Kunins L (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on March 10, 2021.