**Effective Date** ..... **7/1/2023**
**Next Review Date** ..... **7/1/2024**
**Coverage Policy Number** ..... **IP0104**

# Setmelanotide for Employer Group Plans

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Pharmacogenetic Testing – (0500)

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## Overview

This policy supports medical necessity review for setmelanotide (**Imcivree®**) subcutaneous injection.

Receipt of sample product does not satisfy any criteria requirements for coverage.

## Medical Necessity Criteria

**Setmelanotide (Imcivree) is considered medically necessary when ONE of the following is met:**

1. **Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) or Leptin Receptor (LEPR) Deficiency.** Individual meets **ALL** of the following criteria:
   A. Age 6 years or older
   B. Genetic testing demonstrates biallelic variants in *POMC*, *PCSK1* or *LEPR* that are interpreted as pathogenic, likely pathogenic or of uncertain significance
   C. **ONE** of the following:

i. For age 18 years or older: Currently has a body mass index (BMI) of greater than or equal to 30 kg/$m^2$
ii. For age 6 to 17 years: Currently has a BMI of greater than or equal to 95$^{th}$ percentile for age and sex

D. Medication is prescribed by, or in consultation with, an endocrinologist, a geneticist or a physician who specializes in metabolic disorders

**Dosing**. Approve up to a maximum dose of 3 mg injected subcutaneously once daily.

2. **Obesity Due to Bardet-Biedl Syndrome.** Individual meets **ALL** of the following criteria:
   A. Age 6 years or older
   B. Documented diagnosis of Bardet-Biedl Syndrome is confirmed by **ONE** of the following:
      i. At least **FOUR** of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies or male hypogonadism
      ii. **BOTH** of the following:
         a. At least **THREE** of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies or male hypogonadism
         b. At least **TWO** of the following secondary features of Bardet-Biedl Syndrome: speech disorder/delay, strabismus/cataracts/astigmatism, brachydactyly/syndactyly, developmental delay, polyuria/polydipsia (nephrogenic diabetes insipidus), ataxia/poor coordination/imbalance, mild spasticity, diabetes mellitus, dental crowding/hypodontia/small roots/high arched palate, left ventricular hypertrophy/congenital heart disease or hepatic fibrosis
   C. **ONE** of the following criteria:
      i. For age 18 years or older: Currently has a body mass index (BMI) of greater than or equal to 30 kg/$m^2$
      ii. For less than age 18 years: Currently has a BMI of greater than or equal to 97$^{th}$ percentile for age and sex
   D. Medication is prescribed by, or in consultation with, an endocrinologist, a geneticist or a physician who specializes in metabolic disorders

      **Dosing**. Approve up to a maximum dose of 3 mg injected subcutaneously once daily.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

## Reauthorization Criteria

Continuation of setmelanotide (Imcivree) is considered medically necessary when **ONE** of the following is met:

1. **Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) OR Leptin Receptor (LEPR) Deficiency.** Individual meets the following criteria:
   A. Age 6 years or older
   B. Genetic testing demonstrates homozygous or compound heterozygous variants in *POMC*, *PCSK1* or *LEPR* that are interpreted as pathogenic, likely pathogenic or of uncertain significance
   C. **ONE** of the following:
      i. For age 18 years or older: Has lost greater than or equal to 5% of baseline body weight since initiating Imcivree therapy
      ii. For age 6 to 17 years, **BOTH** of the following:
         1. Has continued growth potential
         2. Has lost greater than or equal to 5% baseline BMI since initiating Imcivree therapy

D. Medication is prescribed by, or in consultation with, an endocrinologist, a geneticist or a physician who specializes in metabolic disorders

2. **Obesity Due to Bardet-Biedl Syndrome.** Individual meets **ALL** of the following criteria:
   A. Age 6 years or older
   B. **ONE** of the following:
      i. For age 18 years or older: Has lost greater than or equal to 5% of baseline body weight since initiating Imcivree therapy
      ii. For less than age 18 years: Has lost greater than or equal to 5% of baseline BMI since initiating Imcivree therapy
   C. Medication is prescribed by, or in consultation with, an endocrinologist, a geneticist or a physician who specializes in metabolic disorders

## Authorization Duration

Initial approval duration:
1. **Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) OR Leptin Receptor (LEPR) Deficiency**: 4 months
2. **Obesity Due to Bardet-Biedl Syndrome**: 12 months

Reauthorization approval duration:
1. **Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) OR Leptin Receptor (LEPR) Deficiency**: 12 months
2. **Obesity Due to Bardet-Biedl Syndrome**: 12 months

## Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Other Genetic Obesity Syndromes.** Imcivree is not indicated for genetic obesity syndromes other than POMC-, PCSK1-, or LEPR-deficient obesity or Bardet-Biedl syndrome.

2. **General Obesity.** Imcivree is not indicated in this setting and there are no clinical data to support its use.[1]

## Background

**OVERVIEW**
Imcivree, a melanocortin 4 receptor agonist, is indicated for chronic weight management in patients ≥ 6 years of age with monogenic or syndromic obesity due to:[1]

- **Proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency**, as determined by an FDA-approved test demonstrating variants in *POMC, PCSK1,* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.
- **Bardet-Biedl Syndrome**.

As a limitation of use, Imcivree is not indicated for obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign.[1] Imcivree is also not indicated for obesity not related to POMC, PCSK1, or LEPR deficiency or not related to Bardet-Biedl syndrome, including obesity associated with other genetic syndromes and general (polygenic) obesity.

In the pivotal trial for Imcivree obesity due to POMC deficiency (homozygous or compound heterozygous variants in *POMC* or *PCSK1*) or LEPR deficiency (homozygous or compound heterozygous variants in *LEPR*), obesity was defined according to patient age.[2] For patients 6 to < 18 years of age, obesity was defined as body

weight ≥ 95th percentile for age on growth chart assessment. For patients ≥ 18 years of age, obesity was defined as a body mass index (BMI) ≥ 30 kg/m$^2$.

Per the Imcivree prescribing information, select patients for treatment with Imcivree who have a clinical diagnosis of Bardet-Biedl syndrome.[1] It is noted that in the pivotal trial, adults had a BMI ≥ 30 kg/m$^2$ and pediatric patients had a weight ≥ 97th percentile using growth chart assessments. Patients were enrolled who had a clinical diagnosis of Bardet-Biedl syndrome. The clinical diagnosis was based on Beales criteria, which require that four primary features, or three primary and two secondary features, of Bardet-Biedl syndrome be met.[3]

For obesity due to POMC, PCSK1, or LEPR deficiency, weight loss should be evaluated after 12 to 16 weeks of Imcivree treatment.[1] If a patient has not lost at least 5% of baseline body weight, or 5% of baseline body mass index for a patient with continued growth potential, Imcivree should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. For obesity and a clinical diagnosis of Bardet-Biedl syndrome, evaluate weight loss after 1 year of treatment. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for a patient < 18 years of age, discontinue Imcivree.

**Disease Overview**
Monogenic obesity is a rare and severe early-onset form of obesity.[4] Unlike general obesity, environmental factors are much less impactful on obesity development in these patients. Fewer than 50 patients worldwide have been identified with POMC deficiency (*POMC* or *PCSK1* mutations); the prevalence of LEPR deficiency is unknown but is expected to account for less than 3% of severe early-onset obesity. The true prevalence of these disorders is unknown and likely underestimated due to lack of provider awareness and genetic testing.[2] Clinical presentation is mainly characterized by major hyperphagia and ravenous hunger.[3] Patients with these disorders experience very rapid and early increase in weight, occurring within the first few days of life to early childhood. Lifestyle interventions may provide initial weight loss but are very difficult to maintain long-term in this population due to constant, insatiable hunger.[5] Isolated case reports of bariatric surgery have demonstrated some efficacy but are generally regarded as disappointing relative to the general population, likely related to the underlying energy imbalance. Caution is urged before considering bariatric surgery in patients with monogenic obesity disorders.

Bardet-Biedl syndrome is a rare genetic disease of obesity with an estimated prevalence of 1:100,000 individuals in Northern Europe and America, although the prevalence can be higher in certain consanguineous populations.[6] It is generally inherited in an autosomal recessive fashion. There are many gene mutations which are known to lead to the development of Bardet-Biedl syndrome. Additionally, an estimated 20% to 30% of patients with Bardet-Biedl syndrome do not have an identified genetic mutation. Diagnosis is based on the presence of characteristic clinical findings.

## References


1. Imcivree subcutaneous injection [prescribing information]. Boston, MA: Rhythm; June 2022.
2. Clément K, van den Akker E, Argente J, et al; setmelanotide POMC and LEPR Phase 3 Trial Investigators. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020 Dec;8(12):960-970.
3. Haws RM, Gordon G, Han JC, et al. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome: Phase 3 trial design. *Contemp Clin Trials Commun*. 2021 May 3;22:100780.
4. Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. *Obes Facts*. 2016;9(3):158-73.
5. Poitou C, Mosbah H, Clément K. Mechanisms in endocrinology: update on treatments for patients with genetic obesity. *Eur J Endocrinol*. 2020 Nov;183(5):R149-R166.
6. Bardet-Biedl syndrome. National Organization of Rare Disorders. Updated 2017. Available at: https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/ Accessed on December 27, 2022.