Prior Authorization
Metabolic Disorders – Imcivree® (setmelanotid subcutaneous injection)

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Product Identifier(s)

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National Formulary Medical Necessity

Cigna covers setmelanotide (Imcivree®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior Authorization is recommended for prescription benefit coverage of Imcivree. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of individuals treated with Imcivree as well as the monitoring required for adverse events and long-term efficacy, approval requires Imcivree to be prescribed by or in consultation with a physician who specializes in the condition being treated.

FDA Indication(s)

1. Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency. Approve for the duration noted if the individual meets the following criteria (A or B):
   A) Initial Therapy. Approve for 4 months if the individual meets the following criteria (i, ii, iii, and iv):
i. Individual is ≥ 6 years of age; AND

ii. Individual meets both of the following criteria (a and b):
   a) Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND
   b) The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND

iii. Individual meets one of the following criteria (a or b):
   a) Individual is ≥ 18 years of age: Individual currently has a body mass index (BMI) ≥ 30 kg/m²; OR
   b) Individual is 6 to 17 years of age: Individual currently has a body weight ≥ 95th percentile for age on growth chart assessment; AND

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

B) Individual is currently receiving Imcivree. Approve for 1 year if the individual meets the following criteria (i, ii, iii, and iv):
   
   Note: For an individual who has not completed at least 4 months of Imcivree therapy, refer to Initial Therapy criteria.

   i. Individual is ≥ 6 years of age; AND
   
   ii. Individual meets both of the following criteria (a and b):
      a) Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND
      b) The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND

   iii. Individual meets one of the following criteria (a or b):
      a) Individual has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR
      b) Individual meets both of the following [(1) and (2)]:
         (1) Individual has continued growth potential; AND
         (2) Individual has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND

   iv. Imcivree 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. Approve for 1 year if the individual meets one of the following (A or B):

   A) Initial Therapy. Approve if the individual meets all of the following criteria (i, ii, iii, and iv):
   
   i. Individual is ≥ 6 years of age; AND
   
   ii. Individual has a clinical diagnosis of Bardet-Biedl Syndrome by meeting one of the following (a or b):
      a) Individual has at least FOUR of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, or male hypogonadism; OR
      b) Individual meets both of the following [(1) and (2)]:
         (1) Individual has at least THREE of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, or male hypogonadism; AND
         (2) Individual has 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; AND

   iii. Individual meets one of the following criteria (a or b):
      a) Individual is ≥ 18 years of age: Individual currently has a body mass index (BMI) ≥ 30 kg/m²; OR
      b) Individual is < 18 years of age: Individual currently has a body weight ≥ 97th percentile for age on growth chart assessment; AND

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

   B) Individual is Currently Receiving Imcivree. Approve if the individual meets the following criteria (i, ii, and iii):
Note: For an individual who has not completed at least 1 year of Imcivree therapy, refer to Initial Therapy criteria.

i. Individual is ≥ 6 years of age; AND  

ii. Individual meets one of the following criteria (a or b):
   a) Individual has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR  
   b) Individual meets both of the following [(1) and (2)]:  
      1) Individual is < 18 years of age; AND  
      2) Individual has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND  

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

### Conditions Not Covered

Setmelanotide (Imcivree) is considered experimental, investigational or unproven for ANY other use 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.
   
   Note: Examples of genetic obesity syndromes include Prader-Willi syndrome and Alström 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:

- **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/m².

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/m² 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. 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. Clinical presentation is mainly characterized by major hyperphagia and ravenous hunger. 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. 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. 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.

**Revision History**

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<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
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<tbody>
<tr>
<td>Early Annual Revision</td>
<td>No criteria changes.</td>
<td>01/04/2023</td>
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