

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Metabolic Disorders – Imcivree Utilization Management Medical Policy

- Imcivree® (setmelanotide subcutaneous injection – Rhythm)

REVIEW DATE: 01/14/2026; selected revision 04/01/2026 and 06/10/2026

OVERVIEW

Imcivree, a melanocortin 4 receptor (MCR4) agonist, is indicated to reduce excess body weight and maintain weight reduction long term by reducing hunger and food intake and increasing energy expenditure in patients ≥ 2 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.**

Imcivree is additionally indicated to reduce excess body weight and maintain weight reduction long term in patients ≥ 4 years of age with **Acquired hypothalamic obesity**.¹

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 acquired hypothalamic obesity, 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 regarding 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, with LEPR deficiency, obesity was defined as body weight $\geq 95^{\text{th}}$ percentile for age on growth chart assessment^{1,10} and for patients with POMC (including PCSK1), obesity was defined as body mass index (BMI) $\geq 95^{\text{th}}$ percentile for age on growth chart assessment¹¹ or a body weight $\geq 95^{\text{th}}$ percentile.¹ For both LEPR and POMC, in patients ≥ 18 years of age, obesity was defined as a body mass index (BMI) ≥ 30 kg/m².

The use of Imcivree in pediatric patients 2 to < 6 years of age is supported by a 1-year open-label study in 12 pediatric patients with POMC or LEPR deficiency or Bardet-Biedl Syndrome (patients with PCSK1 were eligible, but none were enrolled).¹ POMC and LEPR deficiency were confirmed by genetic testing demonstrating biallelic variants interpreted as pathogenic, likely pathogenic, or of undetermined significance; Bardet-Biedl Syndrome was diagnosed clinically with genetic confirmation. Obesity was defined as BMI $\geq 97^{\text{th}}$ percentile for age and gender and body weight ≥ 15 kg at the time of enrollment.¹²

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, patients ≥ 16 years of age had a BMI ≥ 30 kg/m² and patients 6 to 15 years of age had a weight $\geq 97^{\text{th}}$ percentile for age and gender on growth chart assessment.¹³ 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

The percentage of body weight loss from baseline or percentage of baseline BMI for a patient with continued growth potential was assessed as the efficacy endpoints in the clinical trials. Patients with < 5% weight loss or < 5% of BMI loss were not considered to have a response to Imcivree (assessed at 1 year in patients with Bardet-Biedl syndrome and after 12 weeks in patients with POMC, PCSK1, or LEPR deficiency).

In the pivotal study for the indication of acquired hypothalamic obesity, patients ≥ 4 years of age with a BMI $\geq 95^{\text{th}}$ percentile (in those ≥ 4 to < 18 years of age) and a BMI $\geq 30 \text{ kg/m}^2$ (in those ≥ 18 years of age) were assessed.⁹ The patients had acquired hypothalamic obesity following hypothalamic tumor, lesion, or injury. The primary efficacy endpoint was mean percent change in BMI from baseline after 52 weeks (Imcivree vs. placebo).¹ The percent change from baseline BMI was -15.84 vs. 2.55, Imcivree vs. placebo, respectively, with a placebo-adjusted difference of -18.40%.

Disease Overview

Genetic obesity disorders are considered to be brain diseases that result in a disruption of the neuroendocrine system of the hypothalamus.⁴ These disorders are often a result of genetic defects in the leptin-melanocortin pathway which is essential for the homeostatic regulation of body weight. A defect in any of the genes involved in the leptin-melanocortin pathway can therefore result in reduced function or defective protein products leading to impaired signaling. Some examples of affected genes that result either in syndromic or non-syndromic genetic obesity are *LEPR*, Src homology 2B adaptor protein, *POMC*, *PCSK1*, or *MCR4* as well as other genes involved in the leptin-melanocortin pathway. Bardet-Biedl syndrome and Alström syndrome are also part of the genetic obesity spectrum. The distinctive features of these genetic defects lead to early-onset obesity and hyperphagia. Patients with these disorders experience a 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.

Acquired hypothalamic obesity is characterized by accelerated and sustained weight gain, often accompanied by hyperphagia (i.e., insatiable hunger, impaired satiety, and abnormal food-seeking behaviors), energy imbalance, and obesity.⁹ Injury to the hypothalamus (e.g., tumor growth, surgical injury, radiation injury, inflammation due to infection, traumatic brain injury, hemorrhage) can impair MCR4 pathway signaling and lead to acquired hypothalamic obesity.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Imcivree. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director

or Pharmacist). 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 patients 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imcivree is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Acquired Hypothalamic Obesity. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 4 years of age; AND

ii. Patient has or had a hypothalamic tumor, hypothalamic lesion, or hypothalamic damage or injury; AND

Note: Examples of the above include craniopharyngioma, astrocytoma, or other malignant or non-malignant hypothalamic-pituitary tumors; surgery, chemotherapy, or radiation for intracranial tumors; traumatic brain injury, hemorrhage, or stroke; inflammation due to infection.

iii. Patient meets ONE of the following (a or b):

a) Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m²; OR

b) Patient is < 18 years of age: Patient currently has a BMI ≥ 95 th percentile for age and gender on growth chart assessment; AND

iv. The medication is prescribed by or in consultation with an endocrinologist, a physician who specializes in metabolic disorders, or a neurologist; OR

B) Patient is Currently Receiving Imcivree. Approve if the patient meets ALL of the following (i, ii, and iii):

Note: For a patient who has not completed at least 1 year of Imcivree therapy, refer to Initial Therapy criteria.

i. Patient is ≥ 4 years of age; AND

ii. Patient has lost $\geq 5\%$ baseline BMI since initiating Imcivree therapy; AND

iii. The medication is prescribed by or in consultation with an endocrinologist, or a physician who specializes in metabolic disorders, or a neurologist.

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

2. Obesity Due to Bardet-Biedl Syndrome. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 2 years of age; AND

- ii. Patient has a clinical diagnosis of Bardet-Biedl Syndrome by meeting ONE of the following (a or b):
 - a) Patient 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) Patient meets BOTH of the following [(1) and (2)]:
 - (1) Patient 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) Patient 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. Patient meets ONE of the following (a, b, or c):
 - a) Patient is ≥ 16 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m²; OR
 - b) Patient is 6 to < 16 years of age: Patient currently has a body weight ≥ 97 th percentile for age on growth chart assessment; OR
 - c) Patient is 2 to < 6 years of age: Patient currently has a BMI ≥ 97 th percentil for age and gender on growth chart assessment; AND
 - iv. The medication is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders; OR
- B) Patient is Currently Receiving Imcivree.** Approve if the patient meets ALL of the following (i, ii, and iii):
- Note: For a patient who has not completed at least 1 year of Imcivree therapy, refer to Initial Therapy criteria.
- i. Patient is ≥ 2 years of age; AND
 - ii. Patient meets ONE of the following (a or b):
 - a) Patient has lost $\geq 5\%$ of baseline body weight since initiating Imcivree therapy; OR
 - b) Patient meets both of the following [(1) and (2)]:
 - (1) Patient is < 18 years of age; AND
 - (2) Patient has lost $\geq 5\%$ of baseline BMI since initiating Imcivree therapy; AND
 - iii. The 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.

- 3. Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency.** Approve for the duration noted if the patient meets ONE of the following (A or B):
- A) Initial Therapy.** Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
- i. Patient is ≥ 2 years of age; AND
 - ii. Patient meets BOTH of the following (a and b):
 - a) Genetic testing demonstrates homozygous or compound heterozygous variants 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. Patient meets ONE of the following (a, b, or c):
 - a) Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m²; OR
 - b) Patient is 6 to 17 years of age and meets ONE of the following [(1) or (2)]:
 - (1) Patient with LEPR deficiency: Patient currently has a body weight $\geq 95^{\text{th}}$ percentile for age and gender on growth chart assessment; OR
 - (2) Patient with POMC or PCSK1: Patient currently has a BMI $\geq 95^{\text{th}}$ percentile for age and gender on growth chart assessment OR a body weight $\geq 95^{\text{th}}$ percentile for age and gender on growth chart assessment; OR
 - c) Patient is 2 to ≤ 5 years of age: Patient currently has a BMI $\geq 97^{\text{th}}$ percentile for age and gender on growth chart assessment; AND
 - iv. The medication is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders; OR
- B) Patient is Currently Receiving Imcivree.** Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
- Note: For a patient who has not completed at least 4 months of Imcivree therapy, refer to Initial Therapy criteria.
- i. Patient is ≥ 2 years of age; AND
 - ii. Patient meets BOTH of the following (a and b):
 - a) Genetic testing demonstrates homozygous or compound heterozygous variants 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. Patient meets ONE of the following (a or b):
 - a) Patient has lost $\geq 5\%$ of baseline body weight since initiating Imcivree therapy; OR
 - b) Patient meets both of the following [(1) and (2)]:
 - (1) Patient is < 18 years of age; AND
 - (2) Patient has lost $\geq 5\%$ of baseline BMI since initiating Imcivree therapy; AND
 - iv. The 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imcivree is not recommended in the following situations:

- 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. A Phase III trial included six patients with Alström syndrome, none of the six patients met the primary endpoint ($\geq 10\%$ weight loss after 52 weeks of Imcivree).⁷
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

- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/10/2024
Annual Revision	Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency. <u>Initial Therapy.</u> The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age). A criterion was added that for a patient that is 2 to ≤ 5 years of age, the patient currently has a body weight ≥ 97th percentile for age on growth chart assessment. <u>Patient is Currently Receiving Imcivree.</u> The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age). Obesity Due to Bardet-Biedl Syndrome. <u>Initial Therapy.</u> The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age). <u>Patient is Currently Receiving Imcivree.</u> The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age).	01/08/2025
Annual Revision	Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency. <u>Initial Therapy</u> and <u>Patient is Currently Receiving Imcivree:</u> “Mutations” was replaced with “variants” for the requirement that genetic testing demonstrates homozygous or compound heterozygous “variants” in one of the following genes.	01/14/2026
Selected Revision	Obesity Due to Acquired Hypothalamic Obesity. This condition of approval was added to the policy.	04/01/2026

01/14/2026

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Selected Revision	Obesity Due to Acquired Hypothalamic Obesity. Removed “obesity due to” and diagnosis is updated to Acquired Hypothalamic Obesity. For initial therapy, for a patient < 18 years of age, body weight $\geq$ 95th percentile for age on a growth chart assessment was updated to body mass index (BMI) $\geq$ 95th percentile for age and gender on growth chart assessment. For continuation of therapy, patient has lost $\geq$ 5% of baseline body weight since initiating Imcivree therapy OR patient meets both of the following [(1) and (2)]: Patient is < 18 years of age AND patient has lost $\geq$ 5% of baseline BMI since initiating Imcivree therapy was removed. These criterion were replaced with patient has lost $\geq$ 5% BMI since initiating Imcivree therapy (regardless of age). Obesity Due to Bardet-Biedl Syndrome. For initial therapy, patient $\geq$ 18 years of age was updated to patient $\geq$ 16 years of age. Patient < 18 years of age was updated to patient 6 to < 16 years of age. A criterion was added for patient 2 to < 6 years of age requiring that the patient currently has a BMI $\geq$ 97th percentile for age and gender on growth chart assessment. Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency. For initial therapy, patient 6 to 17 years of age, was broken into patient with LEPR deficiency and patient with POMC or PCSK1. Criterion for patient with POMC or PCSK1 was added as patient currently has a BMI $\geq$ 95th percentile for age and gender on growth chart assessment OR a body weight $\geq$ 95th percentile for age and gender on growth chart assessment. Patient 2 to $\leq$ 5 years of age was updated to patient currently has a BMI $\geq$ 97th percentile for age and gender on growth chart assessment; previously was patient currently has a body weight $\geq$ 97th percentile for age on growth chart assessment. For continuation of therapy, the criterion patient has continued growth potential was updated to patient is < 18 years of age.	06/10/2026
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