POLICY: Metabolic Disorders – Imcivree Utilization Management Medical Policy
- Imcivree™ (setmelanotide subcutaneous injection – Rhythm Pharmaceuticals)

EFFECTIVE DATE: 06/01/2021
LAST REVISION DATE: 01/08/2025

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

OVERVIEW

Imcivree, a melanocortin 4 receptor 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**.

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 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, 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.

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 baseline BMI ≥ 97th percentile for age and sex and body weight ≥ 20 kg.

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]

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).

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.

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. **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 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.** 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/m^2; OR
       - **b)** Patient is 6 to 17 years of age: Patient currently has a body weight ≥ 95th percentile for age on growth chart assessment; OR
       - **c)** Patient is 2 to ≤ 5 years of age: Patient currently has a body weight ≥ 97th percentile for age 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.
   - **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 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.** Patient meets ONE of the following (a or b):
       - **a)** Patient has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR
       - **b)** Patient meets both of the following [(1) and (2)]:
         - **(1)** Patient has continued growth potential; AND
         - **(2)** Patient has lost ≥ 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.

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 or b):
- **a)** Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m^2; OR
- **b)** Patient is < 18 years of age: Patient currently has a body weight ≥ 97th percentile for age 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.

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 ≥ 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 ≥ 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.

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 (≥ 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]

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

REFERENCES

1. Imcivree® subcutaneous injection [prescribing information]. Boston, MA: Rhythm; December 2024.
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;183(5):R149-R166.
6. Bardet-Biedl syndrome. National Organization of Rare Disorders. Updated July 2022. Available at: https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/ Accessed on January 3, 2025.
7. Haqq AM, Chung WK, Dolfus H, et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *Lancet Diabetes Endocrinol.* 2022;10(12):859-868.
8. Argente J, Verge CF, Okorie U, et al. Setmelanotide in patients aged 2-5 years with rare MC4R pathway-associated obesity (VENTURE): a 1-year open-label, multicenter, phase 3 trial. *Lancet Diabetes Endocrinol.* 2025;13(1):29-37.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/04/2023
Annual Revision	No criteria changes.	01/10/2024
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
Annual Revision	**Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency.** Initial Therapy. 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. Patient is Currently Receiving Imcivree. The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age). **Obesity Due to Bardet-Biedl Syndrome.** Initial Therapy. The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age). Patient is Currently Receiving Imcivree. The age criterion was updated to ≥ 2 years of age (previously ≥ 6 years of age).	01/08/2025
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/15/2025