PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Imcivree Prior Authorization Policy
- Imcivree® (setmelanotide subcutaneous injection – Rhythm)

REVIEW DATE: 01/14/2026; selected revision 04/01/2026

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

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, 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 ≥ 97^{th} 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).

In the pivotal study for the indication of acquired hypothalamic obesity, patients ≥ 4 years of age with a BMI ≥ 95^{th} percentile (in those ≥ 4 to < 18 years of age) and a BMI ≥ 30 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-Biedel 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 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 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.

- **Imcivree® (setmelanotide subcutaneous injection – Rhythm)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Obesity Due to 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/m^2; OR
       - **b)** Patient is < 18 years of age: Patient currently has a body weight ≥ 95th percentile for age 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 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 physician who specializes in metabolic disorders, or a neurologist.

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; 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 ≥ 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.

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/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; 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 ≥ 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.

CONDITIONS NOT COVERED

- **Imcivree® (setmelanotide subcutaneous injection – Rhythm)**

is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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]

REFERENCES

1. Imcivree® subcutaneous injection [prescribing information]. Boston, MA: Rhythm; March 2026.
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. Welling MS, van Rossum EFC, and van den Akker ELT. Antiobesity pharmacotherapy for patients with genetic obesity due to defects in the leptin-melanocortin pathway. *Endocrine Reviews*. 2025;46:418-446.
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.
9. Rhythm Pharmaceuticals. Presentation: Cardiometabolic results from a phase 3 trial of setmelanotide in acquired hypothalamic obesity. Available at: TOS 2025 Miller Cardio. Accessed on 3/27/2026.

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.** 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
Annual Revision	**Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency.** Initial Therapy and Patient is Currently Receiving Imcivree: "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