Drug Coverage Policy

Effective Date.....08/01/2024
Coverage Policy Number.....IP0104
Policy Title.....Imcivree

Metabolic Disorders – Imcivree

- Imcivree® (setmelanotide subcutaneous injection – Rhythm)

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 and have discretion in making individual coverage determinations. 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 Healthcare Coverage Policy

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 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.

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.

Medical Necessity Criteria

Imcivree is considered medically necessary when ONE of the following are met:

FDA-Approved indications

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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 the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 6 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 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; 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 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 ≥ 6 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.

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

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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 ≥ 6 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 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 ≥ 6 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.

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.

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

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, 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; November 2023.
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 5, 2024.
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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency:** **Updated** the genetic testing requirement by changing *biallelic variants* to *homozygous or compound heterozygous pathogenic variants*. **Updated** the age 6-17 BMI requirement to a body weight requirement. **Removed** age requirements from the continuation of therapy weight loss requirement. **Obesity Due to Bardet-Biedl Syndrome.** **Updated** the less than 18 years of age BMI requirement to a body weight requirement. **Removed** age requirement from the adult continuation of therapy weight loss requirement. **Conditions Not Covered**	08/01/2024

	Added clinical trial outcome information and examples to Other Genetic Obesity Syndromes.	

The policy effective date is in force until updated or retired.