setmelanotide (Imcivree®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO289

Description

Setmelanotide (Imcivree) is a subcutaneously administered melanocortin-4 (MC4R) receptor agonist.

Length of Authorization

- Initial:
  POMC/PCSK1/LEPR deficiency: 6 months
  Bardet-Biedl Syndrome: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
setmelanotide (Imcivree)	chronic weight management in monogenic or syndromic obesity due to POMC, PCSK1, or LEPR deficiency, variants interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)*	10 mg/mL solution in a 1 mL multiple-dose vial	9 mL/30 days (9 vials)
	chronic weight management in monogenic or syndromic obesity due to Bardet-Biedl syndrome (BBS)*		

**Treatment for weight loss/weight management is in the following category of medications that are not covered under the prescription benefit for select groups. Drugs used for weight management are excluded from coverage for select groups. Please reference the 'Pharmacy Prescription Benefit Exclusions' and 'General Exclusions' sections of the member handbook/certificate of coverage for further information.*

Initial Evaluation

I. **Setmelanotide (Imcivree)** may be considered medically necessary when the following criteria are met:
   A. Medications for weight loss are a covered benefit for the member's plan (please reference member handbook/certificate of coverage for further information); **AND**
   B. Member is 6 to 20 years of age; **AND**
   C. Medication is prescribed by, or in consultation with, an endocrinologist, geneticist, or metabolic disease specialist; **AND**
   D. Medication is not being used in combination with other medications intended for weight management; **AND**
   E. A diagnosis of one of the following:
      1. **Proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiency**; **AND**

i. Documentation of genetic testing demonstrating variants in *POMC, PCSK1*, or *LEPR* genes; **AND**
ii. Genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS); **AND**
iii. Documentation of a diagnosis of obesity, defined as:
    a. Members 18 to 20 years of age: Body mass index (BMI) is ≥30 kg/m^2 (defined as obese) for adults; **OR**
    b. Members 6 to 17 years of age: Bodyweight of ≥ 95th percentile for age and sex (defined as obese); **OR**

2. **Bardet-Biedl Syndrome (BBS); AND**
    i. Provider attestation of a clinical diagnosis of Bardet-Biedl Syndrome as defined by:
        a. At least four of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, male hypogonadism; **OR**
        b. Member has both of the following:
            i. At least three primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, male hypogonadism; **AND**
            ii. At least two 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**
    ii. Documentation of a diagnosis of obesity, defined as:
        a. Members 16 to 20 years of age: Body mass index (BMI) is ≥30 kg/m^2 for adults; **OR**
        b. Members 6 to 15 years of age: Bodyweight of ≥ 97th percentile for age and sex

II. Setmelanotide (Imcivree) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Other causes or types of obesity (e.g., obesity due to suspected POMC, PCSK1 or LEPR deficiency with *POMC, PCSK1* or *LEPR* variants classified as benign or likely benign)

B. Obesity associated with other genetic syndromes (e.g., Prader-Willi syndrome, Alström syndrome)
C. General obesity

III. Setmelanotide (Imcivree) is considered investigational when used for all other conditions, including but not limited to:
A. Members younger than 6 years of age
B. Hypothalamic obesity

Renewal Evaluation

I. Medications for weight loss are a covered benefit for the member's plan (please reference member handbook/certificate of coverage for further information); **AND**
II. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
III. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. Member is 6 to 20 years of age; **AND**
V. Medication is not being used in combination with other medications intended for weight management; **AND**
VI. Member has a diagnosis of obesity due to one of the following:
- **Proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiency**; **AND**
    i. Member has received at least 16 weeks of therapy with setmelanotide (Imcivree); **AND**
        1. Member has achieved/maintained ≥5% weight loss from baseline body weight or ≥5% of baseline BMI; **OR**
    ii. Member has received less than 16 weeks of treatment; **AND**
        1. Member has experienced weight loss or weight has remained stable; **OR**
- **Bardet-Biedl Syndrome (BBS)**; **AND**
    i. Member has received at least one year of therapy with setmelanotide (Imcivree); **AND**
        1. Member has achieved/maintained ≥5% weight loss from baseline body weight or ≥5% of baseline BMI; **OR**
    ii. Member has received less than 1 year of therapy with setmelanotide (Imcivree); **AND**

1. Member has experienced weight loss or weight has remained stable

Supporting Evidence

I. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Program on the Oregon Health Plan (OHP) provides benefits for medically necessary and medically appropriate health care service for children and youth under age 21. There is a path to coverage for agents used for weight management via EPSDT for members up to 21 years of age when prior authorization criteria are met. Per the OHP prioritized list of healthcare services, there is currently no path to coverage for setmelanotide (Imcivree) and/or treatments used for chronic weight management in patients 21 years of age or older as weight loss is in the category of indications that are excluded from the health plan's benefit.

II. The MC4R pathway is thought to be one of the critical components in homeostatic regulation of hunger, caloric intake, energy expenditure, and body weight. Genetic variants in this pathway can lead to symptoms of early-onset, severe obesity, and severe, insatiable hunger (hyperphagia).

III. Setmelanotide (Imcivree) is FDA-approved for the treatment of chronic weight management in adult and pediatric patients 6 years of age and older 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 (VUS) and in obesity due to Bardet-Biedl syndrome (BBS).

IV. Setmelanotide (Imcivree) represents the first and only FDA-approved treatment for patients with obesity due to POMC, PCSK1, or LEPR deficiency and BBS. Setmelanotide (Imcivree) is an MC4R agonist that is intended to partially, or completely restore, signaling at the MC4R, which is impacted by these deficiencies. Other obesity drugs on the market do not target the underlying cause of obesity; setmelanotide (Imcivree) is expected to be the first-line therapy for all patients with obesity and a confirmed diagnosis of POMC, PCSK1, LEPR deficiency or BBS, used in conjunction with lifestyle and behavior management strategies. Neither guidelines for general obesity nor treatment algorithms for genetic causes of obesity have been updated to include setmelanotide (Imcivree).

V. Obesity due to POMC, PCSK1, or LEPR deficiency is due to variants in the *POMC, PCSK1*, or *LEPR* genes. Approximately 150 reported cases have been reported in medical literature for all three causes combined. Individuals experience rapid and early increase in weight, occurring within the first few days of life to early childhood. Hyperphagia leads to progressive weight gain and early-onset obesity, which causes early-onset insulin resistance, hyperlipidemia, cardiovascular disease, and other obesity-associated comorbidities.

VI. BBS is an autosomal recessive disorder with an estimated 1,500 to 2,500 individuals living with the disease in the US. The majority of individuals with BBS experience rapid weight gain in early

childhood, with over 50% developing obesity before the age of five. There are many gene mutations which are known to lead to the development of BBS; however, up to 30% of patients do not have an identified genetic mutation. Diagnosis is based on the presence of characteristic clinical findings based on Beales criteria; four primary features OR three primary and two secondary features are required to make a clinical diagnosis. Primary features of BBS include retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties, and hypogonadism. Key secondary features include 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.

VII. Efficacy and safety of setmelanotide (Imcivree) for chronic weight management was studied in two, 52-week, open label studies, each with an 8-week, double-blind withdrawal period. Study 1 enrolled ten patients 6 years of age or older diagnosed with obesity and genetically confirmed or suspected POMC, PCSK1 and Study 2 enrolled eleven patients with LEPR deficiency demonstrating variants in genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS). Individuals were classified as obese based on ≥BMI 30 kg/m^2 for adults or weight ≥95th percentile using growth chart assessments for pediatric patients. In Study 1, the mean baseline BMI and body weight was 40 kg/m^2 and 119kg. In study 2, the mean baseline BMI and body weight was 48 kg/m^2 and 133 kg. Setmelanotide (Imcivree) was titrated to a goal of 3mg subcutaneously daily. No background lifestyle or behavioral intervention to promote weight loss were allowed. The primary endpoint evaluated the proportion of patients who achieved a ≥10% reduction in body weight after 52 weeks. A key secondary endpoint included mean percent change in weight from baseline. In Study 1, 80% of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint and 46% of patients with obesity due to LEPR deficiency achieved a greater than or equal to 10% weight loss after 1 year of treatment ($p<0.0001$ and $p=0.0002$). Of the eight participants who met the 10% weight loss threshold in the POMC trial, all met the 20% threshold, seven met the 25% threshold, three met the 30% threshold, and one met the 35% threshold. Of the five participants who met the 10% weight loss threshold in the LEPR trial, all met the 15% threshold, two met the 20% threshold, and none met the 25% threshold. The mean percent change in weight from baseline in individuals with POMC/PCSK1 and LEPR variants experienced was 23% and 10%.

VIII. The clinical trial for BBS was a 66-week clinical study, which included a 14-week randomized, double-blind, placebo-controlled period and a 52-week open-label period. The study enrolled patients 6 years of age or older with a clinical diagnosis of BBS and classified as obese based on ≥BMI 30 kg/m^2 for individuals 16 years of age and older or weight ≥97th percentile using growth chart assessments for patients 6-15 years of age. Clinical diagnosis of BBS in study participants required four primary features or three primary and two secondary features, per Beales 1999. The mean baseline BMI and body weight was 42 kg/m^2 and 112kg. The primary endpoint evaluated the proportion of patients who achieved a ≥10% reduction in body weight after 52 weeks. In 31 individuals with obesity due to BBS who completed 52 weeks from the start of setmelanotide treatment at time of prespecified data cutoff, 39% of patients lost 10% or more

of their BMI at 52 weeks, with an average loss of 9% of their baseline BMI, and 61% of patients lost 5% or more of their BMI.

IX. Across all trials, onset of adverse events (AEs) were typically observed during the first weeks of treatment, and most treatment-related AEs were considered mild or moderate in severity, transient, and infrequently led to discontinuation. The most common pooled AE (≥20%) included injection site reactions, skin hyperpigmentation, gastrointestinal AEs (nausea, vomiting, diarrhea, abdominal pain), headache, depression, and spontaneous penile erection/sexual adverse reactions. Skin darkening plateaued within the initial months of treatment. The setmelanotide (Imcivree) labeling includes warnings for disturbances in sexual arousal, skin pigmentation, and depression and suicidal ideation.

X. Extension studies evaluating long-term outcomes of setmelanotide (Imcivree) are ongoing, and available data showed continued efficacy for maintaining weight loss and an acceptable safety profile for up to two years of treatment in patients with obesity due to POMC/PCSK1 or LEPR deficiency and BBS.

XI. For obesity due to POMC, PCSK1, or LEPR deficiency, the setmelanotide (Imcivree) prescribing information recommends evaluating weight loss after 12 to 16 weeks of treatment. 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, treatment 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 BBS, the prescribing information recommends evaluating 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, treatment should be discontinued. Compared weight loss at the time of renewal should be evaluated with baseline weight.

XII. Setmelanotide (Imcivree) is administered as a once daily subcutaneous injection. In pediatric patients aged 6 -12 years of age, the recommended starting dosage is 1 mg (0.1 mL) daily for 2 weeks. The recommended starting dose in patients ≥12 years of age is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks. The recommended target dose is 3 mg (0.3 mL) injected subcutaneously once daily for all patients.

Investigational or Not Medically Necessary Uses

I. Setmelanotide (Imcivree) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Other causes or types of obesity (e.g., obesity due to suspected POMC, PCSK1 or LEPR deficiency with POMC, PCSK1 or LEPR variants classified as benign or likely benign)
      i. A documented limitation of use in the prescribing information notes setmelanotide (Imcivree) is not indicated for the treatment of obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC, PCSK1*, or *LEPR* variants classified as benign or likely benign, as treatment would not be expected to be effective. Therefore, patients with variants classified as benign or likely benign are considered not medically necessary.

B. Obesity associated with other genetic syndromes (e.g., Prader-Willi syndrome, Alström syndrome) and general (polygenic) obesity
    i. A documented limitation of use in the prescribing information notes setmelanotide (Imcivree) is not indicated for the treatment of obesity associated with other genetic syndromes and general (polygenic) obesity (e.g., Prader-Willi syndrome, Alström syndrome), as treatment would not be expected to be effective. Therefore, treatment of general obesity or obesity associated with other genetic syndromes is considered not medically necessary.
    ii. In the pivotal trial for BBS, the trial also included three patients with Alström syndrome, none of whom met the primary endpoint. Setmelanotide (Imcivree) received a complete response letter (CRL) from the FDA in June 2022 for Alström syndrome.
C. Members younger than 6 years of age
    i. An ongoing phase 3 trial (NCT04966741) is evaluating setmelanotide in pediatric patients aged 2 to <6 years of age. At this time, safety, and efficacy of setmelanotide (Imcivree) in patients < 6 years of age is not established and therefore considered investigational.
D. Hypothalamic obesity
    i. Phase 2/3 trials are evaluating the use of setmelanotide in hypothalamic obesity. At this time, safety, and efficacy of setmelanotide (Imcivree) in hypothalamic obesity is not established and therefore considered investigational.

References

1. IMCIVREE [prescribing information]. Boston, MA. Rhythm Pharmaceuticals, Inc.; November 2023.
2. "About Child & Teen BMI." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html. Last reviewed Sept. 24, 2022. Accessed Aug 14, 2023.
3. Food and Drug Administration (FDA). Clinical Review: Imcivree. 2020. Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213793Orig1s000MedR.pdf. Accessed August 30, 2023.
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. Clément K, van den Akker E, Argente J, et al. 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;8(12):960-970. doi:10.1016/S2213-8587(20)30364-8
6. Haqq AM, Chung WK, Dollfus 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 [published correction appears in Lancet Diabetes Endocrinol. 2023 Feb;11(2):e2]. Lancet Diabetes Endocrinol. 2022;10(12):859-868. doi:10.1016/S2213-8587(22)00277-7

7. Bardet-biedl syndrome. National Organization for Rare Disorders (NORD). Last updated July 12, 2022. Accessed September 13, 2023. https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/
8. Haws RM, Gordon G, Han JC, Yanovski JA, Yuan G, Stewart MW. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome: Phase 3 trial design. *Contemp Clin Trials Commun*. 2021;22:100780. Published 2021 May 3. doi:10.1016/j.conctc.2021.100780
9. Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet*. 1999;36(6):437-446.
10. Poitou C, Mosbah H, Clément K. Mechanisms in endocrinology: update on treatments for patients with genetic obesity. Eur J Endocrinol. 2020 Nov;183(5):R149-R166.
11. Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics*. 2023;151(2):e2022060640. doi:10.1542/peds.2022-060640
12. Oregon Health Plan. Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Program. https://www.oregon.gov/OHA/HSD/OHP/Pages/EPSDT.aspx. Accessed December 5, 2023.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Chronic Weight Management	Chronic weight management in patients ≥12 years of age

Policy Implementation/Update

Action and Summary of Changes	Date
Updated age criteria to limit coverage to those under 21 years of age given EPSDT consideration, as treatment for weight loss are excluded from coverage under OHP otherwise.	12/2023
Policy created	11/2023