Medical Drug Clinical Criteria

Subject:	Imcivree (setmelanotide)		
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Overview

This document addresses the use of Imcivree (setmelanotide). Imcivree is a melanocortin-4 receptor (MC4R) agonist that is intended to treat certain individuals with obesity by partially or completely restore signaling at the MC4 receptor. Imcivree is indicated for adult and pediatric patients 2 years of age or older with monogenic or syndromic obesity due to one of the following:

1. Proopiomelanocortin (POMC), Proprotein convertase subtilisin/kexin type 1 (PCSK 1), or Leptin receptor (LEPR) deficiency. Patients should be selected for therapy based on genetic testing demonstrating gene variants that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS);
2. Bardet-Biedl syndrome (BBS). Patients should be selected for therapy who have a clinical diagnosis of BBS.

Please refer to the following clinical criteria for other weight loss agents:

- Zepbound (tirzepatide) Clinical Criteria
- Wegovy (semaglutide) Clinical Criteria
- Saxenda (liraglutide) Clinical Criteria
- Agents for Obesity – Stimulants Clinical Criteria
  - Phentermine: Adipex-P, Lomaira, generic phentermine
  - Phendimetrazine/phendimetrazine ER
  - Benzphetamine
  - Diethylpropion/diethylpropion ER
  - Combination therapy: Phentermine/topiramate: Qsymia
- Agents for Obesity – Miscellaneous Clinical Criteria
  - Alli, Xenical (orlistat)
  - Contrave (naltrexone/bupropion)
- Agents for Obesity – Step Therapy Clinical Criteria

Imcivree is the first FDA approved treatment for chronic weight management in obese patients with confirmed POMC, PCSK1, and LEPR deficiency. Individuals with these specific genetic aberrations experience excessive appetite and weight gain, resulting in morbid obesity, even as early as infancy. Individuals may experience other disorders of the endocrine system due to involvement in various hormone signaling pathways. Comorbidities may include postprandial hypoglycemia, hypogonadism, hypothyroidism, adrenal insufficiency, and high risk of infection. Imcivree is also the first FDA approved treatment for chronic weight management in obese patients with Bardet-Biedl syndrome (BBS). BBS is an autosomal recessive syndrome associated with mutations in at least 15 genes. It is characterized by obesity and several other abnormalities such as intellectual disability, eye, dental, and renal abnormalities, and/or other unique physical features. Historically, patients with these conditions have relied on management of excessive appetite with calorie restrictions, lifestyle modification, and close supervision to control weight. Imcivree can partially or completely restore signaling at the MC4 receptor resulting in appetite suppression and weight loss in certain individuals.

Imcivree was studied in two open label, single-arm, multicenter, multi-phase trials which enrolled individuals with genetically confirmed or suspected POMC, PCSK1, or LEPR deficiency. 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. The clinical trial for BBS enrolled individuals with a clinical diagnosis of BBS and classified as obese based on ≥BMI 30 kg/m^2 for those 16 years of age or older, or for those less than 16 years old, weight ≥97th percentile using growth chart assessments for pediatric patients. Pediatric BMI may be assessed using tools on the CDC website located here. After 1 year of treatment, results showed that 8/10 individuals with POMC/PSCK1 variants (80%) and 5/11 individuals with LEPR variants (45.5%) achieved at least 10% weight loss after treatment with Imcivree. In individuals with BBS, 38.7% of individuals achieved at least 10% BMI loss at 52 weeks.

A later study, VENTURE (NCT04966741), gained FDA approval to expand use to those aged 2 to less than 5 years. Individuals were required to have a baseline BMI greater than or equal to the 97th percentile for age and sex, and have a body weight of at least 15

kilograms at enrollment. This study included those who had genetically confirmed POMC/PSCK1/LEPR variants or genetically confirmed BBS. Even though the study allowed those with PSCK1 variants, there were 0 trial participants with this variant. The primary endpoints were the percentage of patents who reached at least a 0.2-point decrease in BMI Z score at week 52, as well as the mean percentage change in BMI at week 52. No serious side effects were reported, and all adverse events were mild or moderate (e.g. skin hyperpigmentation, vomiting, nasopharyngitis, upper respiratory tract infection, and injection site reactions were most common). Efficacy showed a reduction in mean BMI percentages in both populations (POMC/LEPR deficiency -26%; BBS -18%). Additionally, both groups showed a decrease in BMI Z score at week 52 (POMC/LEPR deficiency 86%; BBS 80%).

Imcivree labeling includes warnings for disturbances in sexual arousal, skin pigmentation, and depression and suicidal ideation. Individuals with suicidal ideation/behavior or history of suicide attempt were excluded from clinical trials; and individuals should be monitored for new onset or worsening depression during treatment. Response to Imcivree treatment should be monitored closely: initially after 12-16 weeks of therapy for POMC/PSCK1/LEPR deficiency and after 1 year for BBS. Treatment should be discontinued if individual does not lose at least 5% of baseline bodyweight or 5% of baseline BMI in patients with continued growth potential.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Imcivree (setmelanotide)

Initial requests for Imcivree (setmelanotide) for POMC/PCSK1/LEPR deficiency may be approved if the following criteria are met:

I. Individual is 2 years of age or older; **AND**
II. Documentation is provided that individual has a diagnosis of obesity, defined as:
    A. BMI of 30 kg/m^2 or greater for adults; **OR**
    B. Bodyweight of more than the 95th percentile for age on growth chart assessment for individuals aged 6 to 17 years; **OR**
    C. Baseline BMI greater than or equal to the 97th percentile for age and sex, and body weight of at least 20 kg for individuals aged 2-5 years;

AND

III. Documentation is provided that obesity is due to Proopiomelanocortin (POMC), Proprotein convertase subtilisin/kexin type 1 (PCSK 1), or Leptin receptor (LEPR) deficiency, verified by genetic testing; **AND**
IV. Genetic testing demonstrates that variants in POMC, PCSK1, or LEPR genes are pathogenic, likely pathogenic, or of uncertain significance; **AND**
V. Individual is NOT receiving two or more medications for weight loss at the same time.

Initial Authorization Period for POMC, PCSK1, or LEPR deficiency: 16 weeks.

Initial requests for Imcivree (setmelanotide) for BBS may be approved if the following criteria are met:

I. Individual is 2 years of age or older; **AND**
II. Documentation is provided that individual has a diagnosis of obesity, defined as:
    A. BMI of 30 kg/m^2 or greater for individuals 16 years of age and above; **OR**
    B. Bodyweight of more than the 97th percentile for age on growth chart assessment for individuals aged 6-15 years; **OR**
    C. Baseline BMI greater than or equal to the 97th percentile for age and sex, and body weight of at least 20 kg for individuals aged 2-5 years;

AND

III. Obesity is due to Bardet-Biedl syndrome (BBS), as defined by one of the following [A or B] (Haws 2021):
    A. Four (4) primary features of BBS:
        1. Primary Features:
            a. Rod-cone dystrophy
            b. Polydactyly
            c. Obesity
            d. Learning disabilities
            e. Hypogonadism in males
            f. Renal anomalies;

        OR

    B. Three (3) primary features [above] **AND** 2 secondary features of BBS:
        1. Secondary Features:
            a. Speech disorder/delay
            b. Strabismus/cataracts/astigmatism
            c. Brachydactyly/syndactyly

d. Developmental delay
e. Polyuria/polydipsia (nephrogenic diabetes insipidus)
f. Ataxia/poor coordination/imbalance
g. Mild spasticity (especially lower limbs)
h. Diabetes mellitus
i. Dental crowding/hypodontia/small roots/high arched palate
j. Left ventricular hypertrophy/congenital heart disease
k. Hepatic fibrosis;

AND

IV. For individuals less than 6 years old, genetic testing demonstrates homozygous or compound heterozygous loss-of-function variants in BBS genes; **AND**
V. Individual is NOT receiving two or more medications for weight loss at the same time.

Initial Authorization Period for BBS: 1 year.

Requests for subsequent authorization for Imcivree (setmelanotide) may be approved if the individual meets ALL of the following criteria:

I. Documentation is provided that individual has achieved/maintained weight loss of at least 5% of baseline body weight or 5% of baseline BMI for patients with continued growth potential; **AND**
II. Individual is NOT receiving two or more medications for weight loss at the same time.

Subsequent Authorization Period [all diagnoses]: 6 months.

Requests for Imcivree (setmelanotide) may not be approved for any of the following:

I. Obesity with POMC, PCSK1, or LEPR variants classified as benign or likely benign (for POMC/PCSK1/LEPR deficiency requests); **OR**
II. Individual has end stage renal disease (eGFR less than 15 mL/min/1.73 m^2; **OR**
III. Individual is 2 years of age to less than 6 years of age with weight less than 20 kilograms with severe renal impairment (eGFR 15-29 mL/min/1.73 m2); **OR**
IV. Individual has a history of suicide attempts or has active suicidal ideation; **OR**
V. When the above criteria are not met and for all other indications.

Quantity Limits

Imcivree (setmelanotide) Quantity Limit

Drug	Limit
Imcivree 10 mg/mL multi-dose vial	9 vials per 30 days

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J3590	Unclassified biologics (when specified as [Imcivree] (setmelanotide))
C9399	Unclassified drugs or biologicals (when specified as [Imcivree] (setmelanotide))

ICD-10 Diagnosis

	All diagnosis pend
E88.82	Obesity due to disruption of MC4R pathway [Proopiomelanocortin (POMC), Proprotein convertase subtilisin/kexin type 1 (PCSK 1), or Leptin receptor (LEPR) deficiency]
Q87.83	Bardet-Biedl syndrome

Document History

Revised: 05/16/2025
Document History:

- 05/16/2025 – Annual Review: Expanded FDA approved age to 2 y/o for both approved indications (POMC/PCSK1/LEPR deficiency; BBS). Updated baseline BMI requirements for this new age expansion. Added genetic testing to verify clinical diagnosis for BBS for those 2 years to less than 6 years old. Updated severe renal deficiency age exclusions. Coding Reviewed: Removed HCPCS NOC J3590 and added J3490. Removed all diagnosis pend. Added ICD-10-CM E88.82 and Q87.83.
- 05/17/2024 – Annual Review: Added may not approve in those 6 to less than 12 years old with severe renal impairment; added may not approve in those with a history of suicide attempts or has active suicidal ideation. Coding Reviewed: No changes.
- 05/19/2023 – Annual Review: Wording and formatting changes. Coding Reviewed: No changes.
- 08/19/2022 – Select Review: Update criteria to include new indication for Bardet-Biedl syndrome; update approval duration to 6 months; update renal impairment exclusion per label; wording and formatting updates. Coding Reviewed: Removed HCPCS J3490. Added HCPCS C9399.
- 05/20/2022 – Annual Review: No Changes. Coding Reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 02/19/2021 – Annual Review: Add new clinical criteria document for Imcivree. Coding Reviewed: Added J3490, J3590. All Diagnosis pend.

References

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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 Dec;8(12):960-970. doi: 10.1016/S2213-8587(20)30364-8. Epub 2020 Oct 30. PMID: 33137293.
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. doi: 10.1016/S2213-8587(22)00360-6.]. *Lancet Diabetes Endocrinol*. 2022;10(12):859-868. doi:10.1016/S2213-8587(22)00277-7.
7. Haws RM, Gordon G, Han JC, et al. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alstrom syndrome: Phase 3 trial design. Contemp Clin Trials Commun. 2021 May 3; 22:100780.
8. "About Child & Teen BMI." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 29 June 2020, www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.