BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

IMCIVREE™ (setmelanotide) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for IMCIVREE (setmelanotide)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Weight Loss Specialist, Cardiologist, Endocrinologist, or Geneticist, or in consultation with one

Indication
- Diagnosis of monogenic or syndromic obesity due to **ONE** of the following:

- Genetically determined proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency interpreted as pathogenic, likely pathogenic, or of uncertain significance
- Clinical features of Bardet Biedl syndrome (BBS)

Age Requirement

- 2 years of age or older who weigh at least 15 kilograms (kg)

Baseline Clinical Evaluation

- **ONE** of the following:
  - Genetic confirmation of bi allelic homozygous or compound heterozygous variants in *POMC*, *PCSK1*, or *LEPR* genes interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)
  - Four primary features OR three primary plus two secondary features of Bardet Biedl syndrome with genetic confirmation of mutation in *BBS1–BBS21* genes
- **ONE** of the following:
  - Body mass index (BMI) greater than or equal to 30 kg/m² for adults
  - Weight greater than or equal to 95th percentile for age on growth chart for pediatric patients
- Full body skin examination
- Does not have **ANY** of the following:
  - Obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC, PCSK1,* or *LEPR* variants classified as benign or likely benign
  - Other types of obesity not related to POMC, PCSK1, LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity
  - Double heterozygous variants in two different genes
  - Prior gastric bypass surgery resulting in greater than 10 percent weight loss durably maintained with no evidence of weight regain
  - Intensive diet and/or exercise regimen with or without other weight loss agents that resulted in weight loss or stabilization

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- **For all patient ages:** There is no end stage renal disease (estimated glomerular filtration rate less than 15 mL/min/1.73 m²)
- **For patients age 2 to less than 6 years of age who weigh less than 20 kilograms (kg):** There is no severe renal impairment (estimated glomerular filtration rate of 15 to 29 mL/min/1.73 m²)

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Additional Requirements
- It is not approved for use in neonates or infants due to benzyl alcohol preservative
- Avoid use during pregnancy, as weight loss does not benefit pregnant women and may harm the fetus, only consider use if therapy's benefits clearly outweigh potential risks

Documentation Requirements
- A completed request form must be submitted including:
  - Chart notes
  - Lab results (including genetic testing and BMI or growth chart percentile)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 4 months for POMC, PCSK1, or LEPR deficiency
- 12 months for Bardet Biedl syndrome
- OR end of plan year
- Individual must have lost at least 5 percent of baseline body weight (or 5 percent of baseline BMI for individual less than 18 years of age) to be eligible for continuation

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications
- Continues to be seen by a Weight Loss Specialist, Cardiologist, Endocrinologist, or Geneticist, or in consultation with one

Clinical Response
- **BOTH** of the following:
  - First renewal: Lost at least 5 percent of baseline body weight or 5 percent of baseline BMI for individuals with continued growth potential
  - Second renewal: Achieved and maintains a 10 percent weight loss

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No significant adverse drug effects such as:
  - Suicidal thoughts or behaviors

  - New onset or worsening of depression
  - Penile erections lasting longer than 4 hours
- **For all patient ages:** There is no end stage renal disease (estimated glomerular filtration rate less than 15 mL/min/1.73 m²)
- **For patients age 2 to less than 6 years of age who weigh less than 20 kilograms (kg):** There is no severe renal impairment (estimated glomerular filtration rate of 15 to 29 mL/min/1.73 m²)

Additional Requirements

- It is not approved for use in neonates or infants due to benzyl alcohol preservative
- Avoid use during pregnancy, as weight loss does not benefit pregnant women and may harm the fetus, only consider use if therapy's benefits clearly outweigh potential risks

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Imcivree (setmelanotide) is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to genetically determined proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptors (LEPRs) deficiency **confirmed** by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or a variant of uncertain significance (VUS), or clinical feature of Bardet-Biedl syndrome (BBS).

Setmelanotide is **not indicated for** the treatment of patients with obesity due to **suspected** POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign or with other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity, as setmelanotide would not be expected to be effective.

Weight loss should be evaluated after 12-16 weeks of treatment. If a patient has not lost ≥ 5% of baseline bodyweight, or 5% of baseline BMI for patients with continued growth potential, setmelanotide should be discontinued.

Certain genes play a role in controlling energy balance and weight. In most obese individuals, the cause is attributed to interactions among multiple genes and environmental factors that remain poorly understood. A defect to one or more of these genes affects hunger levels, satiety, and energy output (metabolism). In a very small percentage of individuals, obesity may occur due to changes in a single gene. The most commonly implicated gene encodes melanocortin 4 (MC4) receptors (the *MC4R* gene), however, other genes have been implicated in obesity.

Melanocortins are a family of melanocyte stimulating hormones (MSHs), some of which regulate hunger, caloric intake, energy expenditure, and bodyweight primarily thorough the MC4 receptor. Impairment in the MC4 receptor pathway leads to hyperphagia and early-onset severe obesity.

In normal physiology, LEPRs are expressed on POMC neurons in the brain. The hormone leptin (from adipose tissue in the periphery) activates the LEPRs causing the POMC neurons to release MSH. The PCSK1 gene codes for enzymes that also generate MSH from POMC-producing neurons.

MSH binds to and activates MC4 receptors on MC4 receptor-expressing neurons. This binding stimulates a cascade of neurological signaling that ultimately leads to suppression of hunger, decreased food intake, and increased energy expenditure.

Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In patients with obesity due to POMC, PCSK1, and LEPR deficiency associated with insufficient activation of the MC4 receptor, setmelanotide may re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure. Nonclinical evidence shows that MC4 receptors are important for setmelanotide-regulated appetite and weight loss. The MC1 receptor is expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light.

There are no obesity treatment guidelines that are specific to obesity caused by POMC, PCSK1, or LEPR deficiencies. Additionally, there were no approved treatments or pharmacologic therapy for obesity caused by POMC, PCSK1, or LEPR deficiency. Bariatric surgery (i.e., gastric or intestinal banding or bypass surgery) is not effective in these patients due to the extreme hunger caused by POMC, PCSK1, or LEPR deficiency that still exists post-surgery. There are no clinical data to show that drugs approved for general obesity would result in weight reduction for these cases of genetic-linked obesity. Non-syndromic obese and overweight patients have shown that standard-of-care diet and exercise programs result in a mean weight loss of 1.2-2.5% at 1 year. Lifestyle modification is rarely successful in the short-term and almost never effective in the long term in these patients due to the intense drive to eat caused by the absence of satiety signals.

In of Bardet-Biedl syndrome, mutations in *BBS* genes lead to problems with the structure and function of cilia. Defects in these cell structures probably disrupt important chemical signaling pathways during development and lead to abnormalities of sensory perception. Researchers believe that defective cilia are responsible for most of the features of Bardet-Biedl syndrome.

The cardinal features of BBS are truncal obesity, intellectual impairment, renal anomalies, polydactyly, retinal degeneration and hypogonadism.

Vision loss is one of the major features of BBS. Loss of vision occurs due to gradual deterioration of the retina. Problems with night vision manifest by mid-childhood, followed by blind spots that develop in peripheral vision. Over time, the blind spots enlarge and merge to produce tunnel vision. Most people with BBS also develop blurred central vision and become legally blind by adolescence or early adulthood.

Obesity is another characteristic feature of BBS. Abnormal weight gain begins in early childhood and continues to be an issue throughout life. Other major signs and symptoms of BBS include the presence of extra fingers or toes, intellectual disability or learning problems, and abnormalities of the genitalia. Many also have kidney abnormalities, which can be serious or life-threatening.

The diagnosis of BBS is based on the clinical manifestations (at least four major clinical signs or 3major and 2 minor clinical signs) and can be confirmed by molecular genetic testing of the causative genes in more than 80% of patients.
Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder caused by biallelic loss-of-function pathogenic variants.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Bi-allelic Homozygous:
- Same gene mutation/variant on each allele of the same gene

Bi-allelic Compound Heterozygous:
- Different gene mutation/variant on each allele of the same gene

Double Heterozygous:
- Gene mutations/variants in two different genes

Pathogenic mutation/variant:
- Mutation/variant that is certain to disrupt gene function or certain to cause disease

Likely pathogenic mutation/variant:
- Mutation/variant that could affect gene function or has the potential to cause disease

Mutation/variant uncertain significance (VUS):
- Mutation/variant with unknown significance to gene function or unknown potential to cause disease, usually due to lack of knowledge

Likely benign mutation/variant:
- Mutation/variant with no reason to suspect significance to gene function or potential to cause disease

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Benign mutation/variant:

- Mutation/variant does not cause disease

Bardet-Biedl syndrome (BBS) criteria:

Four primary features are required to be present OR three primary plus two secondary features are required to be present
Primary features: Rod-cone dystrophy Polydactyly Obesity Learning disabilities/Intellectual disabilities Hypogonadism in males Renal anomalies/ Renal malformations (particularly calyceal abnormalities)
Secondary features: Speech disorder/delay Strabismus/cataracts/astigmatism Brachydactyly/syndactyly Developmental delay Polyuria/polydipsia (nephrogenic diabetes insipidus) Ataxia/poor coordination/imbalance Mild spasticity (especially lower limbs) Diabetes mellitus Dental crowding/hypodontia/small roots/high arched palate Left ventricular hypertrophy/congenital heart disease Hepatic fibrosis

Gene mutations that are known to lead to the development of BBS:
BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LZTFL1 (BBS17), BBIP1(BBS18), IFT27 (BBS19), IFT72 (BBS20), and *C8ORF37(BBS21*).

Resources:

Imcivree (setmelanotide) product information, revised by Rhythm Pharmaceuticals, Inc. 03-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

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Bardet–Biedl syndrome. Available at Orphanet: Bardet Biedl syndrome: Updated September 2021. Accessed May 02, 2023. Re-evaluated April 22, 2026.

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Priya S, Nampoothiri S, Sen P, Sripriya S. Bardet–Biedl syndrome: Genetics, molecular pathophysiology, and disease management. Indian J Ophthalmol 2016;64:620-627. Accessed May 02, 2023. Re-evaluated April 22, 2026.

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ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03287960**:** Setmelanotide for the treatment of LEPR deficiency obesity. Available from: http://clinicaltrials.gov. Last update posted January 27, 2021. Last verified January 2021. Accessed March 11, 2021. Re-evaluated April 22, 2026.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02896192**:** Setmelanotide for the treatment of early-onset POMC deficiency obesity. Available from: http://clinicaltrials.gov. Last update posted January 27, 2021. Last verified January 2021. Accessed March 11, 2021. Re-evaluated April 22, 2026.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03746522**:** A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alström Syndrome (AS) Patients With Moderate to Severe Obesity. Available from: http://clinicaltrials.gov. Last update posted July 20, 2021. Last verified July 2021. Accessed April 07, 2023. Re-evaluated April 22, 2026.