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 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.

Criteria:

➢ **Criteria for initial therapy:** Imcivree (setmelanotide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Weight Loss Specialist, Cardiologist, Endocrinologist, or Geneticist

2. Individual is 6 years of age or older

3. Individual has a confirmed diagnosis of monogenic or syndromic obesity due to **ONE** of the following:
    a. Genetically determined proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) deficiency interpreted as pathogenic, likely pathogenic, or of uncertain significance

b. Clinical features of Bardet-Biedl syndrome (BBS)

4. Individual does not have **ANY** of the following:
   a. Obesity due to suspected POMC, PCSK1, or LEPR-deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign
   b. Other types of obesity not related to POMC, PCSK1 LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity
   c. Double heterozygous variants in two different genes
   d. Prior gastric bypass surgery resulting in greater than 10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain
   e. Intensive diet and/or exercise regimen with or without the use of other weight loss agents including herbal medications, that has resulted in weight loss or weight stabilization

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. **ONE** of the following:
      i. Genetic tests demonstrating bi-allelic homozygous or compound heterozygous variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) (see Definitions section)
      ii. Four primary features **OR** three primary plus two secondary features of BBS with genetic confirmation of a mutation in *BBS1-BBS21* genes (see Definitions section)
   b. **ONE** of the following:
      i. Adult has body mass index (BMI) of greater than or equal to 30 kg/m^2
      ii. Weight in pediatric patient is greater than or equal to 95^{th} percentile for age on growth chart assessment
   c. Full body skin examination

6. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual does not have end stage renal disease (estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73 m^2) in any individuals

8. Individual 6 to less than 12 years of age does not have severe renal impairment estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min/1.73 m^2)

Initial approval duration:
4 months for POMC, PCSK1, or LEPR-deficiency
12 months for BBS
Individual must have lost at least 5% of baseline body weight (or 5% of baseline BMI for individual less than 18 years of age) to be eligible for continuation

- **Criteria for continuation of coverage (renewal request):** Imcivree (setmelanotide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Weight Loss Specialist, Cardiologist, Endocrinologist, or Geneticist

2. Individual's condition has responded while on therapy with response defined as **BOTH** of the following:
   a. On first renewal request: Has lost at least 5% of baseline body weight or 5% of baseline BMI for individuals with continued growth potential
   b. On second renewal request: Achieved and maintains a ≥10% weight loss

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Suicidal thoughts or behaviors
   b. New onset or clinically significant worsening of or persistent depression
   c. Penile erections lasting longer than 4-hours

6. Individual does not have end stage renal disease (estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73 m^2) in any individuals

7. Individual 6 to less than 12 years of age does not have severe renal impairment estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min/1.73 m^2)

Renewal duration: 12 months

- 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

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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

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. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Perreault L, Rosenbaum M. Obesity: Genetic contribution and pathophysiology. In: UpToDate, Pi-Sunyer FX, Hussain Z (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated January 09, 2025. Accessed March 04, 2025.

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Forsyth RL, Gunay-Aygun M. Bardet-Biedl Syndrome Overview. 2003 Jul 14 [Updated 2023 Mar 23]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. https://www.ncbi.nlm.nih.gov/books/. Bardet-Biedl Syndrome Overview - GeneReviews® - NCBI Bookshelf (nih.gov). Accessed May 02, 2023. Re-evaluated March 04, 2025.

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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 March 06, 2024.

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 March 06, 2024.

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-BiedlSyndrome (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 March 06, 2024.