09-J3000-90

Original Effective Date: 03/15/21

Reviewed: 04/08/26

Revised: 11/15/26

Subject: Setmelanotide (Imcivree®) Injection

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Setmelanotide (Imcivree) is an injectable melanocortin 4 (MC4) receptor agonist that was first approved by the US Food and Drug Administration (FDA) in November 2020 for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS). In June 2022, the indication was expanded to include Bardet-Biedl syndrome (BBS). In December 2024, the indication was expanded to include pediatric patients aged 2 years and older. In March 2026, the indication was updated to include acquired hypothalamic obesity (HO) in patients aged 4 years and older. Setmelanotide, as sponsored by the innovator drug company, was previously granted orphan drug designation by the FDA for the treatment POMC and LEPR deficiency in 2016 and 2017, respectively, and for BBS in 2019. Setmelanotide also has orphan drug designations for the treatment of Prader-Willi (2015) and Alström syndromes (2020). Of note, the sNDA submitted by Rhythm Pharmaceuticals for the treatment of Alström syndrome was not approved [i.e., issued a complete response letter (CRL) by the FDA in July 2022], and the future of an approval remains unknown.

POMC and LEPR deficiency obesities are autosomal recessive, single-gene disorders that are extremely rare and underdiagnosed. Approximately 50 cases of POMC deficiency obesity have been reported in literature with an estimated prevalence of less than 1 in 1,000,000; while the prevalence of LEPR deficiency obesity is unknown. Rhythm Pharmaceuticals estimates that the US incidence of each condition is 100 to 500 and 500 to 2,000, respectively. Numerous hormones in the body, such as leptin, regulate caloric intake and energy expenditure. Abnormalities in the genes that encode the production of these hormones may predispose an individual to weight gain. These disorders cause symptoms such as extreme, insatiable hunger and subsequent weight gain manifesting in morbid obesity, often as early as infancy. These patients can also experience comorbid disorders of the endocrine system (e.g., diabetes, hypothyroidism, hypogonadotropic hypogonadism, and ACTH deficiency). Before the approval of setmelanotide, there were no FDA-approved treatment options for this population that addressed the underlying cause of the obesity. Setmelanotide is a highly specific MC4 receptor agonist that is intended to partially or completely restore MC4 receptor function in genetic mutations that impact the leptin-melanocortin pathway (e.g., POMC, PCSK1, or LEPR). Receptor activation reduces hunger and promote weight loss through decreased caloric intake and increased energy expenditure.

Bardet-Biedl syndrome (BBS) is a genetic, non-motile ciliopathy that impacts multiple body system. BBS can be caused by mutations in more than 20 different genes. Despite the great number of genes already identified, gene mutations have not been identified in an estimated 20 to 30% of individuals with BBS. It is usually inherited as an autosomal recessive condition. The prevalence is estimated to be 1 in 100,000 in the non-related (non-consanguineous) populations of Northern Europe and America. The cardinal features of BBS are truncal obesity, intellectual impairment, renal anomalies, polydactyly, retinal degeneration and hypogenitalism. Forsythe and Beales suggested that a clinical diagnosis of BBS is made by the presence of either four major features or three major features and two minor features. Major (or primary) features include - retinal cone-rod dystrophy, central obesity, postaxial polydactyly, cognitive impairment, hypogonadism and genitourinary abnormalities, and kidney disease. Minor (or secondary) features include - neurologic abnormalities (e.g., developmental delay, speech delay or impairments, epilepsy, behavior/psychiatric abnormalities), olfactory dysfunction (e.g., anosmia, hyposmia), oral/dental abnormalities, cardiovascular and other thoraco-abdominal abnormalities, gastrointestinal abnormalities (e.g., liver disease/ALT elevation, Hirschsprung disease, celiac disease, Inflammatory bowel disease), and endocrine/metabolic abnormalities (e.g., metabolic syndrome, subclinical hypothyroidism, type 2 diabetes, polycystic ovary syndrome). Genetic testing may help confirm the diagnosis for some patients. The primary treatment goal for patients with BBS involves treating the specific symptoms affecting each individual. As many body systems are involved, care often requires the coordinated effort of a team of specialists.

Acquired hypothalamic obesity (HO) is characterized by rapid and excessive weight gain after hypothalamic injury. This change in weight regulation can be caused by the accompanying symptoms that arise from damage to hypothalamus including daytime fatigue, decreased physical activity, decreased energy expenditure, endocrine dysfunction, sleep disturbances, decreased satiety, and increased food intake sometimes presents as severe, persistent, and insatiable hunger or hyperphagia. The most frequent cause of hypothalamic injury associated with HO is craniopharyngioma or other brain tumors and their treatment via surgical resection or radiation. Additional causes include congenital brain malformations, hemorrhage, and traumatic brain injury. There are an estimated 5,000 to 10,000 patients in the U.S. with acquired HO, with approximately 500 cases diagnosed annually. Before the approval of setmelanotide, there were no FDA-approved treatment options for this population. Many patients undergo traditional obesity management strategies, including lifestyle and behavioral intervention, pharmaceutical approaches approved for general obesity, and bariatric surgery, with little benefit.

The initial FDA approval of setmelanotide for chronic weight management in patients with POMC, PCSK1, or LEPR deficiency was based on the safety and efficacy data from two identically designed, multicenter, open-label, single-arm, phase 3 trials evaluating setmelanotide in patients ages 6 years of age or older with POMC (Study 1, NCT02896192) or LEPR (Study 2, NCT03287960) deficiency obesities. The studies enrolled patients with homozygous or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS for either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not eligible for treatment. In both studies, adult patients had a body mass index (BMI) of ≥30 kg/m^2, and the weight in pediatric patients was ≥95th percentile using growth chart assessments. Dose titration occurred over a 2- to 12-week period, followed by a 10-week, open-label treatment period. Patients who achieved at least a 5-kg weight loss (or at least 5% weight loss if baseline body weight was <100 kg) at the end of the open-label treatment period continued into a double-blind withdrawal period lasting 8 weeks, including 4 weeks of setmelanotide followed by 4 weeks of placebo. Following the withdrawal sequence, patients re-initiated active treatment at the therapeutic dose for up to 32 weeks. Efficacy analyses were conducted in 21 patients (10 in Study 1, and 11 in Study 2) who had completed at least 1 year of treatment at the time of data cutoff. Six additional patients enrolled in the studies (4 in Study 1 and 2 in Study 2) who had not yet completed 1 year of treatment at the time of the cutoff were not included in the efficacy analyses. Of the 21 patients included in the efficacy analysis, 62% were adults and 38% were aged 16 years or younger. In Study 1, 50% of patients were female, 70% were White, the median BMI was 40 kg/m^2 (range: 26.6-53.3) at baseline. In Study 2, 73% of patients were female, 91% were White, and the median BMI was 46.6 kg/m^2 (range: 35.8-64.6) at baseline.

The primary outcome of at least 10% weight loss after 1 year of treatment was achieved in 80% of patients with obesity due to POMC or PCSK1 deficiency and in 45.5% of the LEPR-deficient population.

There was a significant percentage change in median body weight from baseline to year 1 of -26.7% in the POMC trial, and -9.8% in the LEPR trial. When treatment with setmelanotide was withdrawn in the 16 patients who had lost at least 5 kg (or 5% of body weight if baseline body weight was <100 kg) during the 10-week open-label period, these patients gained an average of 5.5 kg in Study 1 and 5 kg in Study 2 over 4 weeks. Re-initiation of treatment with setmelanotide resulted in subsequent weight loss. Patients 12 years and older self-reported their daily maximal hunger in a diary. Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible"). In the POMC trial (n=7), the mean most hunger score decreased from 8.1 at baseline to 5.8 at 1 year (mean percentage change of -27.1%). In the LEPR trial (n=7), the mean most hunger score decreased from 7 at baseline to 4.1 at 1 year (mean percentage change of -43.7%). Supportive of setmelanotide's effect on weight loss, there were general numeric improvements in cardiometabolic parameters, such as blood pressure, lipids, glycemic parameters, and waist circumference. However, because of the limited number of patients studied and the lack of a control group, the treatment effects on these parameters could not be accurately quantified.

Setmelanotide was generally well tolerated. The most common adverse reactions occurring with an incidence of 23% or more included injection site reactions (96%), skin hyperpigmentation (78%), nausea (56%), headache (41%), diarrhea (37%), abdominal pain (33%), back pain (33%), fatigue (30%), vomiting (30%), depression (26%), upper respiratory tract infection (26%), and spontaneous penile erection (23%; evaluated in 13 male patients). Notably, 11% of participants experienced the adverse reaction of suicidal ideation. One patient withdrew from the study due to mild hypereosinophilia.

The FDA approval of setmelanotide for chronic weight management in patients with BBS was based on a 66-week trial (Study 3, NCT03746522) which included a 14-week randomized, double-blind, placebo-controlled period (period 1) and a 52-week open-label period (period 2), The study enrolled patients aged 6 years and above with obesity and a clinical diagnosis of BBS. Adult patients had a BMI of ≥30 kg/m^2 and pediatric patients had weight ≥97th percentile using growth chart assessments. To maintain blinding during period 1, dose titration to a fixed dose of 3 mg once daily was performed during the first 2 weeks of both period 1 and period 2. Efficacy analyses were conducted in 44 patients at the end of period 1 (week 14) and in 31 patients during the active-treatment period, defined as the period from randomization to week 52 in patients initially randomized to setmelanotide, and from week 14 to Week 66 in patients initially randomized to placebo. Analyses of the active-treatment period include patients who had either completed 52 weeks from the start of setmelanotide treatment or discontinued the study early at the time of the prespecified data cutoff.

A total of 44 patients were enrolled; 50% were adults, 32% were aged 12 to <18 years, and 18% were aged 6 to <12 years; 46% were male; 77% were White, 5% were Black; and the mean BMI was 41.5 kg/m^2 (range: 24.4-66.1 kg/m2) at baseline. The mean percent change in BMI after 52 weeks of setmelanotide treatment was -7.9%; 61.3% of patients achieved a ≥5% BMI decrease from baseline, and 38.7% had a ≥10% decrease in BMI. The difference in BMI after week 14 in period 1 was also significantly different but more modest at -4.5%. Patients 12 years and older who were able to self-report their hunger (n=14), recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2. Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 10 ("hungriest possible"). Hunger scores decreased in setmelanotide -treated patients during the 14-week placebo-controlled period and during the open-label treatment period (mean baseline score: 6.99 vs. mean week 52 score: 4.87, difference of -2.2). There were also general numeric improvements in blood pressure, lipids, and waist circumference. However, because of the limited number of patients studied and the lack of a control group, the treatment effects on these parameters could not be accurately quantified.

The FDA approval of setmelanotide for weight reduction in adults and pediatric patients aged 4 years and older with acquired HO was based on a randomized, double-blinded, placebo-controlled 56- to 60-week clinical trial (NCT05774756)]. The trial enrolled patients 4 years and older with acquired HO due to hypothalamic injury or dysfunction. Adult patients had a BMI of ≥30 kg/m^2 and pediatric patients had a BMI ≥95th percentile for age and sex. Patients were randomized to either setmelanotide or placebo and entered an up to 8-week dose titration period followed by a 52-week treatment period. A total of 142 patients with acquired HO were randomized and analyzed; 47% were adults, 31% were aged 12 to less than 18 years, and 23% were 4 to less than 12 years; 40% were male; 75% were White; and the mean BMI was 36 kg/m^2 (range: 21 to 70 kg/m^2). The proportion of patients who discontinued trial drug was

10.6% of the setmelanotide-treated group and 12.5% of the placebo-treated group. The primary efficacy parameter was mean percent change in BMI from baseline after 52 weeks, After 52 weeks of treatment at the therapeutic dose, the mean percent change in BMI compared to placebo was -18.4 (-15.84 vs. 2.55), and greater proportions of patients treated with setmelanotide achieved at least 5%, 10%, and 15% BMI reduction compared to placebo. In patients 12 years and older who were able to self-report their hunger (n=110), recorded their daily maximal hunger in a diary, which was then assessed by the Daily HungerQuestionnaire Item 2. Hunger was scored on an 11-point scale from 0 ("not hungry at all") to 1 ("hungriest possible"). After 52 weeks of treatment at the therapeutic dose, setmelanotide resulted in a statistically significant reduction in hunger compared to placebo of -0.82 (-2.27 vs. -1.44). Setmelanotide also resulted in a reduction in waist circumference and general numeric improvements in blood pressure, lipids, and glycemic parameters compared with placebo.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of setmelanotide (Imcivree) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. Member has a diagnosis of **ANY** of the following ("a", "b", or "c"):
    a. Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing**; AND** a bi-allelic, homozygous or compound heterozygous mutation in the *POMC*, *PCSK1*, or *LEPR* gene has been identified and interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) – *the genetic testing result and interpretation must be submitted*
    b. Acquired hypothalamic obesity (HO) resulting from an injury to or dysfunction of the hypothalamus (such as, but not limited to, treatment of brain tumors via surgical resection, chemotherapy, or radiation; or traumatic brain injury, hemorrhage, or stroke) - *medical record documentation describing the member's hypothalamic injury or dysfunction, including the specific cause(s) of the injury or dysfunction and approximate date of injury to or dysfunction of the hypothalamus must be submitted*
    c. Bardet-Biedl syndrome (BBS), **AND** the diagnosis has been confirmed by **ANY** the following ("i", "ii", or "iii) – *medical record documentation of the member's qualifying clinical features, or genetic testing results must be submitted*
        i. Member has a bi-allelic, homozygous or compound heterozygous pathogenic or likely pathogenic mutation in a gene that is associated with 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)]*
        ii. At least **FOUR** of the following six major (or primary) BBS features:

            Major features:

            - Retinal cone-rod dystrophy
            - Central obesity
            - Postaxial polydactyly (extra digit at the 5th finger or toe)
            - Cognitive impairment

- Hypogonadism and genitourinary abnormalities
- Kidney disease

iii. **THREE** primary BBS feature, **AND** at least **TWO** of the following six minor BBS (or secondary) features:

Minor features:

- Neurologic abnormalities (e.g., developmental delay, speech delay or impairments, epilepsy, behavior/psychiatric abnormalities)
- Olfactory dysfunction (e.g., anosmia, hyposmia)
- Oral/dental abnormalities
- Cardiovascular and other thoraco-abdominal abnormalities
- Gastrointestinal abnormalities (e.g., liver disease/ALT elevation, Hirschsprung disease, celiac disease, Inflammatory bowel disease)
- Endocrine/metabolic abnormalities (e.g., metabolic syndrome, subclinical hypothyroidism, type 2 diabetes, polycystic ovary syndrome)

2. Member has a body mass index (BMI) of 30 kg/m^2 or greater if an adult (i.e., 18 years of age or older), or a bodyweight greater than the 95th percentile for age on growth chart assessment if a child/adolescent, despite attempting appropriate lifestyle modifications (e.g., diet and/or exercise regimens) - *baseline height and weight (for adults) or growth chart assessment (for children) within the past 90 days must be submitted*
3. Member has a baseline estimated glomerular filtration (eGFR) of at least 15 mL/min/1.73 m^2, **OR**, for member's aged 2 to less than 6 years and less than 20 kg, at least 30 mL/min/1.73 m^2
4. One of the following:
   a. Member is at least 2 years of age or older for POMC, PCSK1, and LEPR deficiency or BBS
   b. Member is 4 years of age or older for acquired HO
   c. Member's age is within FDA labeling for the requested indication
5. Setmelanotide is prescribed by, or in consultation with, a specialist in endocrinology or medical genetics
6. The dosage of setmelanotide does not exceed the following based on the member's indication for use, age and body weight:
   a. 12 years of age and older:
      i. For POMC, PCSK1, and LEPR deficiency or BBS:
         - First 2 weeks (weeks 1 and 2) - 2 mg (0.2 mL) once daily
         - After the first 2 weeks - 3 mg (0.3 mL) once daily
            - For the first 30-day supply, limit of eight 10 mg/1 mL vials
            - After the first 30 days, a limit of ten 10 mg/1 mL vials per 30-day supply
      ii. For acquired HO:
         - Weeks 1 to 2: 0.5 mg (0.05 mL) once daily
         - Weeks 3 to 4: 1 mg (0.1 mL) once daily
         - Weeks 5 to 6: 2 mg (0.2 mL) once daily
         - Weeks 7 and onward: 3 mg (0.3 mL) once daily

- For the first 30-day supply, limit of three 10 mg/1 mL vials
- For the second 30-day supply, limit of eight 10 mg/1 mL vials
- After the first 60 days, a limit of ten 10 mg/1 mL vials per 30-day supply

b. 6 to less than 12 years of age:

i. For POMC, PCSK1, and LEPR deficiency or BBS:

- First 2 weeks (weeks 1 and 2): 1 mg (0.1 mL) once daily
- Weeks 3 and 4: 2 mg (0.2 mL) once daily
- After the first 4 weeks: 3 mg (0.3 mL) once daily
  - For the first 30-day supply, limit of five 10 mg/1 mL vials
  - After the first 30 days, a limit of ten 10 mg/1 mL vials per 30-day supply

ii. For acquired HO:

- Weeks 1 to 2: 0.5 mg (0.05 mL) once daily
- Weeks 3 to 4: 1 mg (0.1 mL) once daily
- Weeks 5 to 6: 2 mg (0.2 mL) once daily
- Weeks 7 and onward: 3 mg (0.3 mL) once daily
  - For the first 30-day supply, limit of three 10 mg/1 mL vials
  - For the second 30-day supply, limit of eight 10 mg/1 mL vials
  - After the first 60 days, a limit of ten 10 mg/1 mL vials per 30-day supply

c. 2 to less than 6 years of age (all indications):

i. First 2 weeks (weeks 1 and 2): 0.5 mg (0.05 mL) once daily [all weights]

ii. Weeks 3 and 4:

- Less than 20 kg (44 lbs) - 0.5 mg (0.05 mL) once daily
  - For the first 30-day supply, limit of two 10 mg/1 mL vials
- 20 kg (44 lbs) to less than 30 kg (66 lbs) - 1 mg (0.1 mL) once daily
  - For the first 30-day supply, limit of three 10 mg/1 mL vials
- 30 kg (66 lbs) to less than 40 kg (88 lbs) - 1 mg (0.1 mL) once daily
  - For the first 30-day supply, limit of three 10 mg/1 mL vials
- 40 kg (88 lbs) or more - 1 mg (0.1 mL) once daily
  - For the first 30-day supply, limit of three 10 mg/1 mL vials

iii. Weeks 5 and 6:

- Less than 20 kg (44 lbs) - 0.5 mg (0.05 mL) once daily
- 20 kg (44 lbs) to less than 30 kg (66 lbs) - 1 mg (0.1 mL) once daily
- 30 kg (66 lbs) to less than 40 kg (88 lbs) – 1.5 mg (0.15 mL) once daily
- 40 kg (88 lbs) or more – 1.5 mg (0.15 mL) once daily

iv. After the first 6 weeks:

- Less than 20 kg (44 lbs) - 0.5 mg (0.05 mL) once daily

        - After the first 30 days, a limit of two 10 mg/1 mL vials per 30-day supply
    - 20 kg (44 lbs) to less than 30 kg (66 lbs) - 1 mg (0.1 mL) once daily
        - After the first 30 days, limit of three 10 mg/1 mL vials per 30-day supply
    - 30 kg (66 lbs) to less than 40 kg (88 lbs) – 1.5 mg (0.15 mL) once daily
        - After the first 30 days, limit of five 10 mg/1 mL vials per 30-day supply
    - 40 kg (88 lbs) or more - 2 mg (0.2 mL) once daily
        - After the first 30 days, limit of six 10 mg/1 mL vials per 30-day supply

Approval duration: 6 months (for POMC, PCSK1, and LEPR deficiency) or 12 months (for BBS or acquired HO)

Continuation of setmelanotide (Imcivree) **meets the definition of medical necessity** when **ALL** of the following criteria are met (”1” to “6”):

1. An authorization or reauthorization for setmelanotide has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of obesity due to a generically confirmed POMC, PCSK1, or LEPR deficiency or Bardet-Biedl syndrome, or acquired hypothalamic obesity (if another health plan, documentation of a health plan-paid claim for setmelanotide during the 90 days immediately before the authorization request must be submitted); **OR** the member has previously met **ALL** indication-specific criteria
2. Member has had a beneficial response to setmelanotide treatment as demonstrated by the following:
    a. Less than 6 months of treatment (for POMC, PCSK1, and LEPR deficiency) or less than 12 months of treatment (for BBS or acquired HO): at least a 5% reduction in baseline body weight (or 5% reduction in baseline BMI for members with continued growth potential) – *supportive documentation from member’s medical record must be submitted*
    b. 6 or more months of treatment (for POMC, PCSK1, and LEPR deficiency) or 12 or more months of treatment (for BBS or acquired HO): member continues to have clinical benefit with setmelanotide treatment (for example, reduced hunger and maintenance of prior weight loss or reduced BMI)
3. Member has an estimated glomerular filtration (eGFR) of at least 15 mL/min/1.73 m^2, **OR**, for member’s aged 2 to less than 6 years and less than 20 kg, at least 30 mL/min/1.73 m^2
4. One of the following:
    a. Member is 2 years of age or older for POMC, PCSK1, and LEPR deficiency or BBS
    b. Member is 4 years of age or older for acquired HO
    c. Member’s age is within FDA labeling for the requested indication
5. Setmelanotide is prescribed by, or in consultation with, a specialist in endocrinology or medical genetics
6. The dosage of setmelanotide does not exceed the following based on age and body weight (all indications):
    a. 6 years of age and older: 3 mg (0.3 mL) once daily
        - Limit of ten 10 mg/1 mL vials per 30-day supply
    b. 2 to less than 6 years of age:
        - Less than 20 kg (44 lbs) - 0.5 mg (0.05 mL) once daily
            - Limit of two 10 mg/1 mL vials per 30-day supply
        - 20 kg (44 lbs) to less than 30 kg (66 lbs) - 1 mg (0.1 mL) once daily

        - Limit of three 10 mg/1 mL vials per 30-day supply
    - 30 kg (66 lbs) to less than 40 kg (88 lbs) – 1.5 mg (0.15 mL) once daily
        - Limit of five 10 mg/1 mL vials per 30-day supply
    - 40 kg (88 lbs) or more - 2 mg (0.2 mL) once daily
        - Limit of six 10 mg/1 mL vials per 30-day supply

Approval duration: 1 year

Setmelanotide (Imcivree) does **NOT meet the definition of medical necessity** for other uses, including but not limited to the following orphan indications, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes:

- Prader-Willi syndrome
- Alström syndrome

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged:
    - 4 years and older with acquired hypothalamic obesity (HO)
    - 2 years and older with syndromic or monogenic obesity due to:
        - Bardet-Biedl syndrome (BBS)
        - Pro-opiomelanocortin (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)
- Limitations of Use: Setmelanotide is not indicated for the treatment of patients with the following conditions as it would not be expected to be effective:
    - 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 HO, BBS or POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity
- Dosage in patients with acquired HO

  Adults and pediatric patients aged 6 years and older:
    - The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks. If the starting dosage is not tolerated, discontinue the product.
    - The dosage is titrated over the first 6 weeks as follows:
        - Weeks 1 to 2: 0.5 mg once daily
        - Weeks 3 to 4: 1 mg once daily

- Weeks 5 to 6: 2 mg once daily
- Weeks 7 and onward: 3 mg once daily

Pediatric patients aged 4 to less than 6 years:

- The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 week.
- The dosage is titrated over the first 6 weeks based on the patient's weight. Refer to the product labeling for the recommended dose titration.

- Dosage in patients with BBS or POMC, PCSK1, or LEPR deficiency

  Adults and pediatric patients 12 years of age and older:

  - The recommended starting dose is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks, and the recommended target dose is 3 mg (0.3 mL) injected subcutaneously once daily. Monitor patients for gastrointestinal (GI) adverse reactions.
    - If the starting dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 1 mg once daily dose is tolerated for at least one week, increase the dosage to 2 mg (0.2 mL) once daily.
    - If the starting dose is tolerated for 2 weeks, increase the dose to 3 mg (0.3 mL) once daily. If the 3 mg once daily dose is not tolerated, decrease the dosage to 2 mg (0.2 mL) once daily

  Pediatric patients 6 to less than 12 years of age:

  - The recommended starting dose is 1 mg (0.1 mL) injected subcutaneously once daily for 2 weeks, and the recommended target dose is 3 mg (0.3 mL) injected subcutaneously once daily. Monitor patients for GI adverse reactions
    - If the starting dose is not tolerated, reduce to 0.5 mg (0.05 mL) once daily. If the 0.5 mg once daily dose is tolerated for at least one week, increase the dosage to 1 mg (0.1 mL) once daily.
    - If the starting dose is tolerated for 2 weeks, increase the dosage to 2 mg (0.2 mL) once daily.
    - If the 2 mg daily dose is not tolerated, reduce the dosage to 1 mg (0.1 mL) once daily. If the 2 mg daily dose is tolerated, increase the dosage to 3 mg (0.3 mL) once daily.

  Pediatric patients 2 to less than 6 years of age:

  - The recommended starting dosage is 0.5 mg (0.05 mL) injected subcutaneously once daily for 2 weeks.
  - If tolerated for 2 weeks, increase the dosage based on baseline body weight (refer to the package labeling for the weight-based recommendations).

Dose Adjustments

- Hepatic impairment - The impact of hepatic impairment on the pharmacokinetics of setmelanotide is unknown, and specific guidelines for dosage adjustments are not available.
- Renal impairment - Dosage adjustments are required and depend on the indication and the patient age and weight. Refer to the product labeling for recommendations.

Drug Availability

- 10 mg/mL solution in a 1-mL multiple-dose vial
- Store unopened vials in the refrigerator at 2°C to 8°C (36°F to 46°F). After removal from the refrigerator, vials may be kept at temperatures ranging from refrigerated to room temperature (2°C to 25°C (36°F to 77°F)) for up to 30 days with brief excursions up to 30°C (86°F). After the vial is punctured (opened), discard after 30 days.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- In patients with a prior serious hypersensitivity reaction to setmelanotide or any of the excipients in Imcivree. Serious hypersensitivity reactions have included anaphylaxis.

Precautions/Warnings

- **Disturbance in Sexual Arousal**: Sexual adverse reactions may occur in patients treated with setmelanotide. Spontaneous penile erections in males (23%) and sexual adverse reactions in females (7% in setmelanotide-treated patients and 0% in placebo-treated patients from an unapproved population) occurred in clinical studies. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.
- **Depression and Suicidal Ideation**: Some drugs that target the central nervous system, such as setmelanotide, may cause depression or suicidal ideation. Patients with a history of severe depression were excluded from setmelanotide clinical studies. Depression (26%) and suicidal ideation (11%) occurred in setmelanotide clinical studies. Monitor patients for new onset or worsening of depression. Consider discontinuing setmelanotide if patients experience suicidal thoughts or behaviors.
- **Hypersensitivity Reactions**: Serious hypersensitivity reactions, including anaphylaxis, have been reported with setmelanotide. These reactions generally occurred within minutes to hours after injecting setmelanotide. If hypersensitivity reactions occur, advise patients to promptly seek medical attention and discontinue use of setmelanotide. Setmelanotide is contraindicated in patients with a prior serious hypersensitivity reaction to setmelanotide or any of the excipients in Imcivree.
- **Skin Hyperpigmentation, Darkening of Pre-Existing Nevi, and Development of New Melanocytic Nevi**: Generalized or focal increases in skin pigmentation occurred in the majority of patients (67% in patients aged 6 years and older; 83% in patients 2 to less than 6 years) treated in clinical trials. This effect is reversible upon discontinuation of the drug. Setmelanotide may also cause the development of new melanocytic nevi or darkening of preexisting nevi due to its pharmacologic effect. Development of new melanocytic nevi and darkening or increase in size of existing melanocytic nevi occurred in 16% of patients aged 6 years and older and 33% of patients aged 2 to less than 6 years. Perform a full body skin examination prior to initiation and periodically during treatment with setmelanotide to monitor pre-existing and new skin pigmentary lesions.
- **Acute Adrenal Insufficiency in Patients with Acquired HO**: In a clinical trial of adults and pediatric patients aged 4 years and older with acquired HO and secondary adrenal insufficiency, serious adverse reactions related to acute adrenal insufficiency were reported by 5% of setmelanotide-treated patients and no placebo-treated patients. In patients with secondary adrenal insufficiency, monitor for clinical signs of acute adrenal insufficiency.
- **Sodium Imbalance in Patients with Acquired HO and Central Diabetes Insipidus**: In a clinical trial of adults and pediatric patients aged 4 years and older with acquired HO and concomitant central diabetes insipidus (DI)/arginine vasopressin (AVP) deficiency, hyponatremia was reported in 6% of setmelanotide-treated patients and 2% of placebo-treated patients, and hypernatremia was reported in 5% of setmelanotide -treated patients and 4% of placebo-treated patients. In patients with acquired HO and concomitant DI/AVP deficiency, monitor serum sodium levels with changes in fluid intake and hydration status. Adjust the doses of concomitant therapies for DI/AVP deficiency as needed.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

E66.8	Other obesity
Q87.83	Bardet-Biedl syndrome

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/14/26.

GUIDELINE UPDATE INFORMATION:

03/15/21	New Medical Coverage Guideline.
05/15/22	Review and revision to guideline consisting of updating the description section and references.
10/15/22	Revision to guideline consisting of updating the description section, position statement, dosage/administration, and references to include the new indication of Bardet-Biedl syndrome (BBS).
05/15/23	Review and revision to guideline consisting of updating the description section and references.
10/01/23	Revision: Added ICD10 code Q87.83 and deleted code Q87.89.
05/15/24	Review and revision to guideline consisting of updating the precautions and references. New contraindication regarding a prior serious hypersensitivity reaction was added to the FDA-approved labeling.
05/15/25	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions/warnings, and references. The FDA-approved indications were expanded to include pediatric patients 2 years of age and older. New weight-based dosing for patients 2 to 6 years of age.
05/15/26	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions and references. New FDA-approved indication for acquired hypothalamic obesity.
11/15/26	Revision to guideline consisting of updating the documentation requirements for acquired hypothalamic obesity.