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DRUG POLICY

Imcivree (setmelanotide) subcutaneous injection

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Imcivree (setmelanotide) policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Imcivree is indicated to reduce excess body weight and maintain reduction long term in adults and pediatric patients aged:

1. 4 years and older with acquired hypothalamic obesity (HO)
2. 2 years and older with Bardet-Biedl syndrome (BBS)
3. 2 years and older with pro-opiomelanocortin (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)

Limitations of Use

Imcivree is not indicated for the treatment of patients with the following conditions as Imcivree would not be expected to be effective:

1. Obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign
2. Other types of obesity not related to acquired HO, BBS, or POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity

Required Documentation

The following information is necessary for initial and continuation authorization requests:

- A. Medical records documenting the following:
 - 1. Past medical & surgical history
 - 2. Medication history
 - 3. Body mass index (BMI) OR stature (in centimeters) plus weight (in kilograms)
 - 4. Creatinine clearance (CrCl)
- B. For obesity due to *POMC*, *PCSK1*, or *LEPR* deficiency only:
 - 1. *POMC*, *PCSK1*, or *LEPR* genetic testing results

Prescriber Specialties

The requested medication must be prescribed by or in consultation with one of the following:

- 1. Acquired hypothalamic obesity: endocrinologist, neurologist, specialist in rare genetic disorders of obesity
- 2. Obesity due to *POMC*, *PCSK1*, or *LEPR* deficiency or Bardet-Biedl syndrome: endocrinologist, geneticist, specialist in rare genetic disorders of obesity

Initial Criteria for Approval

- A. Imcivree may be considered **medically necessary** to reduce excess body weight and maintain reduction long term for members with acquired hypothalamic obesity (HO) when ALL of the following criteria are met:
 - 1. The member is 4 years of age or older
 - 2. The member has obesity, defined as one of the following:
 - i. Adults (18 years of age or older): BMI ≥ 30 kg/m²; OR
 - ii. Pediatrics (4-17 years of age): $\geq 95^{\text{th}}$ percentile using CDC growth chart assessments [See Appendix]
 - 3. The member has a diagnosis of acquired HO due to hypothalamic tumor, hypothalamic lesion, or hypothalamic damage or injury
 - 4. The member has a creatinine clearance (CrCl) of ≥ 30 mL/min
 - 5. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)

Initial approval will be granted for **12 months**.

- B. Imcivree may be considered **medically necessary** to reduce excess body weight and maintain weight reduction long term for members with obesity due to proopiomelanocortin (*POMC*), proprotein convertase subtilisin/kexin type 1 (*PCSK1*), or leptin receptor (*LEPR*) deficiency when ALL of the following criteria are met:
 - 1. The member is 2 years of age or older
 - 2. The member has obesity, defined as one of the following:
 - i. Adults (18 years of age or older): BMI ≥ 30 kg/m²; OR
 - ii. Pediatrics (2-17 years of age): $\geq 95^{\text{th}}$ percentile using CDC growth chart assessments [See Appendix]
 - 3. The member has a bi-allelic, homozygous or presumed compound heterozygous variant in at least one of the following genes:
 - i. Proopiomelanocortin (*POMC*)
 - ii. Proprotein convertase subtilisin/kexin type 1 (*PCSK1*)
 - iii. Leptin receptor (*LEPR*)
 - 4. Variant(s) in *POMC*, *PCSK1*, or *LEPR* genes meet ALL of the following:
 - i. Loss-of-function (LOF) variant for each allele confers a severe obesity phenotype

- ii. Variant(s) are interpreted as pathogenic, likely pathogenic, or of uncertain significance
- 5. The member has NOT received prior gastric bypass surgery which has resulted in $\geq 10\%$ weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
- 6. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)

Initial approval will be granted for **3 months**.

C. Imcivree may be considered **medically necessary** to reduce excess body weight and maintain weight reduction long term for members with obesity due to Bardet-Biedl Syndrome (BBS) when ALL of the following criteria are met:

- 1. The member is 2 years of age or older
- 2. Member has a clinical diagnosis of BBS as per Beales criteria (member has 4 primary features OR 3 primary and 2 secondary features) (see Appendix B)
- 3. The member has obesity, defined as one of the following:
 - i. Adults (18 years of age or older): BMI ≥ 30 kg/m²; OR
 - ii. Pediatrics (2-17 years of age): $\geq 95^{\text{th}}$ percentile using CDC growth chart assessments [See Appendix]
- 4. The member has NOT received prior gastric bypass surgery which has resulted in $\geq 10\%$ weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
- 5. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)

Initial approval will be granted for **3 months**.

Continuation of Therapy

- A. Imcivree may be considered **medically necessary** to reduce excess body weight and maintain reduction long term for members with acquired hypothalamic obesity (HO) when ALL of the following criteria are met:
 - a. The member is 4 years of age or older
 - b. The member has obesity, defined as one of the following:
 - i. Adults (18 years of age or older): BMI ≥ 30 kg/m²; OR
 - ii. Pediatrics (4-17 years of age): $\geq 95^{\text{th}}$ percentile using CDC growth chart assessments [See Appendix]
 - c. The member has a diagnosis of acquired HO due to hypothalamic tumor, hypothalamic lesion, or hypothalamic damage or injury
 - d. The member has a creatinine clearance (CrCl) of ≥ 30 mL/min
 - e. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)
 - f. The member has responded to therapy with Imcivree as demonstrated by a reduction in weight from baseline, pre-treatment weight consistent with one of the following:
 - i. For members who received less than 12 months of therapy with Imcivree, one of the following must be met:
 - Member has reduction in weight of at least 5% of baseline body weight
 - Member is <18 years of age and has a reduction in BMI of at least 5% from baseline
 - ii. For members who received at least 12 months of therapy with Imcivree and achieved or sustained a reduction in weight of at least 10% from baseline weight

Approval will be for 12 months

- B. Imcivree may be considered **medically necessary** to reduce excess body weight and maintain weight reduction long term for members with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency when ALL of the following criteria are met:
1. The member is 2 years of age or older
 2. The member has a bi-allelic, homozygous or presumed compound heterozygous variant in at least one of the following genes:
 - i. Proopiomelanocortin (*POMC*)
 - ii. Proprotein convertase subtilisin/kexin type 1 (*PCSK1*)
 - iii. Leptin receptor (*LEPR*)
 3. Variant(s) in *POMC*, *PCSK1*, or *LEPR* genes meet ALL of the following:
 - i. Loss-of-function (LOF) variant for each allele confers a severe obesity phenotype
 - ii. Variant(s) are interpreted as pathogenic, likely pathogenic, or of uncertain significance
 4. The member has NOT received prior gastric bypass surgery which has resulted in $\geq 10\%$ weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
 5. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)
 6. The member has responded to therapy with Imcivree as demonstrated by a reduction in weight from baseline, pre-treatment weight consistent with one of the following:
 - i. For members who received less than 12 months of therapy with Imcivree, one of the following must be met:
 - Member has reduction in weight of at least 5 kg during initial 3 months of treatment with Imcivree
 - Member has reduction in weight of $\geq 5\%$ if baseline body weight < 100 kg during initial 3 months of treatment with Imcivree
 - ii. For members who received at least 12 months of therapy with Imcivree and achieved or sustained a reduction in weight of at least 10% from baseline weight

Approval will be for 12 months

- C. Imcivree may be considered **medically necessary** to reduce excess body weight and maintain weight reduction long term for members with obesity due to Bardet-Biedl Syndrome (BBS) when ALL of the following criteria are met:
1. The member is 2 years of age or older
 2. Member has a clinical diagnosis of BBS as per Beales criteria (member has 4 primary features OR 3 primary and 2 secondary features) (see Appendix B)
 3. The member has NOT received prior gastric bypass surgery which has resulted in $\geq 10\%$ weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
 4. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)
 5. The member has responded to therapy with Imcivree as demonstrated by a reduction in weight from baseline, pre-treatment weight consistent with one of the following:
 - i. For members who received less than 12 months of therapy with Imcivree, one of the following must be met:
 - Member has reduction in weight of at least 5 kg during initial 3 months of treatment with Imcivree
 - Member has reduction in weight of $\geq 5\%$ if baseline body weight < 100 kg during initial 3 months of treatment with Imcivree

- ii. For members who received at least 12 months of therapy with Imcivree and has achieved or sustained a reduction in weight of at least 10% from baseline weight

Approval will be for 12 months

Imcivree (setmelanotide) is considered **not medically necessary** for patients who do not meet the criteria set forth above.

Members currently receiving the requested medication as samples or via the manufacturer's patient assistance program will be required to meet the criteria for initial approval. This ensures that members are treated equally regardless of their provider's ability to access medication samples.

Quantity Limits

- 9 mL (90 mg) per 30 days

APPENDIX

APPENDIX A: CDC Growth Chart

CDC Clinical Growth Charts available at: https://www.cdc.gov/growthcharts/clinical_charts.htm

APPENDIX B: Beales Diagnostic Criteria

Beales Diagnostic Criteria

- A. Primary features
 - 1. Rod-cone dystrophy
 - 2. Polydactyly
 - 3. Obesity
 - 4. Learning disability
 - 5. Hypogonadism in males
 - 6. Renal abnormalities
- B. Secondary features
 - 1. Speech disorder/delay
 - 2. Strabismus/cataracts/astigmatism
 - 3. Brachydactyly/syndactyly
 - 4. Developmental delay
 - 5. Polyuria/polydipsia (nephrogenic diabetes insipidus)
 - 6. Ataxia/poor coordination/imbalance
 - 7. Mild spasticity (especially lower limbs)
 - 8. Diabetes mellitus
 - 9. Dental crowding/hypodontia/small roots/high arched palate
 - 10. Left ventricular hypertrophy/congenital heart disease
 - 11. Hepatic fibrosis

CLINICAL RATIONALE

Genetic and hypothalamic disorders affecting the melanocortin pathway are recognized causes of severe, early-onset obesity characterized by hyperphagia and impaired satiety. The melanocortin-4 receptor (MC4R) pathway plays a central role in regulation of appetite and energy expenditure.

Rare forms of obesity, including proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), and leptin receptor (LEPR) deficiencies, result from biallelic variants that impair melanocortin

signaling. These conditions are associated with severe hyperphagia and early-onset obesity and are generally refractory to standard interventions, including lifestyle modification, pharmacotherapy, and bariatric surgery.

Bardet-Biedl syndrome (BBS) is a rare ciliopathy characterized by multisystem involvement including retinal dystrophy, polydactyly, cognitive impairment, renal abnormalities, and obesity. Obesity in BBS is thought to be mediated, in part, by dysfunction of hypothalamic signaling and impaired activation of the MC4R pathway.

Acquired hypothalamic obesity (HO) occurs following damage to the hypothalamus (e.g., due to tumors, surgery, radiation, or trauma). Disruption of hypothalamic signaling leads to decreased satiety, reduced energy expenditure, and rapid, often treatment-refractory weight gain.

Imcivree (setmelanotide) is a selective MC4R agonist designed to restore downstream signaling in the melanocortin pathway. By reactivating MC4R, Imcivree reduces hunger and caloric intake and promotes weight loss in individuals with obesity due to impaired MC4R pathway signaling.

Efficacy

Efficacy in POMC, PCSK1, and LEPR deficiencies was established in Phase III, open-label trials with a withdrawal period in patients with genetically confirmed or suspected POMC, PCSK1, or LEPR deficiency. At 1 year, 80% of patients with POMC or PCSK1 deficiency and 46% with LEPR deficiency achieved $\geq 10\%$ weight loss. Mean percent weight change was approximately -23% (POMC/PCSK1) and -9.7% (LEPR). Improvements in hunger scores were observed supporting a treatment effect. These data demonstrate clinically meaningful and sustained reductions in weight and hyperphagia in a population with otherwise limited treatment options.

Efficacy in BBS was demonstrated in a 66-week trial including a randomized, placebo-controlled period followed by open-label treatment. Mean percent BMI reduction at 52 weeks was approximately -7.9%. A total of 61.3% of patients achieved $\geq 5\%$ BMI reduction and 38.7% achieved $\geq 10\%$ reduction. Statistically significant weight reduction versus placebo was observed during the controlled phase. Although weight loss magnitude is lower than in monogenic deficiencies, these results are clinically meaningful given the chronic, syndromic nature of BBS and limited therapeutic options.

Efficacy in acquired HO was evaluated in a randomized, double-blind, placebo-controlled trial. At 52 weeks, treatment resulted in a placebo-adjusted BMI reduction of -18.4%. Approximately 76% of patients achieved $\geq 5\%$ BMI reduction and 61% achieved $\geq 10\%$ reduction. Significant reductions in hunger scores were also observed. These findings support a robust treatment effect in a population typically resistant to conventional weight management strategies.

Safety

Across clinical trials, the most common adverse reactions included injection site reactions, hyperpigmentation, nausea, and headache. Notable risks include depression and suicidal ideation, disturbances in sexual arousal, skin hyperpigmentation and changes, and hypersensitivity reactions. In patients with acquired HO, there are additional risks of adrenal insufficiency and sodium imbalance. Overall, the safety profile is considered manageable with appropriate monitoring.

Imcivree addresses an underlying pathophysiologic mechanism in select rare obesity disorders. Clinical trial data demonstrate meaningful reductions in weight and hunger across POMC, PCSK1, and LEPR deficiencies, BBS, and acquired HO. Given the severity of disease, limited alternative treatments, and targeted mechanism of action, use is appropriate in carefully selected patients meeting diagnostic criteria.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- No applicable codes

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POLICY HISTORY

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