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 for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to:

1. 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)
2. Bardet-Biedl syndrome (BBS)

Limitations of Use

Imcivree (setmelanotide) is not indicated for the treatment of patients with the following conditions as Imcivree (setmelanotide) 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 POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity

POLICY

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

Initial Criteria for Approval

A. Imcivree may be considered **medically necessary** for chronic weight management in adult and pediatric patients 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. Diagnosis must be made by or in consultation with an endocrinologist, a geneticist, or a specialist in rare genetic disorders of obesity
   2. The patient is obese, defined as one of the following:
      i. Adult patients (18 years of age or older): BMI ≥ 30 kg/m^2; OR
      ii. Pediatric patients (6-17 years of age): ≥ 95th percentile using CDC growth chart assessments [See Appendix]
   3. The patient 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 patient is 6 years of age or older
   6. The patient has a creatinine clearance (CrCl) of ≥ 30 mL/min
   7. The patient has NOT received prior gastric bypass surgery which has resulted in ≥ 10% weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
   8. 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.**

B. Imcivree may be considered **medically necessary** for chronic weight management in adult and pediatric patients with obesity due to Bardet-Biedl Syndrome (BBS) when ALL of the following criteria are met:
   1. Diagnosis must be made by or in consultation with an endocrinologist, a geneticist, or a specialist in rare genetic disorders of obesity
   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 patient is obese, defined as one of the following:
      i. Adult patients (18 years of age or older): BMI ≥ 30 kg/m^2; OR
      ii. Pediatric patients (6-17 years of age): ≥ 95th percentile using CDC growth chart assessments [See Appendix]

4. The patient is 6 years of age or older
5. The patient has a creatinine clearance (CrCl) of ≥ 30 mL/min
6. The patient has NOT received prior gastric bypass surgery which has resulted in ≥ 10% weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
7. 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 (setmelanotide) may be considered **medically necessary** for the **continuation of** chronic weight management in adult and pediatric patients 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. Diagnosis must be made by or in consultation with an endocrinologist, a geneticist, or a specialist in rare genetic disorders of obesity
2. The patient 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 patient is 6 years of age or older
5. The patient has a creatinine clearance (CrCl) of ≥ 30 mL/min
6. The patient has NOT received prior gastric bypass surgery which has resulted in ≥ 10% weight loss durably maintained from baseline, pre-operative weight with no evidence of weight regain
7. Other contributing factors or causes of obesity have been ruled out & eliminated (e.g., other genetic variations, chronic medical conditions, medications, etc.)
8. The patient 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 continuation requests for months 4-12 of Imcivree: reduction in weight of at least 5 kg (or ≥ 5% if baseline body weight < 100 kg) during initial 3 months of treatment with Imcivree
    ii. For continuation requests for months 12+ of Imcivree: reduction in weight of at least 10% annually during previous treatment with Imcivree

Approval will be for **12 months**

B. Imcivree may be considered **medically necessary** for the **continuation of** chronic weight management in adult and pediatric patients with obesity due to Bardet-Biedl Syndrome (BBS) when ALL of the following criteria are met:

1. Diagnosis must be made by or in consultation with an endocrinologist, a geneticist, or a specialist in rare genetic disorders of obesity
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 patient is 6 years of age or older
4. The patient has a creatinine clearance (CrCl) of ≥ 30 mL/min
5. The patient has NOT received prior gastric bypass surgery which has resulted in ≥ 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.)

7. The patient 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 continuation requests for months 4-12 of Imcivree: reduction in weight of at least 5 kg (or ≥ 5% if baseline body weight < 100 kg) during initial 3 months of treatment with Imcivree
   - **ii.** For continuation requests for months 12+ of Imcivree: reduction in weight of at least 10% annually during previous treatment with Imcivree

Approval will be for **12 months**

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

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

Background

Genetic variants are thought to contribute to 5% to 30% of severe early-onset obesity (Clément, 2020b). Of those, obesity due to POMC, PCSK1, or LEPR deficiency has been reported in approximately 150 cases in the medical literature for all three conditions combined (FDA, 2020b). POMC deficiency and LEPR deficiency are rare genetic disorders that result from biallelic variants in POMC or PCSK1 and LEPR, respectively (Clément, 2020a). These genetic variants disrupt the melanocortin pathway that contributes to

regulation of bodyweight. Neurons in the hypothalamus and melanocortin pathway activate the melanocortin 4 receptor (MC4R). Leptin binds to the LEPR on POMC-expressing neurons in the hypothalamus. In the fed state, leptin stimulates POMC production, which is processed by PCSK1 into melanocortin peptides (α-melanocyte-stimulating hormone [α-MSH] and β-MSH) that bind to and activate MC4R, which causes a reduction in food intake.

Patients with POMC deficiency and LEPR deficiency have severe hyperphagia (i.e., severe hunger) and early-onset (i.e., before 5 years of age) severe obesity (Clément, 2020a; Clément, 2020b). Variants in POMC can also result in adrenocorticotropic hormone deficiency, hypothyroidism, hypogonadism, and hypopigmentation due to loss of POMC-derived melanocortin peptides, and these patients sometimes have red hair. Patients with variants in PCSK1 can have postprandial hypoglycemia, hypogonadism, hypercortisolism, and malabsorption due to impaired prohormone processing. Variants in LEPR can also result in hypogonadism, hypothyroidism, growth hormone deficiency, high infection risk, and sepsis-related mortality, potentially from impaired immune function.

Genetic forms of obesity are typically refractory to standard medical care (e.g., lifestyle modification, bariatric surgery, medications), and data regarding safety and efficacy of these treatments are scarce (Clément, 2020b). Imcivree (setmelanotide) was recently approved by the FDA for the treatment of patients with obesity due to POMC, PCSK1, or LEPR deficiency and is the first and only treatment approved for this indication (FDA, 2020b; Imcivree prescribing information, 2020). Phase III clinical trials are evaluating Imcivree (setmelanotide) for the treatment of other obesity disorders linked to the MC4R pathway, including Bardet-Biedl syndrome and Alström syndrome (RxPipeline, 2020). The anticipated completion date for primary data from the phase III trial is December of 2020 and if results are positive, approval for the supplemental indication could occur in 2021.

Efficacy

The efficacy of Imcivree (setmelanotide) was assessed in two Phase III, single-arm, open-label, multinational, 52-week clinical trials. The trials enrolled patients with either a POMC deficiency (i.e., homozygous or compound heterozygous variants in POMC [n = 9] or PCSK1 [n=1]) or an LEPR deficiency (i.e., homozygous or compound heterozygous variants in LEPR). Patients also had to be ≥ 6 years of age and have a confirmed diagnosis of obesity* (mean BMI: 40.4 kg/m2 [POMC trial]; 48.2 kg/m2 [LEPR trial]). Patients were excluded if they participated in a recent diet or exercise regimen resulting in weight loss or stabilization, had a previous gastric bypass surgery resulting in > 10% weight loss with no evidence of weight regain, had a history or presence of renal or hepatic dysfunction, were diagnosed with a DSM-III disorder that would interfere with study, had a history or presence of suicidal behavior or ideation, or had significant dermatologic findings or history of skin cancer or melanoma.

Dose titration occurred over a 2-week to 12-week period (the final 2 weeks at a therapeutic dose), followed by a 10-week, open-label treatment period. Patients who achieved ≥ 5 kg weight loss (or ≥ 5% weight loss if baseline body weight was < 100 kg) at the end of the open-label treatment period continued into an 8-week double-blind withdrawal period, including 4 weeks of Imcivree followed by 4 weeks of placebo. Following the withdrawal sequence, patients re-initiated treatment with Imcivree at the therapeutic dose for up to 32 weeks. Results from both clinical trials are outlined in Table 1 below. Overall, Imcivree was associated with significant weight loss and reduction in hunger scores in individuals with POMC or LEPR deficiency obesity after approximately 1 year of treatment and was generally well tolerated.

Table 1: Efficacy of Imcivree (setmelanotide) for Severe Obesity Due to LEPR or POMC Deficiency

Study		**Clément, 2020a (N = 10)**			**Clément, 2020a (N = 11)**		
Treatments		**Imcivree**	**90% CI**	**p-value**	**Imcivree**	**90% CI**	**p-value**
R	**Patients who achieved ≥ 10% weight loss at 1 year**	8 (80%) (N = 10)	Not available	< 0.0001	5 (45.5%) (n = 11)	Not available	0.0001

	Mean % change in body weight at 1 year	-25.6% (n = 10)	-28.8 to -22.0	< 0.0001	-12.5% (n = 9)	-16.1 to -8.8	< 0.0001
	Mean % change in the most hunger score in patients ≥ 12 years of age	-27.1% (n = 7)	-40.6 to -15.0	0.0005	-43.7% (n = 7)	-54.8 to -29.1	< 0.0001

Safety

The most common treatment-related adverse event in both clinical trials were injection site reaction, which was reported by all patients in both trials. Hyperpigmentation was reported in all patients in the POMC trial, and in five out of 11 patients in the LEPR trial. Nausea was reported in five patients in the POMC trial (with vomiting in three patients), and in four patients in the LEPR trial. In both trials, no serious adverse events were considered to be related to Imcivree treatment. Increases in heart rate and blood pressure were not seen. In the POMC trial, no treatment-emergent adverse event led to study drug withdrawal or death. In the LEPR trial, treatment-related grade 1 intermittent spontaneous penile erections were reported in one patient, which resolved without sequelae, and the patient completed the trial. Grade 1 hypereosinophilia, possibly related to Imcivree treatment, was reported in 1 patient which resolved following discontinuation.

Warnings and precautions with Imcivree (setmelanotide) include disturbance in sexual arousal, depression and suicidal ideation, and skin pigmentation and darkening of pre-existing nevi. There is also a warning for risk of serious adverse events due to benzyl alcohol preservative in neonates and low birth weight infants. Approximately 61% of adult and pediatric patients with POMC- or LEPR-deficiency who received Imcivree (setmelanotide) (N = 28) screened positive for antibodies to setmelanotide, and 39% screened negative (Imcivree prescribing information, 2020). The 61% of patients who screened positive for antibodies to setmelanotide were inconclusive for antibodies to setmelanotide in the confirmatory assay. There was no observation of a rapid decline in setmelanotide concentrations to suggest the presence of anti-drug antibodies.

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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