Clinical Policy: Setmelanotide (Imcivree)

Reference Number: ERX.SPA.404
Effective Date: 11.25.20
Last Review Date: 08.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Setmelanotide (Imcivree™) is melanocortin-4 receptor pathway activator.

FDA Approved Indication(s)
Imcivree is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndrome 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).
- Bardot-Biedl syndrome (BBS)

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

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Imcivree is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Genetic Obesity Disorders (must meet all)**:**

1. Diagnosis of obesity due to POMC deficiency, PCSK1 deficiency, LEPR deficiency, or BBS;
2. Prescribed by or in consultation an endocrinologist or expert in rare genetic disorders of obesity;
3. Member meets one of the following (a or b):
   a. Age ≥ 6 and < 18 years with one of the following weight percentiles for age on growth chart assessment (*see Appendix D*) (i or ii):
      i. POMC, PCSK1, or LEPR deficiency: > 95th percentile;
      ii. BBS: > 97th percentile;
   b. Age ≥ 18 years of age and body mass index (BMI) ≥ 30 kg/m^2;
4. One of the following (a or b):
   a. Genetic testing confirms that variants in the following genes are interpreted as pathogenic, likely pathogenic, or of uncertain significance (i, ii, or iii):
      i. POMC;
      ii. PCSK1;
      iii. LEPR;

b. Diagnosis of BBS is confirmed clinically per Beales criteria *(see Appendix D);*
5. Documentation of baseline weight (in past 60 days) in kilograms;
6. Documentation of creatinine clearance ≥ 15 mL/min/1.73 m^2;
7. If member has had prior gastric bypass surgery, member meets one of the following (a or b):
   a. Member has not had > 10% weight loss from baseline pre-operative weight;
   b. Member has regained weight after an initial response to surgery;
8. Documentation that member is actively enrolled in a weight loss program that involves a reduced calorie diet and increased physical activity adjunct to therapy;
9. Dose does not exceed the following (a and b):
   a. First 2 weeks (i or ii):
      i. Age ≥ 6 and < 18 years: 1 mg per day;
      ii. Age ≥ 18 years: 2 mg per day;
   b. Maintenance: 3 mg per day.

Approval duration:
POMC, PCSK1, or LEPR deficiency – 4 months
BBS – 12 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Genetic Obesity Disorders (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by one of the following (a, b, or c):
   a. Initial re-authorization for POMC, PCSK1, or LEPR deficiency: After 12-16 weeks of treatment, reduction of at least 5% of baseline body weight or 5 % of baseline BMI;
   b. Initial re-authorization for BBS: After 1 year of treatment, reduction of at least 5% of baseline body weight or 5% of baseline BMI;
   c. Subsequent re-authorizations for all indications: Maintenance of ≥ 5% reduction in weight or BMI compared with baseline;
3. If request is for a dose increase, new dose does not exceed 3 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less);
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;
B. Obesity disorders not caused by POMC, PCSK1, or LEPR deficiency or by BBS;
C. Obesity disorder in patients with POMC, PCSK1, or LEPR gene variants that are interpreted as benign or likely benign.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BBS: Bardet-Biedl syndrome
BMI: body mass index
FDA: Food and Drug Administration
LEPR: leptin receptor

PCSKI1: proprotein convertase subtilisin/kexin type 1

POMC: pro-opiomelanocortin

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Body mass index calculator: https://globalrph.com/medcalcs/body-mass-index-bmi/
- CDC Clinical Growth Charts from 3rd to 97th percentiles:
  - 2 to 20 years: Boys Stature-for-age and Weight-for-age percentiles https://www.cdc.gov/growthcharts/data/set2clinical/cj41c071.pdf
  - 2 to 20 years: Girls Stature-for-age and Weight-for-age percentiles https://www.cdc.gov/growthcharts/data/set2clinical/cj41c072.pdf
- A clinical diagnosis of BBS is confirmed using Beales criteria. There must be presence of at least 4 primary features, OR 3 primary and 2 secondary features:
  - Primary features: rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism in males, renal anomalies
  - 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

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Obesity due to POMC, PCSK1, or LEPR deficiency or due to BBS	≥ 12 years and older: 2 mg SC once daily for 2 weeks; if tolerated, titrate up to 3 mg SC once daily Age 6 to 12 years: 1 mg SC once daily for 2 weeks; if tolerated, titrate up to 3 mg SC once daily	3 mg/day

VI. Product Availability
Vial: 10 mg/mL (1 mL multi-dose)

VII. References
1. Imcivree Prescribing Information. Boston, MA: Rhythm Pharmaceuticals, Inc.; June 2022. Available at: https://www.imcivree.com . AccessedJuly 1, 2022.
2. Styne DM, Arslanian SA, Conner EL, et al. Pediatric Obesity: Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017; 102: 709–757.
3. Clement K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMN deficiency: single-arm, open-label, multicenter, phase 3 trials. *Lancet Diabetes Endocrinol.* 2020; 8: 960-70. DOI: 10.1016/S2213-8587(20)30364-8.
4. Haws RM, Gordon G, Han JC, et al. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome: Phase 3 trial design. Contemporary Clinical Trials Communications. 2021; 22: 100780.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	05.19.20	08.20
Drug is now FDA approved - criteria updated per FDA labeling: added PCSK1-deficiency obesity, revised lower age limit from 12 years to 6 years old; revised percentile for age on growth chart assessment from 97th to 95th percentile; clarified that genetic variants in POMC, PCSK1, and LEPR should be interpreted as pathogenic, likely pathogenic, or of uncertain significance; clarified that baseline documentation of weight be in kg; revised specialist requirement from bariatric physician to experts in rare genetic disorders of obesity; added creatinine clearance requirement for normal renal function or mild renal impairment; added criteria requiring documentation of weight loss program to align with other weight-loss agent policies; expanded initial approval duration from 12 weeks to 4 months; added in Section III that coverage will be excluded for obesity disorder in patients with POMC, PCSK1, or LEPR genes variants that are interpreted as benign or likely benign; references reviewed and updated.	01.05.21	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.27.21	02.22
RT4: updated criteria to include new FDA approved indication of obesity due to BBS; revised creatinine clearance and positive response requirements per prescribing information; for POMC, PCSK1, or LEPR deficiency, removed initial maintenance approval duration of 6 months as weight loss should be evaluated after 4 months per prescribing information (requests for continued maintenance therapy may be approved using the continued approval criteria).	07.01.22	08.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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