Clinical Policy: Setmelanotide (Imcivree)

Reference Number: CP.PHAR.491
Effective Date: 11.25.20
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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 to reduce excess body weight and maintain weight reduction long term by reducing hunger and food intake and increasing energy expenditure in adults and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to:

- Bardet-Biedl syndrome (BBS)
- 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)

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.

It is the policy of health plans affiliated with Centene Corporation® 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 (*see Appendix D*);
2. Prescribed by or in consultation with an endocrinologist or expert in rare genetic disorders of obesity;
3. Member meets one of the following (a or b):
   a. Age ≥ 2 and < 6 years with body mass index (BMI) ≥ 97th percentile standardized for age and sex (*see Appendix D)*;

   b. 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;
   c. Age ≥ 18 years of age with BMI ≥ 30 kg/m^2;
4. Weight ≥ 15 kg;
5. 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*);
6. Documentation of baseline weight (in past 60 days) in kilograms;
7. Documentation of creatinine clearance ≥ 15 mL/min/1.73 m^2;
8. 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;
9. For age ≥ 6 years: Documentation that member is actively enrolled in a weight loss program that involves a reduced calorie diet and increased physical activity adjunct to therapy;
10. Dose does not exceed any of the following (a and b):
    a. First 2 weeks (i, ii, or iii):
       i. Age ≥ 2 years and < 6 years: 0.5 mg per day
       ii. Age ≥ 6 years and < 12 years: 1 mg per day;
       iii. Age ≥ 12 years: 2 mg per day;
    b. Maintenance (i or ii):
       i. Age ≥ 2 years and < 6 years: the FDA approved maximum recommended dose based on weight (*see Section V);*
       ii. Age ≥ 6 years: 3 mg per day.

Approval duration:
POMC, PCSK1, or LEPR deficiency – 4 months
BBS
- **Medicaid/HIM** – 12 months
- **Commercial** – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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 one of the following (a or b):
   a. Age ≥ 2 years and < 6 years: the FDA approved maximum recommended dose based on weight (*see Section V*);
   b. Age ≥ 6 years: 3 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid 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
PCSK1: proprotein convertase subtilisin/kexin type 1
POMC: pro-opiomelanocortin
VUS: variant of uncertain significance

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity to setmelanotide or any of its excipients
- Boxed warning(s): 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:
  - Stature-for-age and Weight-for-age percentiles
    - Boys 2 to 20 years: https://www.cdc.gov/growthcharts/data/set2clinical/cj41c071.pdf
    - Girls 2 to 20 years: https://www.cdc.gov/growthcharts/data/set2clinical/cj41c072.pdf
  - BMI-for-age
    - Boys 2 to 20 years: https://www.cdc.gov/growthcharts/data/set2clinical/cj41c073.pdf
    - Girls 2 to 20 years: https://www.cdc.gov/growthcharts/data/set2clinical/cj41c074.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

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Obesity due to POMC, PCSK1, or LEPR deficiency or due to BBS</td><td>≥ 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

Age 2 to < 6 years: 0.5 mg SC once daily for 2 weeks; if tolerated, titrate up to recommended maintenance dose SC once daily as determined by body weight:
<table>
<tr><th>Patient Weight/Treatment Week</th><th>Daily Dose</th></tr>
<tr><td colspan="2">15 kg to less than 20 kg</td></tr>
<tr><td>• Week 1 and onward</td><td>0.5 mg</td></tr>
<tr><td colspan="2">20 kg to less than 30 kg</td></tr>
<tr><td>• Week 1-2</td><td>0.5 mg</td></tr>
<tr><td>• Week 3 and onward</td><td>1 mg</td></tr>
<tr><td colspan="2">30 kg to less than 40 kg</td></tr>
<tr><td>• Weeks 1-2</td><td>0.5 mg</td></tr>
<tr><td>• Weeks 3-4</td><td>1 mg</td></tr>
<tr><td>• Week 5 and onward</td><td>1.5 mg</td></tr>
<tr><td colspan="2">Greater than or equal to 40 kg</td></tr>
<tr><td>• Weeks 1-2</td><td>0.5 mg</td></tr>
<tr><td>• Weeks 3-4</td><td>1 mg</td></tr>
<tr><td>• Weeks 5-6</td><td>1.5 mg</td></tr>
<tr><td>• Weeks y and onward</td><td>2 mg</td></tr>
</table></td><td>Age ≥ 6 years: 3 mg/day

Age < 6 years: See regimen</td></tr>
</table>

VI. Product Availability

Vial: 10 mg/mL (1 mL multi-dose)

VII. References

1. Imcivree Prescribing Information. Boston, MA: Rhythm Pharmaceuticals, Inc.; December 2024. Available at: https://www.imcivree.com. Accessed January 9, 2025.
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.
5. Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics. 2023 Feb 1;151(2):e2022060640. doi: 10.1542/peds.2022-060640. PMID: 36622115.
6. Malhotra S, Sivasubramanian R, and Srivastava G. Evaluation and management of early onset genetic obesity in childhood. Journal of Pediatric Genetics 2021;10(3):194-204.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	01.05.21	02.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	11.11.22	02.23
1Q 2024 annual review: no significant changes; references reviewed and updated.	11.13.23	02.24
1Q 2025 annual review: for BBS initial criteria, added standard approval language for Commercial line of business of "6 months or to the member's renewal date, whichever is longer"; updated contraindications section to include hypersensitivity to setmelanotide or any of its excipients per PI; references reviewed and updated. RT4: updated criteria to reflect pediatric extension for age ≥ 2 years per PI.	01.09.25	02.25

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.