

Clinical Policy: Setmelanotide (Imcivree)

Reference Number: PA.CP.PHAR.491

Effective Date: 11/2022

Last Review Date: 01/2026

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 in adults and pediatric patients aged:

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

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 acquired HO, BBS, or POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity

Policy/Criteria

It is the policy of PA Health & Wellness 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 one of the following (a or b):
 - a. POMC, PCSK1, or LEPR deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes are interpreted as pathogenic, likely pathogenic, or of uncertain significance (*see Appendix D*);
 - b. BBS confirmed by genetic testing or clinically per Beales criteria with ONE of the following (i or ii):
 - i. Member has at least 4 primary features of BBS: rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism in males, renal anomalies; OR
 - ii. Both of the following (1 and 2):
 1. Member has at least 3 primary features of BBS: rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism in males, renal anomalies;
2. Member has at least 2 secondary features of BBS: 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; Prescribed by or in consultation with an endocrinologist or expert in rare genetic disorders of obesity;
3. Member meets one of the following (a, b or c):
 - a. Age ≥ 2 and < 6 years with body mass index (BMI) $\geq 97^{\text{th}}$ 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: $\geq 95^{\text{th}}$ percentile;
 - ii. BBS: $\geq 97^{\text{th}}$ percentile;
 - c. Age ≥ 18 years of age and body mass index (BMI) $\geq 30 \text{ kg/m}^2$;
 4. Weight $\geq 15 \text{ kg}$;
 5. Documentation of baseline weight (in past 60 days) in kilograms;
 6. Documentation of creatinine clearance $\geq 15 \text{ mL/min/1.73 m}^2$;
 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. For age ≥ 6 years: Member has documentation of counseling regarding lifestyle changes and behavioral modification (e.g., healthy diet and increased physical activity);
 9. Dose does not exceed 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 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: 12 months

B. Acquired Obesity Disorder (must meet all):

1. Member has hypothalamic injury;
2. Documentation of weight gain associated with hypothalamic injury and one of the following (a or b):
 - a. Age 4 to < 18 years: BMI $\geq 95^{\text{th}}$ percentile standardized for age and sex;
 - b. Age 18 years older: BMI $\geq 30 \text{ kg/m}^2$;
3. For age ≥ 6 years: Member has documentation of counseling regarding lifestyle changes and behavioral modification (e.g., healthy diet and increased physical activity);
4. Dose does not exceed the following (a and b):
 - a. First 2 weeks: 0.5mg per day;
 - b. Maintenance (i or ii):

- i. Age \geq 4 years and $<$ 6 years: the FDA approved maximum recommended dose based on weight (*see Section V*);
- ii. Age \geq 6 years: 3mg per day.

Approval duration: 12 months

C. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. Genetic Obesity Disorders (must meet all):

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by one of the following (a, or b):
 - a. Initial re-authorization: After 1 year of treatment, reduction of at least 5% of baseline body weight or 5% of baseline BMI;
 - b. Subsequent re-authorizations for all indications: Maintenance of \geq 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 \geq 2 years and $<$ 6 years: the FDA approved maximum recommended dose based on weight (*see Section V*);
 - b. Age \geq 6 years: 3 mg per day.

Approval duration: 12 months

B. Acquired Obesity Disorder (must meet all):

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
 - a. Initial re-authorization: After 1 year of treatment, reduction of at least 5% of baseline body weight or 5% of baseline BMI;
 - b. Subsequent re-authorizations for all indications: Maintenance of \geq 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 \geq 4 years and $<$ 6 years: the FDA approved maximum recommended dose based on weight (*see Section V*);
 - b. Age \geq 6 years: 3 mg per day.

Approval duration: 12 months

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.PHARM.01) applies; or

- Approval duration: 6 months;**
or
2. Refer to PA.CP.PMN.53

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 – PA.CP.PMN.53;
- B. Obesity disorders not caused by POMC, PCSK1, or LEPR deficiency or by BBS or acquired HO;
- 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

HO: hypothalamic obesity

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>

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose																														
Obesity due to POMC, PCSK1, or LEPR deficiency or due to BBS	<p>≥ 12 years and older: 2 mg SC once daily for 2 weeks; if tolerated, titrate up to 3 mg SC once daily</p> <p>Age 6 to <12 years: 1 mg SC once daily for 2 weeks; if tolerated, titrate up to 3 mg SC once daily</p> <p>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:</p> <table border="1" data-bbox="574 720 1167 1346"> <thead> <tr> <th data-bbox="574 720 987 793">Patient Weight/Treatment Week</th> <th data-bbox="987 720 1167 793">Daily Dose</th> </tr> </thead> <tbody> <tr> <td colspan="2" data-bbox="574 793 1167 831">15 kg to less than 20 kg</td> </tr> <tr> <td data-bbox="574 831 987 869">• Week 1 and onward</td> <td data-bbox="987 831 1167 869">0.5 mg</td> </tr> <tr> <td colspan="2" data-bbox="574 869 1167 907">20 kg to less than 30 kg</td> </tr> <tr> <td data-bbox="574 907 987 945">• Week 1-2</td> <td data-bbox="987 907 1167 945">0.5 mg</td> </tr> <tr> <td data-bbox="574 945 987 982">• Week 3 and onward</td> <td data-bbox="987 945 1167 982">1 mg</td> </tr> <tr> <td colspan="2" data-bbox="574 982 1167 1020">30 kg to less than 40 kg</td> </tr> <tr> <td data-bbox="574 1020 987 1058">• Weeks 1-2</td> <td data-bbox="987 1020 1167 1058">0.5 mg</td> </tr> <tr> <td data-bbox="574 1058 987 1096">• Weeks 3-4</td> <td data-bbox="987 1058 1167 1096">1 mg</td> </tr> <tr> <td data-bbox="574 1096 987 1134">• Week 5 and onward</td> <td data-bbox="987 1096 1167 1134">1.5 mg</td> </tr> <tr> <td colspan="2" data-bbox="574 1134 1167 1171">Greater than or equal to 40 kg</td> </tr> <tr> <td data-bbox="574 1171 987 1209">• Weeks 1-2</td> <td data-bbox="987 1171 1167 1209">0.5 mg</td> </tr> <tr> <td data-bbox="574 1209 987 1247">• Weeks 3-4</td> <td data-bbox="987 1209 1167 1247">1 mg</td> </tr> <tr> <td data-bbox="574 1247 987 1285">• Weeks 5-6</td> <td data-bbox="987 1247 1167 1285">1.5 mg</td> </tr> <tr> <td data-bbox="574 1285 987 1323">• Weeks 7 and onward</td> <td data-bbox="987 1285 1167 1323">2 mg</td> </tr> </tbody> </table>	Patient Weight/Treatment Week	Daily Dose	15 kg to less than 20 kg		• Week 1 and onward	0.5 mg	20 kg to less than 30 kg		• Week 1-2	0.5 mg	• Week 3 and onward	1 mg	30 kg to less than 40 kg		• Weeks 1-2	0.5 mg	• Weeks 3-4	1 mg	• Week 5 and onward	1.5 mg	Greater than or equal to 40 kg		• Weeks 1-2	0.5 mg	• Weeks 3-4	1 mg	• Weeks 5-6	1.5 mg	• Weeks 7 and onward	2 mg	<p>Age ≥ 6 years: 3 mg/day</p> <p>Age < 6 years: See regimen</p>
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Obesity due to hypothalamic injury	<p>≥6 years and older:</p> <table border="1" data-bbox="574 1383 1167 1577"> <thead> <tr> <th data-bbox="574 1383 906 1421">Week</th> <th data-bbox="906 1383 1167 1421">Daily Dose</th> </tr> </thead> <tbody> <tr> <td data-bbox="574 1421 906 1459">Week 1-2</td> <td data-bbox="906 1421 1167 1459">0.5 mg</td> </tr> <tr> <td data-bbox="574 1459 906 1497">Week 3-4</td> <td data-bbox="906 1459 1167 1497">1 mg</td> </tr> <tr> <td data-bbox="574 1497 906 1535">Week 5-6</td> <td data-bbox="906 1497 1167 1535">2 mg</td> </tr> <tr> <td data-bbox="574 1535 906 1572">Week 7 and onward</td> <td data-bbox="906 1535 1167 1572">3 mg</td> </tr> </tbody> </table> <p>Age 4 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:</p> <table border="1" data-bbox="574 1759 1167 1869"> <thead> <tr> <th data-bbox="574 1759 987 1833">Patient Weight/Treatment Week</th> <th data-bbox="987 1759 1167 1833">Daily Dose</th> </tr> </thead> <tbody> <tr> <td colspan="2" data-bbox="574 1833 1167 1869">15 kg to less than 20 kg</td> </tr> </tbody> </table>	Week	Daily Dose	Week 1-2	0.5 mg	Week 3-4	1 mg	Week 5-6	2 mg	Week 7 and onward	3 mg	Patient Weight/Treatment Week	Daily Dose	15 kg to less than 20 kg		<p>Age ≥ 6 years: 3 mg/day</p> <p>Age < 6 years: See regime</p>																
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Indication	Dosing Regimen		Maximum Dose	
	• Week 1 and onward	0.5 mg		
	20 kg to less than 30 kg			
	• Week 1-2	0.5 mg		
	• Week 3 and onward	1 mg		
	30 kg to less than 40 kg			
	• Weeks 1-2	0.5 mg		
	• Weeks 3-4	1 mg		
	• Week 5 and onward	1.5 mg		
	Greater than or equal to 40 kg			
	• Weeks 1-2	0.5 mg		
	• Weeks 3-4	1 mg		
	• Weeks 5-6	1.5 mg		
	• Weeks 7 and onward	2 mg		

VI. Product Availability

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

VII. References

1. Imcivree Prescribing Information. Boston, MA: Rhythm Pharmaceuticals, Inc.; March 2026. Available at: <https://www.imcivree.com/>. Accessed April 22, 2026.
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
Policy created	10/2022
1Q 2023 annual review: no significant changes; references reviewed and updated.	01/2023
1Q 2024 annual review: no significant changes; references reviewed and updated.	01/2024
1Q 2025 annual review: updated contraindications section to include hypersensitivity to setmelanotide or any of its excipients per PI; references reviewed and updated.	01/2025
1Q 2026 annual review: RT4: updated criteria to reflect pediatric extension for age ≥ 2 years per PI; For BBS diagnosis, moved the clinical criteria components of the Beales criteria into the initial criteria (previously listed within Appendix D); added criteria for FDA approved acquired hypothalamic obesity (HO); references reviewed and updated.	01/2026