Addendum to the Protocol for Imcivree® (setmelanotide)
July 2025

DURB Approval Dates	**10/2021; 1/2023, 7/2025**
Commissioners Approval Dates	**5/23/2022; 2/7/2024**

Addendum:
The purpose of this addendum is to update the age and allow Imcivree for patients 2 years of age and older based on the recent FDA approval. Initial criteria defining obesity have been updated based on the Centers for Disease Control and Prevention (CDC) definition. The continuation of therapy criteria pertaining to therapy response have been updated based on prescribing information changes.

Background:

- Obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency is an ultra-rare disease caused by variants in POMC, PCSK1 or LEPR genes that impair the melanocortin-4 receptor (MC4R) pathway, which is a pathway in the hypothalamus that is responsible for regulating hunger, energy expenditure and consequently body weight. People living with obesity due to POMC, PCSK1 or LEPR deficiency struggle with extreme, insatiable hunger beginning at a young age, resulting in early-onset, severe obesity.
- Bardet-Biedl syndrome is a rare genetic disorder with highly variable symptoms which may include retinal degeneration, obesity, reduced kidney function, polydactyly (extra digits of the hands or feet) among many other features.

Imcivree is MC4 receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to:

- POMC, PCSK1, or 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).
- Bardet-Biedl syndrome (BBS)

As an MC4R agonist, Imcivree is designed to restore impaired MC4R pathway activity arising due to genetic deficits upstream of the MC4 receptor.

Criteria for approval:

Patient meets **ALL** the following:

1. Diagnosis of obesity as defined by the Centers for Disease Control and Prevention (CDC) as:
    a. Patients 20 years or older with BMI $\geq$ 30 kg/m^2
    b. Patients less than 20 years of age with BMI $\geq$ 95th percentile
2. Documented diagnosis of obesity due to ONE of the following:
    a. POMC, PCSK1, or LEPR deficiency with genetic testing confirming that variants in the POMC, PCSK1, and/or LEPR genes are interpreted as pathogenic, likely pathogenic, or of uncertain significance
    b. Confirmed Bardet-Biedl syndrome (BBS)
3. Patient is of the FDA-labeled or compendial approved age
4. Medication is prescribed by or in consultation with an endocrinologist or expert in rare genetic disorders of obesity

5. Documentation of estimated glomerular filtration rate [eGFR] ≥ 15 mL/min/1.73 m^2 is provided
6. Patient does not have any contraindications to therapy
7. The medication requested is prescribed in accordance with a Food and Drug Administration (FDA) established indication and dosing regimens or in accordance with a medically-appropriate off-label indication and dosing according to American Hospital Formulary Service, Micromedex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs (Lexicomp), national guidelines, or other peer-reviewed evidence

Exclusions:

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

a. Obesity due to suspected POMC-, PCSK1-, or LEPR-deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign
b. Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including other genetic syndromes and general (polygenic) obesity

Initial Approval Duration: 6 months

Continuation of therapy:

1. For patients ≥6 years of age and older with obesity due to ONE of the following:
    a. POMC, PCSK1, or LEPR deficiency there is a documented positive response to therapy as evidenced by a reduction in BMI at 1 year from baseline
    b. Bardet-Biedl Syndrome there is a documented positive response to therapy as evidenced by a reduction in BMI at 1 year from baseline
2. For patients aged 2 to less than 6 years of age with obesity due POMC, PCSK1, or LEPR deficiency, or Bardet-Biedl Syndrome, there is a documented positive response to therapy as evidenced by a reduction in BMI at 1 year from baseline
3. The medication requested is prescribed in accordance with a Food and Drug Administration (FDA) established indication and dosing regimens or in accordance with a medically appropriate off-label indication and dosing according to American Hospital Formulary Service, Micromedex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs (Lexicomp), national guidelines, or other peer-reviewed evidence

Renewal Approval Duration: 12 months

References:

1. Imcivree® injection [prescribing information]. Rhythm Pharmaceuticals, Inc. Boston, MA 021116. December 2024.
2. Clinical Pharmacology® Gold Standard Series [Internet database]. Tampa FL. Elsevier 2019. Updated periodically.
3. Ayers KL, Glicksberg BS et al. Melanocortin 4 Receptor Pathway Dysfunction in Obesity: Patient Stratification Aimed at MC4R Agonist Treatment. J Clin Endocrinol Metab. 2018 Jul; 103(7): 2601–2612.
4. Wabitsch M, Flück CE, et all. Natural History of Obesity Due to POMC, PCSK1, and LEPR Deficiency and the Impact of Setmelanotide. J Endocr Soc. 2022 Apr 15;6(6).
5. Forsythe, E., Beales, P. Bardet–Biedl syndrome. Eur J Hum Genet 21, 8–13 (2013)
6. Beales PL, Elcioglu N, Woolf AS, et al. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999;36:437-446.
7. Centers for Disease Control and Prevention. (2024, June 28). Child and Teen BMI Categories. Retrieved June 12, 2025, from https://www.cdc.gov/bmi/child-teen-calculator/index.html
8. Centers for Disease Control and Prevention. (2024, June 28). Adult BMI Categories. Retrieved June 12, 2025, from https://www.cdc.gov/bmi/adult-calculator/bmi-categories.html#cdc_generic_section_3-adult-bmi-calculator