Addendum to Protocol for Imcivree® (setmelanotide)

Approved January 2023
Approved October 2021

Addendum:
Addition of new FDA-approved indication for chronic weight management in adult and pediatric patients 6 years of age and older ***with monogenic or syndromic obesity due to Bardet-Biedl syndrome (BBS)*** *– June 16, 2022*

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 defined as:
    a. Adults (18 years or older): BMI ≥ 30 kg/m2
    b. Children (younger than 18 years old): ≥ 95th weight percentile based on growth charts.

2. 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. Bardet-Biedl syndrome (BBS) confirmed by identification of characteristic findings (e.g., rod-cone dystrophy, polydactyly)
3. Patient is 6 years of age or older.
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 m2
6. Medication is prescribed in accordance with Food and Drug Administration (FDA) established indication and dosing regimens or in accordance with 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 obesity associated with other genetic syndromes and general (polygenic) obesity.

Initial Approval: 4 months

Continuation of therapy:

1. For members with obesity due to POMC, PCSK1, or LEPR deficiency: Member is responding positively to therapy as evidenced by one of the following:
    a. After 16 weeks of treatment: reduction in weight compared with baseline (at least 5% body weight or 5% of BMI)
    b. After 1 year: ≥ 10% reduction in weight compared with baseline
    c. After > 1 year: maintenance of ≥ 10% reduction in weight compared with baseline
2. For members with Obesity and BBS, member responded positively to 1 year of therapy with:
    a. For children younger than 18 years old: ≥ 5% reduction of baseline BMI
    b. For 18 years and older: ≥ 5% reduction of baseline body weight

3. Medication is prescribed in accordance with Food and Drug Administration (FDA) established indication and dosing regimens or in accordance with 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: 12 months

References:

1. Imcivree® injection [prescribing information]. Rhythm Pharmaceuticals, Inc. Boston, MA 021116. June 2022
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)