New Drug Fact Blast

Clinical Services

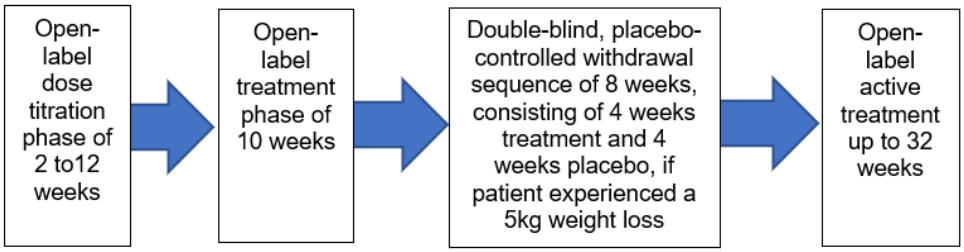
Drug/Manufacturer:	**Imcivree™ (setmelanotide) [Rhythm Pharmaceuticals]**
Dosage Formulations:	10 mg/mL injection in a 1-mL multiple-dose vial
FDA Approval Date: **FDB File Date:**	FDA: November 27, 2020 FDB: December 28, 2020
Indication:	Indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).
Mechanism of Action:	Imcivree is a melanocortin-4 receptor (MC4R) agonist that is intended to partially or completely restore signaling at the MC4 receptor.

Dose/ Administration:	• Adult and pediatric patients 12 years of age or older:
	  ○ Starting dose: 2 mg injected subcutaneously (SC) once daily for 2 weeks.
	  ○ Monitor patients for gastrointestinal (GI) adverse reactions. If the starting dose is not tolerated, reduce to 1 mg once daily.
	  ○ If the 1 mg daily dose is tolerated and additional weight loss is desired, titrate to 2 mg once daily.
	  ○ If the 2 mg daily dose is tolerated, increase the dose to 3 mg once daily.
	  ○ If the 3 mg daily dose is not tolerated, maintain administration of 2 mg once daily.
	• Pediatric patients 6 to 12 years of age:
	  ○ Starting dose: 1 mg injected SC once daily for 2 weeks.
	  ○ Monitor patients for GI adverse reactions. If the starting dose is not tolerated, reduce to 0.5 mg once daily.
	  ○ If the 0.5 mg daily dose is tolerated and additional weight loss is desired, titrate to 1 mg once daily.
	  ○ If the 1 mg daily dose is tolerated, increase the dose to 2 mg once daily.
	  ○ If the 2 mg daily dose is not tolerated, reduce to 1 mg once daily.
	  ○ If the 2 mg daily dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg once daily.
	• Evaluate weight loss after 12 to 16 weeks of treatment. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline body mass index (BMI) for patients with continued growth potential, discontinue Imcivree as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Disease State Clinical Highlights:	• Deficiencies in POMC, PCSK1, and LEPR, which are ultra-rare and underdiagnosed, are caused by variants in *POMC*, *PCSK1* or *LEPR* genes and impair the MC4 receptor pathway in the hypothalamus. This pathway is responsible for regulating hunger and energy expenditure. • Patients with these deficiencies experience symptoms such as extreme hunger and subsequent weight gain manifesting in morbid obesity, often as early as infancy. These patients can also experience many comorbid disorders of the endocrine system like adrenal insufficiency, hypothyroidism, and hypogonadism. • Obesity due to POMC/PCSK1 deficiency has been described in approximately 50 patients in the medical literature, with an estimated prevalence of less than 1 in 1,000,000. Prevalence of obesity due to LEPR deficiency has not been described. Rhythm Pharmaceuticals is currently aware of 20 patients in the United States with these genetic deficiencies, 10 of whom are of age to qualify for therapy at launch.

Drug Clinical Highlights:

- Imcivree is the only FDA-approved treatment for patients with obesity due to POMC, PCSK1, and LEPR deficiency. The approval of Imcivree was based on the results of two (NCT02896192 and NCT03287960) identically designed, open label, single-arm, multicenter, multi-phase clinical trials which included a total of 27 patients.
- Study design:



- Key Exclusion Criteria
  - Prior gastric bypass surgery resulting in > 10% weight loss durably maintained from the baseline preoperative weight, with no evidence of weight regain
  - Any suicidal ideation of Type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS), any lifetime history of suicide attempt, or any suicidal behavior in the last month
  - A Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 (severe depression)
  - History or presence of impaired renal function
- Efficacy Results:

Imcivree Clinical Trials	Study 1: POMC/PCSK1 (n = 10)	Study 2: LEPR (n = 11)
Primary Endpoint: Proportion of participants who achieved ≥ 10% weight loss compared with baseline at approximately 1 year	8 (80%) P < 0.0001	5 (45.5%) P = 0.0002
Key Secondary Endpoint: Mean percentage change from baseline in weight at 1 year	−23.1%	−9.7%
Key Secondary Endpoint: Median change from baseline to 1 year in the most hunger score of the 11-point Likert-type scale* in participants 12 years of age or older	−2.0	−3.0

*Likert-type scale: 0 = “not hungry at all” and 10 = “hungriest possible”

- In Study 1, 80% of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint, achieving a ≥ 10% weight loss after 1 year of treatment with Imcivree. In Study 2, 46% of patients with obesity due to LEPR deficiency achieved a ≥ 10% weight loss after 1 year of treatment with Imcivree.
- Safety/Warnings
  - Disturbance in sexual arousal: Sexual adverse reactions may occur in patients treated with Imcivree. Spontaneous penile erections in males and sexual adverse reactions in females occurred in clinical studies with Imcivree.
  - Depression and suicidal ideation: Some drugs that target the central nervous system, such as Imcivree, may cause depression or suicidal ideation.
  - Skin pigmentation and darkening of pre-existing nevi: Imcivree may cause generalized increased skin pigmentation and darkening of pre-existing nevi due to its pharmacologic effect.

	○ Risk of serious adverse reactions due to benzyl alcohol preservative in neonates and low-birth-weight infants: Imcivree is not approved for use in neonates or infants. • Most common adverse reactions (incidence ≥ 23%): injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection. • Of note, 11% of participants experienced the adverse reaction of suicidal ideation.
Price Per Unit (WAC):	• $330 per milligram • 1 mL multiple-dose vial containing 10 mg/mL will cost $3,300. • At the maximum dose of 3 mg/day, cost is approximately $360,000 per year. • Considering the average dose in clinical trials was closer to 2 mg daily, cost is approximately $240,000 annually.
Therapeutic Alternatives:	• Imcivree is the only member of its class and is a melanocortin-4 receptor (MC4R) agonist that is intended to partially or completely restore signaling at the MC4 receptor, thus directly impacting the cause of the obesity. • There are no FDA-approved treatment alternatives that target the underlying cause of obesity in this patient population.
Prior Authorization Approval Criteria:	**Must meet the following criteria:** <u>Initial Therapy:</u> • Diagnosis of obesity, defined as: ○ Adult patients: BMI of ≥ 30 kg/m2 ○ Pediatric patients: ≥ 95th percentile using growth chart assessments **AND** • Obesity is due to a homozygous or presumed compound heterozygous variant in at least one of the following genes, confirmed by genetic testing: ○ Proopiomelanocortin (*POMC*) ○ Proprotein convertase subtilisin/kexin type 1 (*PCSK1*) ○ Leptin receptor (*LEPR*) **AND** • Documentation of genetic testing demonstrating that the variants in *POMC*, *PCSK1*, or *LEPR* genes are interpreted as pathogenic, likely pathogenic, or VUS **AND** • Participant is 6 years of age or older **AND** • Participant has a CrCl ≥ 30 mL/min • Coverage will not be provided in the following circumstances: ○ Variants in *POMC*, *PCSK1*, or *LEPR* genes which are interpreted as benign or likely benign ○ Prior gastric bypass surgery resulting in > 10% weight loss that was maintained • Initial authorization approved for 4 months <u>Continuation of Therapy:</u> • Documentation of response to therapy, as evidenced by: ○ At least a 5% reduction in baseline body weight **OR** ○ At least a 5% reduction in baseline BMI for patients with continued growth potential • Demonstration of treatment adherence **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Before starting treatment with Imcivree, and at each follow up, patients should be screened for severe depression and any suicidal ideation. If either criterion is met, therapy should not be prescribed or continued.

Implication to State Medicaid Program:	• LOE: August 2032 • Genetic testing is required to confirm diagnosis, and therefore must be considered in cost and coverage determination. Rhythm Pharmaceuticals sponsors the Uncovering Rare Obesity Program through which patients in the United States can receive a free genetic test through a Clinical Laboratory Improvement Amendments–certified independent laboratory if they meet certain eligibility criteria. In addition to the test, the program includes access to genetic counselors and two counseling sessions. • Treatment adherence should be considered as trials demonstrated that patients who stop taking Imcivree, even for a brief period, regain a significant amount of weight and had worsened hunger scores. While expected, the magnitude is significant enough to be considered in criteria as maintaining weight loss will require life-long treatment. • Treatment for Bardet-Biedl syndrome and Alström syndrome are currently in Phase 3 trials with data expected by Q1 2021.

References:

1. Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; 2020
2. Clément 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 POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol. 2020;8(12):960-970. doi:10.1016/S2213-8587(20)30364-8.
3. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30.
4. Rhythm Pharmaceuticals. Our Focus. Available at: https://www.rhythmtx.com/our-focus/. Accessed December 10, 2020.
5. Rhythm Pharmaceuticals Announces FDA Approval of IMCIVREE™ (setmelanotide) as First-ever Therapy for Chronic Weight Management in Patients with Obesity Due to POMC, PCSK1 or LEPR Deficiency. News release. Rhythm Pharmaceuticals, Inc. November 27, 2020. Available at: https://ir.rhythmtx.com/news-releases/news-release-details/rhythm-pharmaceuticals-announces-fda-approval-imcivreetm. Accessed December 10, 2020.
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