NEW DRUG APPROVAL

Brand Name	Imcivree®
Generic Name	setmelanotide
Drug Manufacturer	Rhythm Pharmaceuticals, Inc.

New Drug Approval

FDA Approval Date: November 25, 2020

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity

Dispensing Restriction: Specialty Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Obesity is a very common condition worldwide that has various possible etiologies. There is a growing body of literature that describes rare genetic variants implicated in the melanocortin pathway that cause severe obesity. This pathway consists of neurons that run through the hypothalamus and activate the MC4R and is responsible for regulating hunger and energy expenditure. The POMC-, PCSK1-, and LEPR-expressing neurons are all involved in this pathway. Biallelic variants in POMC, PCSK1, and LEPR are rare genetic disorders that can result in deficiencies that cause obesity.

Due to a lack of awareness and overlapping clinical features with other causes of obesity, POMC, PCSK1, and LEPR deficiencies remain underdiagnosed. These conditions may be more obvious in very young children, as the obesity is often extreme and can onset in early infancy. Although there are very few patients currently identified in the United States with these deficiencies (~20), Rhythm Pharmaceuticals estimates there may be around 100 to 500 U.S. patients with POMC- or PCSK1-deficiency obesity and around 500 to 2,000 U.S. patients with LEPR-deficiency obesity.

Efficacy

The safety and efficacy of Imcivree® for chronic weight management in patients with obesity due to POMC, PCSK1, and LEPR deficiency were assessed in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period. Study 1 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT03287960) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency.

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Table 1. Imcivree Clinical Trials

	Study 1 (NCT02896192)	Study 2 (NCT03287960)
Study Design	• Open label, single-arm, multicenter (Canada, United States, and EU), multi-phase: Open-label dose titration phase (2–12 weeks) → Open-label treatment phase (10 weeks) → Double-blind, placebo-controlled withdrawal sequence* (8 weeks) → Open-label active treatment (up to 32 weeks) *Patients only went on to the withdrawal sequence if they experienced a 5 kg reduction in weight (or ≥5% weight loss for participants with baseline body weight <100 kg). During this phase, patients received 4 weeks of Imcivree followed by 4 weeks of placebo.	
Study Population	• Genetically confirmed or suspected POMC or PCSK1 deficiency • Median baseline BMI: 40 kg/m²	• Genetically confirmed or suspected LEPR deficiency • Median baseline BMI: 46.6 kg/m²

Key Inclusion Criteria	• 6 years of age and older (62% adults)
	• Obesity, defined as:
	  ○ Adult patients: BMI of ≥30 kg/m²
	  ○ Pediatric patients: ≥95th percentile using growth chart assessments
	• Homozygous or presumed compound heterozygous variants that are interpreted as pathogenic, likely pathogenic, or VUS	

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 as indicated by clinically significant abnormal creatinine, blood urea nitrogen, or urinary constituents or moderate to severe renal dysfunction as defined by creatinine clearance (CrCl) <30 mL/min	
Interventions	Open-label dose titration phase: • Adults started at Imcivree 1 mg SC once daily • Pediatric patients (<18 years) started at 0.5 mg SC once daily • Dose up-titrated every 2 weeks by 0.5 mg until reaching therapeutic dose, defined as weight loss of ~2–3 kg/week for adults or ~1–2 kg/week for pediatric patients ○ Maximum dose of 3 mg per day All subsequent phases: patients received Imcivree at established therapeutic dose	

Efficacy Results

Table 2. Imcivree Clinical Trials Efficacy Endpoints (NCT02896192 and NCT03287960)

	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"

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection.

WARNINGS & PRECAUTIONS

- Disturbance in sexual arousal: Spontaneous penile erections in males and sexual adverse reactions in females occurred with Imcivree®. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.
- Depression and suicidal ideation: Depression and suicidal ideation have occurred with Imcivree®. Monitor patients for new onset or worsening depression. Consider discontinuing Imcivree® if patients experience suicidal thoughts or behaviors.
- Skin Pigmentation and Darkening of Pre-Existing Nevi: Imcivree® may cause generalized increased skin pigmentation and darkening of pre-existing nevi. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.
- 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. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

CONTRAINDICATIONS

- None.

Clinical Pharmacology

MECHANISMS OF ACTION

Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. In patients with obesity due to POMC, PCSK1, and LEPR deficiency associated with insufficient activation of the MC4

receptor, setmelanotide may re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.

Dose & Administration

ADULTS

- Age 12 years and older: The starting dose is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for gastrointestinal (GI) adverse reactions.
- If the starting dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 1 mg once daily dose is tolerated and additional weight loss is desired, titrate to 2 mg (0.2 mL) once daily.
- If the 2 mg daily dose is tolerated, increase the dose to 3 mg (0.3 mL) once daily. If the 3 mg once daily dose is not tolerated, maintain administration of 2 mg (0.2 mL) once daily.

PEDIATRICS

- For pediatric patients aged 6 to less than 12 years, the starting dose of Imcivree® is 1 mg (0.1 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for GI adverse reactions.
- If the starting dose is not tolerated, reduce to 0.5 mg (0.05 mL) once daily. If the 0.5 mg once daily dose is tolerated and additional weight loss is desired, the dose may be increased to 1 mg (0.1 mL) once daily.
- If the 1 mg dose is tolerated, increase the dose to 2 mg (0.2 mL) once daily.
- If the 2 mg once daily dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 2 mg once daily dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg (0.3 mL) once daily.

GERIATRICS

Clinical studies of Imcivree® did not include patients aged 65 and over. It is not known whether they respond differently from younger patients.

RENAL IMPAIRMENT

Population pharmacokinetic analysis suggests decreased clearance in patients with renal impairment. The majority of patients in the clinical studies had normal renal function.

HEPATIC IMPAIRMENT

Not available.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 10 mg/mL solution in a 1 mL multiple-dose vial.