

Imcivree™ (setmelanotide) – New orphan drug approval

- On November 27, 2020, [Rhythm Pharmaceuticals](#) announced the [FDA approval](#) of [Imcivree \(setmelanotide\)](#), 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 in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).
- 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 POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.
- Obesity due to POMC, PCSK1 or LEPR deficiency are ultra-rare diseases caused by variants in *POMC*, *PCSK1* or *LEPR* genes that impair the melanocortin-4 (MC4) receptor 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.
- Imcivree is the first FDA approved therapy for these rare genetic diseases of obesity. Imcivree is a MC4 receptor agonist and it is believed to work by restoring impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor.
- The efficacy of Imcivree was established in two identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period. Study 1 included 10 patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency and study 2 included 11 patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency. The primary endpoint was achieving $\geq 10\%$ weight loss after 1 year of treatment with Imcivree.
 - In study 1, 8 of 10 patients (80%, 95% CI: 44.4, 97.5; $p < 0.0001$) achieved the primary endpoint. In study 2, 5 of 11 patients (45.5%, 95% CI: 16.8, 76.6; $p = 0.0002$) achieved the primary endpoint.
 - When treatment with Imcivree was withdrawn in the 16 patients who had lost at least 5 kg (or 5% of body weight if baseline body weight was < 100 kg) during the 10-week open-label period, these patients gained an average of 5.5 kg in study 1 and 5.0 kg in study 2 over 4 weeks. Re-initiation of treatment resulted in subsequent weight loss.
- Warnings and precautions for Imcivree include disturbance in sexual arousal, depression and suicidal ideation, skin pigmentation and darkening of pre-existing nevi, and risk of serious adverse reactions due to benzyl alcohol preservative in neonates and low birth weight infants.
- The most common adverse reactions ($\geq 23\%$) with Imcivree use were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection.

- In adults and pediatric patients 12 years of age and older, the starting dose of Imcivree is 2 mg injected subcutaneously (SC) once daily for 2 weeks. Patients should be monitored for gastrointestinal (GI) adverse reactions.
 - If the starting dose is not tolerated, reduce to 1 mg once daily. If the 1 mg once daily dose is tolerated and additional weight loss is desired, titrate to 2 mg once daily.
 - If the 2 mg daily dose is tolerated and additional weight loss is desired, increase the dose to 3 mg once daily. If the 3 mg once daily dose is not tolerated, maintain administration of 2 mg once daily.
- For pediatric patients aged 6 to less than 12 years, the starting dose of Imcivree is 1 mg injected SC once daily for 2 weeks. Patients should be monitored for GI adverse reactions.
 - If the starting dose is not tolerated, reduce to 0.5 mg 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 once daily.
 - If the 1 mg dose is tolerated, increase the dose to 2 mg once daily.
 - If the 2 mg once daily dose is not tolerated, reduce to 1 mg 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 once daily.
- Weight loss should be evaluated 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 for patients with continued growth potential, Imcivree should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
- Prior to the initiation of Imcivree, patients should be trained on proper injection technique.
- Rhythm Pharmaceuticals plans to launch Imcivree in the first quarter of 2021. Imcivree injection will be available as a 10 mg/mL solution in a 1 mL multiple-dose vial.



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