Drug Monograph

Drug Name: **Imcivree™ (setmelanotide) Injection**
Drug Class: **Melanocortin Receptor Agonist Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Imcivree is available as a multiple-dose vial containing 10 mg of setmelanotide for subcutaneous injection.
Manufacturer:	Manufactured for: Rhythm Pharmaceuticals, Inc., Boston, MA 02116.
Summary of Findings:	The efficacy of Imcivree was demonstrated in two open-label studies enrolling 21 patients with proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiencies. The primary measure of efficacy was the proportion of participants who achieved ≥10% weight loss compared with baseline at approximately one year. Study 1 included patients with POMC and PCSK1 deficiencies. 80% of patients in study 1 achieved ≥10% weight loss at one year ($p<0.0001$). Study 2 included patients with LEPR deficiency, and 45.5% had ≥10% weight loss at one year ($p=0.0002$).
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1-3]

Biallelic variants in POMC, PCSK1 and LEPR are rare genetic disorders that can result in deficiencies that cause obesity. Obesity is very common and was estimated to affect 42% of the United States population in 2018. While there are various possible etiologies for obesity, one for considerationof 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 melanocortin 4 receptor and is responsible for regulating hunger and energy expenditure. The proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR)-expressing neurons are all involved in this pathway. Deficiencies in POMC, PCSK1, and LEPR cause 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. Due to a lack of awareness and overlapping clinical features with other causes of obesity, these rare genetic causes of obesity are undiagnosed.

Dosage Form [4]

Imcivree is available as a multiple-dose vial containing 10 mg of setmelanotide for subcutaneous injection.

Manufacturer [4]

Manufactured for: Rhythm Pharmaceuticals, Inc., Boston, MA 02116.

Indication(s) [4]

Imcivree is 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 in *POMC, PCSK1,* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

Clinical Efficacy [3,4] (mechanism of action/pharmacology, comparative efficacy)

Imcivree is a melanocortin 4 (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 reestablish MC4 receptor pathway activity to reduce hunger and promote weight loss through the decreased calorie intake and increased energy expenditure. Nonclinical evidence shows that MC4 receptors are important for setmelanotide-regulated appetite and weight loss. The MC1 receptor is

expressed on melanocytes, and activation of this receptor leads to accumulation of melanin and increased skin pigmentation independently of ultraviolet light.

Pharmacokinetics:

Protein Binding	79.1%
Volume of Distribution	48.7 L
Metabolism	Metabolized into small peptides by catabolic pathways
Excretion	Renal: 39%
Half-life	11 hours

Clinical Trials Experience: POMC or PCSK1 deficiency

STUDY 1 DESIGN	Open label, single-arm, multicenter, multi-phase (n=10)
INCLUSION CRITERIA	• Genetically confirmed or suspected POMC or PCSK1 deficiency • 6 years of age and older • Obesity defined as BMI of ≥ 30 kg/m^2 for adults, or ≥ 95th percentile using growth chart assessments in pediatric patients • Homozygous or presumed compound heterozygous variants that are interpreted as pathogenic, likely pathogenic, of VUS
EXCLUSION CRITERIA	• Prior gastric bypass surgery resulting in >10% weight loss durable maintained from the baseline preoperative weight, with no evidence of weight regain • Any suicide 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
TREATMENT REGIMEN	Patients received Imcivree (n=10) subcutaneously via open-label titration phase based on age: 1 mg once daily for adults, and 0.5 mg once daily for pediatric patients (<18 years) for 1 year. 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, up to a maximum dose of 3 mg per day.
RESULTS	The primary outcome measured was the proportion of patients who achieved ≥10% weight loss compared with baseline at approximately 1 year. 80% of the Imcivree-treated patients had ≥10% weight loss ($p<0.0001$).
SAFETY	Discussed in the Adverse Effects section below.

LEPR deficiency

STUDY 2 DESIGN	Open label, single-arm, multicenter, multi-phase (n=11)
INCLUSION CRITERIA	• Genetically confirmed or suspected LEPR deficiency • 6 years of age and older • Obesity defined as BMI of ≥ 30 kg/m^2 for adults, or ≥ 95th percentile using growth chart assessments in pediatric patients • Homozygous or presumed compound heterozygous variants that are interpreted as pathogenic, likely pathogenic, of VUS
EXCLUSION CRITERIA	• Prior gastric bypass surgery resulting in >10% weight loss durable maintained from the baseline preoperative weight, with no evidence of weight regain • Any suicide 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
TREATMENT REGIMEN	Patients received Imcivree (n=11) subcutaneously via open-label titration phase based on age: 1 mg once daily for adults, and 0.5 mg once daily for pediatric patients (<18 years) for 1 year. 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, up to a maximum dose of 3 mg per day.
RESULTS	The primary outcome measured was the proportion of patients who achieved ≥10% weight loss compared with baseline at approximately 1 year. 45.5% of the Imcivree-treated patients had ≥10% weight loss (p=0.0002).
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

- Disturbance in sexual arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred with Imcivree.
- Depression and suicidal ideation: Depression and suicidal ideation have occurred. Monitor for new onset for worsening depression.
- 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 for 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.

Adverse Effects [3,4]

Most common, ≥ 10 %	(n =27) %
Injection site reactions	96
Skin hyperpigmentation	78
Nausea	56
Headache	41
Diarrhea	37
Abdominal pain	33
Back pain	33
Fatigue	30
Vomiting	30
Depression	26
Upper respiratory tract infection	26
Spontaneous penile erection	23
Arthralgia	19
Asthenia	19
Dizziness	15
Dry mouth/skin	15
Insomnia	15
Vertigo	11
Alopecia	11
Chills	11
Constipation	11
Influenza-like illness	11
Muscle spasm	11
Pain in extremity	11
Rash	11
Suicidal ideation	11

Drug Interactions [3,4]

- Setmelanotide has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450, transporters and plasma protein binding. No clinical studies evaluation the drug-drug interaction potential of setmelanotide have been conducted.

Dosage and Administration [3,4]

Dosing in adult and pediatric patients 12 years of age and older:

- Starting dose is 2 mg injected subcutaneously once daily for 2 weeks. Monitor for GI adverse reactions.
    - If starting dose is not tolerated, reduce to 1 mg once daily.
- If the 2 mg daily dose is tolerated, increase the dose to 3 mg once daily.

Dosing in pediatric patients 6 to less than 12 years of age:

- Starting dose is 1 mg injected subcutaneously once daily for 2 weeks. Monitor for GI adverse reactions.
    - If starting dose is not tolerated, reduce to 0.5 mg once daily.
- If the 1 mg dose is tolerated, increase the dose to 2 mg once daily.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ml
Setmelanotide	Imcivree	Rhythm Pharmaceuticals	0.5 – 3 mg/day	$3,300

** Wholesale Acquisition Cost

Conclusion

Imcivree is indicated for the for chronic weight management in adult and pediatric patients 6 years of age and older with 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. The safety and efficacy of Imcivree was demonstrated in 2 open-label studies enrolling 21 patients with POMC, PCSK1, or LEPR deficiencies. 45.5% to 80% of patients experienced weight loss of ≥ 10% compared to baseline at 1 year. The most common adverse reactions occurring with an incidence of ≥ 23% included injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection and spontaneous penile erection.

Recommendation

The MO Healthnet Division recommends adding this drug to the current Rare Disease-Imcivree clinical edit.

References

1) Centers for Disease Control and Prevention. Adult Obesity Facts. https://www.cdc.gov/obesity/data/adult.html. Accessed May 2021.
2) LEAD for rare obesity. Leptin Receptor Deficiency. https://www.leadforrareobesity.com/lepr-deficiency. Accessed May 2021.
3) IPD Analytics. New Drug Review- Imcivree. ipdanalytics.com. Accessed May 2021.
4) Imcivree [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; November 2020.

Prepared by: Jaci Schowengerdt, PharmD

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