Abbreviated Drug Review

Imcivree™ (setmelanotide)[1,2]

Indications

- Chronic weight management in adult and pediatric patients 6 years 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 of POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.

Dosage

- If 12 years or older, inject 2 mg subcutaneously (SC) once daily for 2 weeks. If not tolerated decrease to 1 mg once daily. If 2 mg tolerated and additional weight loss desired increase to 3 mg.
- If 6 to less than 12 years, inject 1 mg SC once daily for 2 weeks. If initial dose not tolerated decrease to 0.5 mg daily. If 1 mg tolerated may increase by 1 mg increments to max dose of 3 mg daily.
- Supplied as 10 mg/mL, 1 mL multi-dose vial.

Background

- Functions as a melanocortin (MC) 4 receptor agonist with decreased MC3 and MC1 receptor activity. Central MC4 receptors affect regulation of hunger, satiety, and energy expenditure.
- POMC, PCSK1, and LEPR deficiency are associated with inadequate activation of MC4 receptor.
- Pharmacological treatments for obesity are not funded for adults or children. (Oregon Prioritized List Line 320, Guideline Note 5)[3]
- Medications for weight loss are excluded from OHA coverage. [Oregon Medicaid State Plan 12.a.1927(d)(2) and 12.a.1935(d)(2)][4]

Efficacy

Approval by the FDA was obtained with data from two identical, open-label, single-arm, 1-year trials. The trials included patients at least 6 years of age with a loss of function (LOF) variant for the POMC or PCSK1 genes (trial RM-493-012) or LEPR gene (trial RM-493-015) conferring a severe obesity phenotype. Those with recent intensive diet/exercise regimens or gastric bypass, psychiatric disorders including depression, and those with risk factors or dermatological findings concerning for melanoma (due to affinity for various melantocortin receptors) were excluded. After 12 weeks of therapy which included a 0.5 mg dose increase approximately every 2 weeks, patients continued with 10 weeks of open-label treatment. Patients who achieved at least 5 kg weight loss (or 5% if <100kg) entered a blinded withdrawal that involved 4 weeks of placebo then 4 weeks of active treatment. This was then followed by 32 weeks of open-label treatment. There were 21 total patients with at least 1 year of treatment, while 6 enrolled patients had not completed 1 year at the data cutoff and were excluded from the efficacy analysis. The patients were primarily adults > 16 years (62%), white (70-91%), female (50-73%), and with a median body mass index (BMI) of 40.0-46.6 kg/m^2. The primary endpoint was proportion of patients with >/= 10% weight loss from baseline at 1 year and the key secondary endpoint was the percentage change in bodyweight from baseline. The primary endpoint included the full analysis set (FAS), all patients who received study drug and at least one baseline assessment. The key secondary endpoint used the designated use set (DUS), all patients who received study drug and demonstrated at least 5 kg weight loss (or 5% if <100 kg) in the initial 12 week open-label period. However, the FDA also ran this analysis with the FAS population to reduce the selection bias of excluding patients who did not have an initial response.

	Study 1: POMC or PCSK1 (FAS N=10, DUS N=9)			Study 2: LEPR mutation (FAS N=11, DUS N=7)		
	Setmelanotide	P-Value	95% Confidence Interval	Setmelanotide	P-Value	95% Confidence Interval
Proportion with >/= 10% weight loss at 1 year from baseline (FAS)	8/10 (80%)	<0.0001	44.4% to 97.5%	5/11 (45.5%)	0.0002	16.8% to 76.6%
Percent weight change from baseline, Mean (SD) (FAS)	-23.1% (12.1%)	0.0003	-31.9% to -14.4%	-9.7% (8.8%)	0.0074	-16.0% to -3.3%

Safety

Common adverse reactions: injection site pain (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% males), arthralgia (19%), asthenia (19%), dizziness (15%), dry mouth (15%), dry skin (15%), insomnia (15%), vertigo (15%), and alopecia, chills, constipation, influenza-like illness, muscle spasm, pain in extremity, rash, suicidal ideation (11% for all).
Contraindications: none
Warnings and precautions: disturbance in sexual arousal (23% male, 7% female), depression and suicidal ideation, skin pigmentation and darkening of pre-existing nevi, risk of serious adverse reactions due to benzyl alcohol preservative in neonates and low birth weight infants
Special Populations: Not recommended in pregnant women unless benefit outweighs potential risks, avoid while breastfeeding, not recommended in moderate, severe, and end stage renal disease.

Evidence Gaps/Limitations

- No studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions.

Recommendation

Designate drug as not covered per Oregon Medicaid State Plan.

References

1. Imcivree (setmelanotide) Prescribing Information. Rhythm Pharmaceuticals, Inc. Boston, MA. Nov 2020.
2. FDA Center for Drug Evaluation and Research. NDA 213793 Imcivree (setmelanotide) Clinical Review. Version Nov 5, 2015. Review completed Nov 24, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213793Orig1s000MedR.pdf Accessed: Jan 11, 2021.
3. Oregon Health Authority Health Evidence Review Commission. 1-1-2021 Prioritized List of Health Services. Available at: https://www.oregon.gov/oha/HPA/DSI-HERC/PrioritizedList/1-1-2021%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed Jan 28, 2021.
4. Oregon Health Authority. Oregon State Medicaid Plan version July 30, 2020. Available at: https://www.oregon.gov/oha/HSD/Medicaid-Policy/StatePlans/Medicaid-State-Plan.pdf. Accessed Jan 28, 2020.

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