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Setmelanotide

Updated: July 5, 2024.

OVERVIEW

Introduction

Setmelanotide is a melanocortin 4 receptor agonist that is used for chronic weight management for adults and children with rare genetic forms obesity due to gene defects in the melanocortin pathway. Setmelanotide therapy has not been associated serum aminotransferase or bilirubin elevations or to instances of clinically apparent liver injury.

Background

Setmelanotide (set" me lan' oh tide) is an agonist of the melanocortin 4 (MC4) receptor used in the management of children 6 years or older and adults with obesity due to genetic abnormalities in the hypothalamic leptin-melanocortin pathway. Setmelanotide is a small peptide analogue of melanocyte stimulating hormone with preference for the melanocortin-4 receptor, which plays a role in regulation of hunger, satiety, and energy expenditure. These genetic forms of obesity are very rare and include pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), and leptin receptor (LEPR) deficiencies. These conditions generally present in infancy or childhood with extreme hyperphagia and severe obesity. In small open label clinical trials in these conditions, setmelanotide led to weight loss in most patients, which was usually accompanied by improvements in metabolic features such as lipid and fasting glucose levels. Setmelanotide was approved in the United States in 2020 as therapy for children and adults with obesity due to suspected deficiency of POMC, PCSK1, or LEPR. Indications were expanded in 2023 to include children and adults with obesity due to Bardet-Biedl syndrome. It is not effective in or indicated for typical (polygenic) obesity. Setmelanotide is available in multiple dose vials of 10 mg in 1 mL. The recommended starting dose in adults is 2 mg injected subcutaneously once daily for 2 weeks with increases (to 3 mg) or decreases (to 1 mg) in dose based upon tolerance and efficacy. For children below the age of 12 years, the starting dose is 1 mg with similar titration after 2 weeks. Common adverse events include injection site reactions, skin hyperpigmentation, nausea, vomiting, diarrhea, abdominal pain, headache, back pain, fatigue, depression, and spontaneous penile erection. Uncommon but potentially severe adverse events include hypersensitivity reactions, disturbances of sexual arousal, depression and suicidal ideation, marked skin pigmentation, and darkening of preexisting skin nevi. Solutions of setmelanotide also contain benzyl alcohol as a preservative which can cause serious and fatal adverse reactions in low birth rate infants.

Hepatotoxicity

In the small open label clinical trials of setmelanotide for genetic forms of obesity, there were no reports of abnormalities of serum aminotransferase or bilirubin levels. One patient developed cholecystitis, but it was

considered unrelated to therapy. Since its approval and clinical use, there have been no published cases of clinically apparent liver injury attributed to setmelanotide therapy, but elevations in serum aminotransferase levels during therapy have been described. Thus, setmelanotide therapy has not been linked to clinically apparent liver injury, but the total clinical experience with its use is limited.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Setmelanotide is an 8 amino acid cyclic peptide analogue of alpha melanocyte stimulating hormone and has preference for the MC4 receptor. Partial engagement of the MC1 receptor may account for its side effects of hyperpigmentation and skin darkening. It is metabolized in many tissues intracellularly by proteases into smaller peptides and amino acids and has no effect on hepatic microsomal enzymes.

Outcome and Management

The product label for setmelanotide does not recommend monitoring of routine liver tests during therapy.

Drug Class: Weight Loss Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Setmelanotide – Imcivree®

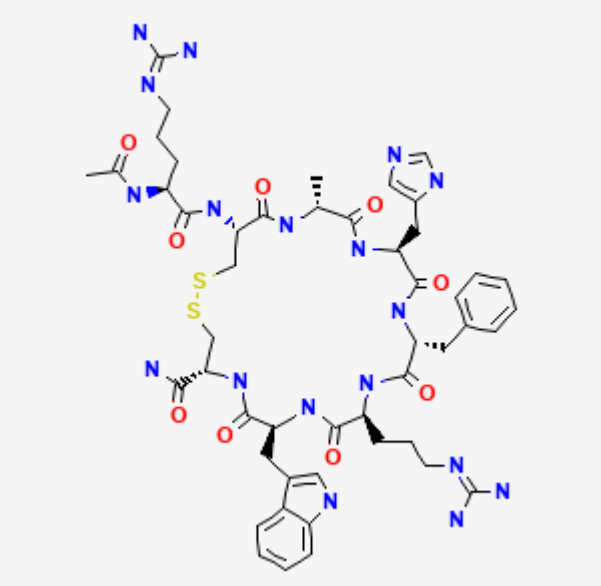
DRUG CLASS

Weight Loss Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Setmelanotide	920014-72-8	C49-H68-N18-O9-S2	

ANNOTATED BIBLIOGRAPHY

References updated: 05 July 2024

Abbreviations: (LEPR), leptin receptor; (PCSK1), proprotein convertase subtilisin/kexin type 1 (PCSK1); POMC, pro-opiomelanocortin; ULN, upper limit of normal range.

FDA. Integrated Review. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213793Orig1s000MedR.pdf

(FDA Integrated review of the data on setmelanotide safety and efficacy submitted in support of the application for its approval as therapy of several rare genetic forms of obesity mentions that "Overall, no trends or clinically meaningful changes were observed in clinical laboratory assessments throughout the studies.").

Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, De Waele K, et al.; Setmelanotide POMC and LEPR Phase 3 Trial Investigators. 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;8:960-970. PubMed PMID: 33137293.

(Among 21 patients with obesity due to POMC deficiency [n=10] or LEPR deficiency [n=11] treated with setmelanotide injections for 12 weeks, followed by an 8 week placebo controlled withdrawal, and then a 32 week open label extension period, most patients lost weight and 80% of POMC vs 45% of LEPR subjects lost more than 10% of body weight, while adverse events included injection site reactions in 100%, hyperpigmentation in 71%, and nausea in 43%, but only one subject discontinued therapy because of an adverse event [eosinophilia], ALT and AST levels tended to improve with the weight loss, and there were no serious hepatic adverse events).

Haws R, Brady S, Davis E, Fletty K, Yuan G, Gordon G, Stewart M, Yanovski J. Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. Diabetes Obes Metab. 2020;22:2133-2140. PubMed PMID: 32627316.

(Among 8 adolescents and adults with obesity due to Bardet-Biedl syndrome treated with setmelanotide, weight loss averaged 9% at 3 months and 16% at 12 months, while side effects included injection site reactions, hyperpigmentation, nausea, and vomiting and there were no discontinuations for adverse events; no mention of ALT or hepatotoxicity).

Markham A. Setmelanotide: first approval. Drugs. 2021;81:397-403. PubMed PMID: 33638809.

(Review of the chemical structure, mechanism of action, history of development, pharmacology, clinical efficacy, and safety of setmelanotide shortly after its approval as therapy of genetic forms of obesity in the US, discusses the frequency of common side effects, but does not mention ALT elevations or hepatotoxicity).

Setmelanotide (Imcivree) for rare genetic forms of obesity. Med Lett Drugs Ther. 2021;63(1629):e3-e4. PubMed PMID: 34544109.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of setmelanotide shortly after its approval for use in the US, discusses common adverse events; no mention of ALT elevations or hepatotoxicity).

Haqq AM, Chung WK, Dollfus H, Haws RM, Martos-Moreno GÁ, Poitou C, Yanovski JA, et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. Lancet Diabetes Endocrinol. 2022;10:859-868. PubMed PMID: 36356613.

(Among 38 patients with obesity due to Bardet-Biedl or Alström syndrome treated with setmelanotide or placebo subcutaneously once daily for 14 weeks, followed by open label drug for 52 weeks, weight loss occurred with

therapy but varied by age and diagnosis, while adverse events occurred in 97% and were severe in 5%, but none were liver related; no mention of ALT elevations or hepatotoxicity).

Roth CL, Scimia C, Shoemaker AH, Gottschalk M, Miller J, Yuan G, Malhotra S, et al. Setmelanotide for the treatment of acquired hypothalamic obesity: a phase 2, open-label, multicentre trial. Lancet Diabetes Endocrinol. 2024;12:380-389. PubMed PMID: 38697184.

(Among 18 patients with acquired hypothalamic obesity treated with setmelanotide for up to one year, the mean weight loss was 15% and adverse events included nausea in 61%, vomiting 33%, hyperpigmentation 33%, diarrhea 22%, and two subjects discontinued therapy because of elevations in serum aminotransferase levels at 4 weeks [recurring after 6 days on re-exposure] and 12 months, specific values and other details not provided).