Health Technology Briefing
January 2024

Setmelanotide for treating acquired hypothalamic obesity in people 4 years and older

Company/Developer	Rhythm Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31151	NICE ID: Not Available	UKPS ID: 669539

Licensing and Market Availability Plans

Currently in phase IIb clinical trial

Summary

Setmelanotide is currently in development for the treatment of acquired hypothalamic obesity. Acquired hypothalamic obesity refers to excess weight gain that may follow from an injury to the hypothalamus, a brain region which coordinates the endocrine system (controls body functions). The hypothalamus affects energy intake, by regulating how much we eat and how much energy is stored and used. Damage to the hypothalamus disrupts the carefully coordinated balance between energy intake and expenditure, often leading to rapid weight gain. Multiple factors likely combine to cause excess weight gain after hypothalamic injury, and individuals vary in the extent to which they experience these different phenomena. Currently, there are no approved pharmacological treatments available, instead only weight management and bariatric surgery are available.

Setmelanotide which is administered as an injection under the skin, attaches to and activates a receptor called melanocortin-4 (MC4). MC4 receptors in the brain are involved in the regulation of hunger, satiety, and energy expenditure. Setmelanotide is expected to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure, and if licensed, will offer a new treatment option for acquired hypothalamic obesity.

Proposed Indication

Treatment of patients with acquired hypothalamic obesity in patients 4 years and older.[1]

Technology

Description

Setmelanotide (Imcivree) is a selective melanocortin-4 (MC4) receptor agonist.[2] MC4 receptors in the brain are involved in the regulation of hunger, satiety, and energy expenditure. In genetic forms of obesity associated with insufficient activation of the MC4 receptor, setmelanotide is believed to re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.[3]

Setmelanotide is currently in development for the treatment of patients who (1) have documented evidence of hypothalamic injury, (2) are aged four years and older and (3) have gained weight associated with hypothalamic injury and (4) have a body mass index (BMI) of ≥30 kg/m^2 for patients ≥18 years or ≥95th percentile for age and sex for patients 4 to <18 years of age. In the phase III clinical trial (NCT05774756), participants received daily subcutaneous injections of setmelanotide.[1]

Key Innovation

Hypothalamic injury often leads to rapid, intractable weight gain causing acquired hypothalamic obesity. There are no approved or effective pharmacological treatments for acquired hypothalamic obesity, and conventional lifestyle management remains ineffective.[4] Setmelanotide is currently approved for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), and deficiency of proprotein convertase subtilisin/kexin type 1 (PCSK1) or biallelic leptin receptor (LEPR) in adults and children six years of age and above.[5]. In a phase II clinical trial (NCT04725240), 13 out of 18 patients aged 6–40 years with documented evidence of hypothalamic obesity treated with setmelanotide, had a ≥10% BMI reduction (mean [standard deviation] percent change, −14.5% [9.5%]).[15] If licensed, setmelanotide may provide a new treatment option for patients aged four years and above with documented evidence of acquired hypothalamic obesity.

Regulatory & Development Status

Setmelanotide currently has Marketing Authorisation in the UK for the treatment of obesity and the control of hunger associated with genetically confirmed BBS, loss-of-function biallelic POMC, and PCSK1 and LEPR deficiency in adults and children six years of age and above.[3]

Setmelanotide has the following regulatory designations/awards:[6,7]

- An orphan drug designation in September 2023 by the EMA for the treatment of acquired hypothalamic obesity.
- A breakthrough therapy designation in November 2022 by the FDA for the treatment of hypothalamic obesity.

Setmelanotide is also currently in phase III development for the following indications:[8,9]

- SH2B1 deficiency obesity
- NC0A1/SRC1 deficiency obesity
- Heterozygous LEPR obesity
- Heterozygous POMC/PCSK1 obesity

Patient Group

Disease Area and Clinical Need

Acquired hypothalamic obesity is a result of impairment in the hypothalamic regulatory centres of body weight and energy expenditure and is caused by structural damage to the hypothalamus, including from surgery or radiotherapy for the treatment of brain tumours, or traumatic brain injury.[10] It is associated with an increased risk of cardiovascular and metabolic morbidity and mortality.[4] Acquired hypothalamic obesity is a complex neuroendocrine disorder characterised by hyperphagia, rapid severe weight gain, reduced basal metabolic rate, and leptin and insulin resistance.[4] Hypothalamic obesity is compounded by a disruption of the hypothalamic-pituitary axis, sleep disruption, visual compromise, and neurological and vascular sequelae. Amongst suprasellar tumours, craniopharyngioma is the most common cause of acquired hypothalamic obesity, either directly or following a surgical or radiotherapeutic intervention.[11]

In England (2022-23) there were 48 finished consultant episodes (FCEs) and 45 admissions for hypothalamic dysfunction, not elsewhere classified (ICD-10 code E23.3), which resulted in 35 day cases and 39 FCE bed days.[12]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for hypothalamic obesity. Conventional weight management (diet and lifestyle modifications) and bariatric surgery are the existing management options.[4,13,14]

Clinical Trial Information

Trial	NCT05774756; A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity. **Phase III** - Recruiting **Location(s):** Two EU countries, UK, US and Canada **Primary completion date:** April 2025
Trial Design	Randomised, triple masked, parallel assignment and placebo-controlled
Population	N=120 (estimated); patients aged 4 years and older with documented evidence of acquired hypothalamic obesity, and weight gain associated with the hypothalamic injury and a BMI of ≥30 kg/m^2 for patients ≥18 years of age or BMI ≥95th percentile for age and sex for patients 4 to <18 years of age
Intervention(s)	Daily subcutaneous injection of setmelanotide
Comparator(s)	Placebo matched to setmelanotide for daily subcutaneous injection
Outcome(s)	Primary outcome measures: - Mean % change in BMI [Time frame: from baseline to week 60] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT04725240, EudraCT 2022-004107-32; A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects With Hypothalamic Obesity. **Phase II** - Completed **Location(s):** US **Study Completion Date:** June 2022
Trial Design	Interventional, single group assignment, open-label
Population	N=18 (actual); patients aged 6–40 years with documented evidence of hypothalamic obesity.
Intervention(s)	Once daily subcutaneous injection of setmelanotide for 16 weeks, with the starting being dose-dependent on age up to a maximum of 3.0 mg.
Comparator(s)	-
Outcome(s)	Primary outcome measure: - Percentage of participants with ≥ 5% reduction in BMI from baseline after 16 weeks of setmelanotide treatment [Time frame: baseline to 16 weeks] See trial record for a full list of other outcomes
Results (efficacy)	At week 16, most patients met the primary endpoint (88.9% [n/N=16/18]; P<0.0001), and 13 of 18 patients who completed treatment had ≥10% BMI reduction (mean [standard deviation] percent change, −14.5% [9.5%]).[15]
Results (safety)	Treatment-related adverse events occurred in all patients. The most frequent adverse events included nausea (61.1%; n=11), vomiting (33.3%; n=6), skin hyperpigmentation (33.3%; n=6), and diarrhoea (22.2%; n=4).[15]

Estimated Cost

Setmelanotide is already marketed in the UK. A vial of setmelanotide (10 mg per 1 ml) costs £2,376.[16]

Relevant Guidance

NICE Guidance

- NICE highly specialised technology guidance. Setmelanotide for treating obesity caused by LEPR or POMC deficiency (HST21). July 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Severe and Complex Obesity (All Ages). A05/S/a

Other Guidance

- Gan H-W, Morillon P, Albanese A, Aquilina K, *et al*. National UK guidelines for the management of paediatric craniopharyngioma. 2023.[13]
- van Iersel L, Brokke KE, Adan RAH, Bulthuis LCM, *et al*. Pathophysiology and individualized treatment of hypothalamic obesity following craniopharyngioma and other suprasellar tumors: A systematic review. 2018.[14]

Additional Information

References

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