NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technologies Evaluation

Setmelanotide for treating obesity caused by LEPR or POMC deficiency

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of setmelanotide within its marketing authorisation for treating obesity caused by leptin receptor (LEPR) deficiency or pro-opiomelanocortin (POMC) deficiency for national commissioning by NHS England.

Background

Obesity is a chronic condition characterised by increased body fat. People who are obese are at an increased risk of developing cardiovascular disease, type 2 diabetes, atherosclerosis (the presence of fatty deposits in the arteries), hypertension and dyslipidaemia (abnormal levels of fats in the blood). The most common method for measuring obesity is body mass index (BMI) which is calculated as the ratio of weight to height squared. In adults, obesity is typically defined by a BMI of 30 kg/m^2 or more. In childhood, obesity is usually defined as a BMI at or above the 95th percentile for individuals of the same age and sex.

LEPR deficiency and POMC deficiency can cause serious debilitating symptoms, particularly obesity and endocrine abnormalities, such as adrenal insufficiency. They are closely related rare genetic obesity disorders resulting from an impaired central leptin-melanocortin system, comprising multiple genes, including LEPR, POMC, and PCSK1. Impaired genes in this pathway can lead to reduced levels of several hormones, including melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone. MSH is needed to activate the melanocortin 4 receptor (MC4R) pathway which regulates energy expenditure, homeostasis, and appetite. In people whose bodies cannot produce sufficient MSH in response to eating food, the melanocortin-4 receptor is not activated and the person remains hungry. Infants with LEPR deficiency are usually a normal weight at birth, but they are constantly hungry, which leads to excessive feeding (hyperphagia) and rapid weight gain. Affected individuals are often severely obese by age 1 and continue to experience excessive hunger and remain obese for life.[1]

LEPR deficiency and POMC deficiency are rare conditions.

- Approximately 88 cases of LEPR deficiency have been reported in medical literature, 21 of which are European.[2] LEPR deficiency affects approximately 2–3% of people with severe early-onset obesity[3] and is known to affect less than 0.1 in 10,000 people in the European Union.[4]

- Approximately 50 cases of POMC deficiency have been reported in the medical literature[5] and it is known to affect less than 0.1 in 10,000 people in the European Union.[6] There is currently one person with POMC deficiency in England.

There are currently no licensed targeted treatments for obesity caused by LEPR deficiency or POMC deficiency, and the weight loss medicines orlistat and methylcellulose are the only treatment options. Standard management of overweight and obesity includes dietary and lifestyle advice, behaviour modification, pharmacological treatments and surgical intervention. Specialist multi-disciplinary weight management interventions (known as tier 3 interventions) are also used in current practice. Tier 3 interventions include dietary, lifestyle and behaviour modification with or without drug therapy. These interventions can be delivered in either primary or secondary care. NICE clinical guideline 189 'Obesity: identification, assessment and management' (CG189) recommends that drug therapy with orlistat should only be considered after dietary, physical activity and behavioural approaches have been started and evaluated. It recommends orlistat for the management of obesity in people with a BMI of 30 kg/m^2 or more, and in people with a BMI of 28 kg/m^2 or more and significant comorbidities. If dietary and lifestyle advice, behaviour modification and drug treatments are unsuccessful, the NICE clinical guideline recommends bariatric surgery for people with: a BMI of 40 kg/m^2 or more; a BMI of between 35 kg/m^2 and 40 kg/m^2 with significant comorbidities, a BMI between 30 kg/m^2 and less than 35 kg/m^2 and with recent-onset of type 2 diabetes.

The technology

Setmelanotide (brand name unknown, Rhythm Pharmaceuticals) is a peptide that binds to and activates the melanocortin 4 receptor. It is believed to restore lost activity in the MC4 pathway, re-establishing weight and appetite control in patients with these rare genetic disorders. It is administered via subcutaneous injection.

Setmelanotide does not currently have a marketing authorisation in the UK for treating obesity caused by LEPR deficiency or POMC deficiency. It is being studied in a clinical trial of people aged 12 years and over with mutations in the LEPR gene, and also in a clinical trial of people 12 years and over with mutations in the POMC and PCSK1 genes.

Setmelanotide is also being studied in trials for other closely related genetic obesity conditions: Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome and POMC heterozygous deficiency obesity.

Intervention(s)	Setmelanotide
Population(s)	People with LEPR deficiency or POMC deficiency aged 12 years and over, with the following obesity markers:

	• adults aged 18 years and over: body mass index (BMI) 30 kg/m^2 and over; • adolescent: weight 97th percentile or more for age on growth chart assessment.
Comparators	• standard management without setmelanotide (including a reduced calorie diet and increased physical activity) • orlistat • methylcellulose • bariatric surgery
Outcomes	The outcome measures to be considered include: • BMI • weight loss • percentage body fat • waist circumference • hunger • incidence of type 2 diabetes • cardiovascular events • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per

	quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Naltrexone–bupropion for managing overweight and obesity (2017). NICE Technology Appraisal 494. Review date: December 2020. Appraisals in development: Liraglutide for managing overweight and obesity [ID740]. Publication expected March 2020 Related Guidelines: Preventing excess weight gain (2015). NICE guideline NG7. Obesity: identification, assessment and management (2014). NICE guideline CG189. Obesity prevention (2006). NICE guideline CG43. Related Evidence Summary: Obese, overweight with risk factors: liraglutide (Saxenda) (2017).NICE evidence summary ES14. Related Public Health Guidance/Guidelines: Weight management: lifestyle services for overweight

	or obese children and young people (2013). NICE guideline PH47. Obesity: working with local communities (2012). NICE guideline PH42. Weight management: lifestyle services for overweight or obese adults (2014). NICE guideline PH53. BMI: preventing ill health and premature death in black, Asian and other minority ethnic groups (2013). NICE guideline PH46. Weight management before, during and after pregnancy (2010). NICE guideline PH27. Related Quality Standards: Obesity in children and young people: prevention and lifestyle weight management programmes (2015). NICE quality standard 94. Promoting health and preventing premature mortality in black, Asian and other minority ethnic groups (2018). NICE quality standard 167. Obesity: clinical assessment and management (2016). NICE quality standard 127. Obesity in adults: prevention and lifestyle weight management programmes (2016). NICE quality standard 111. Related NICE Pathways: Lifestyle weight management services for overweight or obese adults (2016). NICE Pathway Obesity (2018). NICE Pathway. Obesity: working with local communities overview (2016). NICE Pathway.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 139A. Specialist morbid obesity services for (children) NHS England (2017) Commissioning guidance to support devolution to CCGs of adult obesity surgical services in 2016/17 NHS England (2014) Report of the working group into: Joined up clinical pathways for obesity Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2

	https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Department of Health and Social Care (2018) Childhood obesity: a plan for action, chapter 2 Public Health England (2018) Promoting healthy weight in children, young people and families Public Health England (2017) Child weight management: short conversations with families Department of Health & Social Care (2019) The UK strategy for rare diseases: 2019 update to the Implementation Plan for England Department of Health and Social Care (2018) The UK Strategy for Rare Diseases. Second Progress Report from the UK Rare Diseases Policy Board Department of Health and Social Care (2018) Rare Diseases Glossary. Glossary of commonly used terms and rare diseases initiatives Department of Health and Social Care (2016) The UK Strategy for Rare Diseases. Rare Diseases implementation plan for England UK Rare Disease Forum (2016) Delivering for patients with rare diseases: Implementing a strategy A report from the UK Rare Disease Forum Department of Health (2016) NHS outcomes framework 2016 to 2017 Department of Health (2013) The UK strategy for rare diseases

Questions for consultation

How is a diagnosis of LEPR deficiency and POMC deficiency confirmed in clinical practice? Approximately how many people in England have a confirmed diagnosis of LEPR deficiency or POMC deficiency?

How are LEPR deficiency and POMC deficiency clinically distinguished from one another?

How are they distinguished from other closely-related genetic obesity conditions, such as Prader-Willi syndrome, Bardet-Biedl syndrome and Alström syndrome?

Are there any uncaptured health benefits of treatment with setmelanotide?

Which treatments are considered to be established clinical practice in the NHS for obesity caused by LEPR deficiency and POMC deficiency? Are standard treatments (tiers 2 to 4) used for people with LEPR deficiency and POMC deficiency obesity?

Should methylcellulose, orlistat and bariatric surgery be included comparators in this appraisal?

Have all relevant comparators for setmelanotide been included in the scope?

Are the outcomes listed appropriate? Should any other outcomes be included in the scope?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which setmelanotide will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.

References:

1. https://www.uncommonobesity.com/global/clinical-presentation Accessed December 2019

2. Kleinendorst L, et al. (2020) Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. European Journal of Endocrinology 182, 1: 47-56.

3. Challis B, Millington G (2013) Proopiomelanocortin Deficiency GeneReviews. Accessed November 2019

4. https://www.ema.europa.eu/en/documents/orphan-review/eu/3/18/2101-public-summary-opinion-orphan-designation-setmelanotide-treatment-leptin-receptor-deficiency_en.pdf Accessed December 2019

5. Challis B, Millington G (2013) Proopiomelanocortin Deficiency GeneReviews. Accessed November 2019

6. https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161703. Accessed November 2019