NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of setmelanotide within its marketing authorisation for treating obesity and hyperphagia caused by Bardet-Biedl Syndrome (BBS).

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.

BBS is a rare, recessively inherited condition caused by genetic mutations. Symptoms experienced vary but obesity is a key symptom due to the patient's increased appetite (hyperphagia), caused by impairment of an area of the brain that controls appetite, the melanocortin-4 receptor (MC4R) pathway. Diabetes mellitus (specifically, type II diabetes, non-insulin dependent) may affect up to 45% of patients[1]. Problems with weight management may further complicate issues with heart and blood vessels common in patients with BBS. Other symptoms may include cognitive impairment, polydactyly, renal anomalies, hypogonadism and visual impairment.

It is estimated that BBS affects approximately 560 people in the UK[2], with many people having excessive weight gain through the first year of life, and around 70 to 90% develop obesity[3].

There are currently no licensed targeted treatments for obesity in people with BBS. 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. Liraglutide has been recommended alongside a reduced calorie diet and physical activity for people with a BMI of at least 35 kg/m^2 (or 32.5 kg/m^2 for some minority ethnic groups) with non-diabetic hyperglycaemia who are at high risk of cardiovascular disease (TA664).

The technology

Setmelanotide (IMCIVREE, Rhythm Pharmaceuticals) is a MC4R agonist with the potential to restore lost activity in the MC4R pathway and re-establish weight and appetite control in patients with obesity in people with BBS. It is administered via subcutaneous injection.

Setmelanotide does not currently have a marketing authorisation in the UK for treating obesity in people with BBS. It is being studied in a clinical trial of people aged 6 years and over with BBS and moderate to severe obesity.

Setmelanotide has a marketing authorisation in the UK for treating leptin receptor (LEPR) or pro-opiomelanocortin (POMC) deficiency obesity. It is also being studied in trials for another closely related genetic obesity condition, POMC heterozygous deficiency obesity.

Intervention(s)	Setmelanotide
Population(s)	People aged 6 years and over with obesity and hyperphagia in Bardet-Biedl Syndrome, with the following obesity markers: • people aged 18 and over: body mass index (BMI) 30 kg/m2 and over; • people aged 17 and under: weight 97th percentile or more for age on growth chart assessment.
Comparators	• established clinical management without setmelanotide (including a reduced calorie diet and increased physical activity) • bariatric surgery

Outcomes	The outcome measures to be considered include: • BMI • BMI-Z • weight loss • percentage body fat • waist circumference • hunger • incidence of type 2 diabetes • clinical measures of diabetic control • cardiovascular events • mortality • co-morbidities associated with early onset severe obesity including cancer • adverse effects of treatment • health-related quality of life (for patients and carers).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Liraglutide for managing overweight and obesity (2020). NICE Technology Appraisal 664. Review date: 2023. Naltrexone–bupropion for managing overweight and obesity (2017). NICE Technology Appraisal 494. Last reviewed:

	January 2020. Appraisals in development: Semaglutide for managing overweight and obesity. NICE technology appraisals guidance [ID3850]. Publication expected March 2022. Setmelanotide for treating obesity caused by LEPR or POMC deficiency. NICE technology appraisals guidance [ID3764]. Publication expected March 2022. 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

References

1. https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/. Accessed October 2021.

2. www.bbsuk.org.uk. Accessed September 2021.

3. Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Hum Genet. 2013;21:8–13. PubMed PMID: 22713813.