NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome or Alström syndrome

Draft scope

Draft 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) or Alström syndrome (AS).

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 and AS are both rare, recessively inherited conditions caused by genetic mutations. BBS can be caused by mutations in more than 20 different genes while AS is caused by mutations in the *ALMS1* gene. Symptoms experienced with both conditions and their severity vary. In both syndromes, 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 with BBS and is likely to develop in most people with AS[1,2]. Problems with weight management may further complicate issues with heart and blood vessels seen in patients with BBS. Other symptoms in people with BBS may include cognitive impairment, polydactyly, renal anomalies, hypogonadism and visual impairment. Symptoms in people with AS may include progressive blindness or deafness, insulin resistance and type 2 diabetes, hyperlipidemia, kidney dysfunction, cardiomyopathy and short stature as an adult.

It is estimated that BBS affects approximately 560 people in the UK[3], with as many as 90% of people with BBS having excessive weight gain through the first year of life. AS affects 30-80 families in the UK[4,5], but this may be an underestimate as the disorder is likely underdiagnosed.

There are currently no licensed targeted treatments for obesity in people with BBS or AS. 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 or AS. It is administered via subcutaneous injection.

Setmelanotide does not currently have a marketing authorisation in the UK for treating obesity in people with BBS or AS. It is being studied in a clinical trial of people aged 6 years and over with BBS or AS 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 other closely related genetic obesity conditions: Prader-Willi syndrome and POMC heterozygous deficiency obesity.

Intervention(s)	Setmelanotide
Population(s)	People aged 6 years and over with obesity and hyperphagia in Bardet-Biedl Syndrome (BBS) or Alström Syndrome (AS), with the following obesity markers: • people aged 16 and over: body mass index (BMI) 30 kg/m^2 and over; • people aged 15 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) • liraglutide • orlistat • 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 • 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

Questions for consultation

What is the number of people with BBS and AS, respectively, in England? How many of them will be eligible for treatment (have obesity defined as body mass index [BMI] 30 kg/m^2 and over for aged 16 and over, or 97th percentile or more for age on growth chart assessment for those 15 years and under)?

How are BBS and AS clinically distinguished from one another?

What is the impact of the condition on length of life and/or quality of life?

Have all relevant comparators for setmelanotide been included in the scope? Which treatments are considered to be established clinical practice in the NHS for BBS and AS?

Are orlistat and liraglutide used in the treatment for BBS and AS? Would bariatric surgery be considered an alternative to setmelanotide?

Are the outcomes listed appropriate?

How would the impact of hyperphagia (excessive hunger) be captured in health-related quality of life measures?

Are there any subgroups of people in whom setmelanotide is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Are the genetic tests to confirm a diagnosis of either BBS or AS standard practice in the NHS?

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 Committee to identify and consider such impacts.

Do you consider setmelanotide 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)?

Do you consider that the use of setmelanotide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

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

2. https://rarediseases.org/rare-diseases/alstrom-syndrome/. Accessed October 2021.

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

4. NHS England (2013) 2013/14 NHS STANDARD CONTRACT FOR Alström syndrome service (ALL AGES): SECTION B PART 1 - SERVICE SPECIFICATIONS. Ref: A17/S(HSS)e

5. http://www.alstrom.org.uk/what-is/. Accessed September 2021.