NICE National Institute for Health and Care Excellence

NICE guidance

Setmelanotide for treating obesity caused by LEPR or POMC deficiency

Highly specialised technologies guidance
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Contents

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1 Recommendations

1.1 Setmelanotide is recommended, within its marketing authorisation, as an option for treating obesity and controlling hunger caused by pro-opiomelanocortin (POMC) deficiency, including proprotein convertase subtilisin/kexin type 1 or leptin receptor (LEPR) deficiency in people 6 years and over. It is only recommended if the company provides setmelanotide according to the commercial arrangement.

Why the committee made these recommendations

POMC and LEPR deficiencies are rare genetic disorders of obesity that severely affect the quality of life of people with them, and their families and carers. They cause early onset, extreme obesity and hyperphagia (characterised by a feeling similar to starvation) and are linked with many chronic conditions. They are also likely to shorten life expectancy. Current management (best supportive care) focuses on dietary restrictions and lifestyle changes, including exercise.

Results from clinical trials suggest that setmelanotide may reduce weight and body mass index (BMI) in people with obesity caused by POMC and LEPR deficiencies. Evidence also suggests that hunger and quality of life are improved with setmelanotide. Longer-term evidence suggests there might be an ongoing treatment effect with setmelanotide, but this is uncertain.

There are also other uncertainties in the modelling, particularly around the quality-of-life decrement value associated with severe hyperphagia. Despite the uncertainties, setmelanotide is likely to provide important clinical and psychological benefits for people with the condition and their carers, and value for money within the context of a highly specialised service. So, setmelanotide is recommended.

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2 Information about setmelanotide

Marketing authorisation indication

2.1 Setmelanotide (Imcivree, Rhythm Pharmaceuticals) has a marketing authorisation for the 'treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for setmelanotide.

Price

2.3 The list price of setmelanotide is £2,376.00 per 10 mg per ml vial for injection (excluding VAT; company's evidence submission). The company has a commercial arrangement. This makes setmelanotide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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3 Committee discussion

The evaluation committee considered evidence submitted by Rhythm Pharmaceuticals, the views of people with the condition, clinical experts and NHS England, and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

LEPR or POMC deficiency

3.1 Pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiencies are rare genetic disorders of obesity. They are caused by mutations in the LEPR or POMC genes. POMC deficiency also includes mutations in the proprotein convertase subtilisin/kexin type 1 (PCSK1) gene. These genes are involved in signalling through the melanocortin-4 receptor (MC4R) neuroendocrine system in the hypothalamus. This system regulates hunger, satiety (a feeling of fullness) and energy expenditure. Disrupted signalling through MC4R-expressing neurons causes severe, early onset obesity and hyperphagia. Symptoms often happen within the first year of life. For a given weight, obesity-related comorbidities are usually more severe in people with deficiencies affecting the MC4R pathway, including diabetes and cardiovascular disease. People with POMC deficiency are also likely to have adrenal insufficiency, whereas people with LEPR deficiency have a compromised immune system. Both conditions may also cause failure to go through puberty and are associated with fertility and reproductive issues. The prevalence and severity of comorbidities in people with the condition are associated with increased death rates compared with general obesity. The committee concluded that obesity caused by LEPR or POMC deficiency is a debilitating condition associated with multiple comorbidities.

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Effects on quality of life

3.2 The patient experts explained that the quality of life of people with obesity caused by LEPR or POMC deficiency can be extremely poor. They emphasised that the hyperphagia can be debilitating and all-consuming. One patient expert described the feeling of constant hunger as being 'famished' and likened the need to eat to a basic survival instinct. Eating does not relieve the hunger, so people are constantly looking for, or thinking about, food. One carer illustrated the effect of these conditions on people with them by recalling seeing extreme food-seeking behaviours such as stealing food from as young as 2 years. The clinical experts explained that an insatiable appetite associated with dramatic weight gain is usually present within the first few months of life. People with the condition gain weight to such an extent that, by 2 years, they are often around 25 kg, the average weight of an 8-year-old. The committee understood that there is a significant psychological effect of living with the condition for both people with the condition and carers. Because of the social stigma surrounding obesity and lack of understanding of rare genetic disorders of obesity, children with the condition are often bullied at school. This could affect their educational attainment and future employment opportunities. They also struggle to carry out normal activities such as taking part in sports because of mobility issues or finding normal clothing in a large enough size. This often leads to poor mental health and self-esteem. The patient experts highlighted that the symptoms and social stigma are traumatic and are linked to high rates of depression in this population. The carer explained that looking after a child with obesity caused by LEPR or POMC deficiency is both physically and mentally draining. Further stigma happens because children with rare genetic disorders of obesity are often assumed to have been overfed. Also, managing insatiable food intake behaviour causes distress for both people with the condition and carers. The clinical experts explained extreme measures are often needed to limit food access, such as locking cupboard doors. This could affect the whole family including siblings. The committee concluded that obesity caused by LEPR or POMC deficiency has a significant effect on the quality of life of people with the condition, family members and carers.

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Clinical management

Treatment options

3.3 There are no licensed treatments for obesity caused by LEPR or POMC deficiency. Best supportive care includes dietary advice to manage the hyperphagia and exercise modification. A clinical expert explained that regular rigorous exercise is needed to limit weight gain in people with the condition, which is hard to maintain in the long term. The carer explained that a calorie-restrictive diet is also challenging to implement. The burden of care is substantial because all food has to be prepared from scratch to provide the best nutritional value while limiting calorie intake. The carer also noted that this is especially difficult for teenagers who are regularly out of the house at mealtimes. The clinical experts explained that the standard interventions are rarely effective in the long term because they do not address the underlying hyperphagia. The committee concluded that there is an unmet need for a new treatment for the condition.

Relevant comparators

3.4 The committee understood that treatments for general obesity include orlistat, methylcellulose and bariatric surgery. It noted that these were included as comparators in the NICE scope but were excluded from the company's submission. The clinical experts explained that people with POMC and LEPR deficiencies would not have pharmacological treatments for general obesity. This is because these do not correct the MC4R deficiency so are unlikely to result in clinically meaningful weight loss. One clinical expert also explained that bariatric surgery, the mainstay for treating severe general obesity, is ineffective and potentially dangerous in this population. This is because some approaches reduce the stomach size and none treat the hyperphagia, so people remain constantly hungry. The committee understood that, if recommended, setmelanotide would be used in addition to best supportive care with dietary and exercise interventions. So, best supportive care without setmelanotide is the relevant comparator. It concluded that orlistat, methylcellulose and bariatric surgery are not relevant comparators for setmelanotide.

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Genetic testing

3.5 The clinical experts explained that testing for LEPR or POMC deficiencies has recently been routinely commissioned in the NHS. NICE's guideline on overweight and obesity management recommends genetic testing in people with obesity only before surgery. The committee was concerned that because setmelanotide was positioned as a first-line treatment, people might only be referred for testing after exercise and diet modifications had failed. It noted that the marketing authorisation for setmelanotide is limited to people with biallelic, loss-of-function mutations in the POMC, PSCK1 or LEPR genes. That is, people with homozygous mutations (mutations in 2 alleles at the same loci in the same gene) or compound heterozygous mutations (mutations in 2 alleles at different loci in the same gene). The clinical experts explained that the weight gain in babies with biallelic POMC and LEPR deficiency is so dramatic that most people are referred for genetic testing at an early age, usually in their first year of life. They explained that the pathway for testing and knowledge of common genetic variants is well established, both from existing NHS services and a previous research programme. So, the number of additional new cases expected from the rollout of wider genetic testing would likely be minimal. However, people might be diagnosed earlier because of improvements in access to specialist centres and the importance of genetic testing in directing treatment options if setmelanotide is recommended. The committee understood that genetic testing for POMC and LEPR deficiency is routine in NHS practice and that the current pathway would identify most people with the condition from early childhood.

Clinical evidence

Data sources

3.6 The main clinical trial evidence for setmelanotide came from 2 phase 3, single-arm open-label studies, RM-493-012 and RM-493-015, referred to as the 'index trials' in this guidance:

- RM-493-012 enrolled people with obesity caused by biallelic POMC deficiency. RM-493-015 enrolled people with obesity caused by biallelic LEPR deficiency. Both trials enrolled 15 people aged 6 and over with a body

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mass index (BMI) of 30 kg/m^2 or more (or the 97th percentile or more in people under 18 years). After 12 weeks of open-label treatment at the individualised therapeutic dose, there was an 8-week blinded withdrawal phase. The total follow-up period was 52 weeks in both trials.

- The company also provided evidence for setmelanotide from a phase 3, open-label extension study, RM-493-022. RM-493-022 is an ongoing long-term follow-up study of trials RM-493-012 and RM-493-015 due to complete in 2023. It has enrolled 9 people with POMC and 6 people with LEPR deficiencies. These people will have a further 2 years of setmelanotide at the same dose as in the index trials. Results from an interim analysis for people with POMC deficiency are from week 37. At consultation, the company presented unpublished evidence from RM-493-022 from a later data cut that included people with both LEPR and POMC deficiency (exact follow-up period is academic in confidence and cannot be stated here).

  The committee noted that the clinical trials for setmelanotide were single-arm studies. The ERG agreed with the company that indirect treatment comparison was not feasible given the lack of evidence on the natural history of the condition. The ERG flagged that people in the company's clinical trials had setmelanotide alongside diet and exercise modification. The committee considered that this is aligned with the anticipated use in the NHS. But it concluded that the lack of evidence for setmelanotide plus best supportive care compared with best supportive care alone was a key limitation and introduced high uncertainty and probable bias into the evidence base. It agreed that it would take account of this in its decision making.

Primary endpoint

3.7 The primary endpoint in the RM-493-012 and RM-493-015 trials was the proportion of people having at least a 10% weight loss with setmelanotide from baseline to 52 weeks. This primary endpoint was assessed in the full analysis set in the trials, defined as people who had at least 1 dose of setmelanotide and were evaluated at inclusion. A minimum of 10 people were needed in each trial to achieve statistical significance with a power of 94% and an alpha of 0.05 and 0.025 1-sided, with success defined as 50% of people having 10% weight

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loss or more. For this reason, for each outcome in the index trials, the company presented results from 2 separate cohorts:

- the pivotal cohort which included the first 10 people for RM-493-012 and 11 people for RM-493-015
- the supplemental cohort which included a further 5 people for RM-493-012 and 4 people for RM-493-015.

The clinical experts confirmed that a weight loss of 10% would be classed as a clinically meaningful response in clinical practice. But the ERG noted that growing children gain weight naturally, so the primary endpoint may have underestimated fat loss in children. The committee concluded that a weight loss of 10% or more is an appropriate endpoint and would be used to determine response to treatment in clinical practice.

Generalisability of the evidence

3.8 The committee was aware of several potential differences between the populations in RM-493-012 and RM-493-015 and NHS clinical practice. Firstly, there were no people with POMC deficiency and only 1 person with LEPR deficiency from the UK in the trials. The clinical experts explained that the symptoms and genetic variations in people with POMC deficiency were unlikely to differ by location. The weight for age would also likely be consistent in all people with POMC or LEPR deficiencies. POMC deficiency is expected to respond better to setmelanotide and clinical experts expected that a similar response would be seen in a UK population. However, the population with LEPR in the UK is broader and more heterogenous than in some other countries in the trials. This is because of the higher prevalence of consanguineous marriages in some ethnic groups, which increases the risk of biallelic genetic disorders. Therefore, response in people with LEPR deficiency in the UK may not be the same as in the trials. Many people in the trials were from Germany. The clinical experts explained that people with severe obesity in Germany have restrictive inpatient stays for dietary modification and exercise. These people would likely weigh less at baseline than people in the UK, where people have a less intensive regime and continue to live at home during treatment. The committee also noted that the clinical trials for setmelanotide restricted the use of any new dietary and exercise regimes. This

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did not reflect expected clinical practice, because people who lost weight would be encouraged to increase exercise and maintain a healthy lifestyle. So, the treatment effect of setmelanotide in the index trials may have been underestimated. This strict control of diet may also affect people's perception of food, which may have confounded the validity of hunger scores from people enrolled in Germany. The clinical expert noted that people with the most severe condition, for example, those with suicidal ideation, were also excluded from the index trials. So, the severity of the condition in the trials may not have fully represented clinical practice. The committee understood that the population with obesity caused by POMC and LEPR deficiency is small but heterogeneous in the UK. It understood that the level of benefits from the treatment may vary because of this heterogeneity and differences in clinical practices across countries. It concluded that the company's trial populations may be generalisable to those seen in the NHS but there are uncertainties.

Dosing schedule

3.9 The committee noted that the dosing schedule in the marketing authorisation for setmelanotide is:

- starting dose: 0.5 mg in people under 12 years, and 1 mg in people over 12 years.
- maximum dose: 2.5 mg in people under 12 years, and 3 mg in people over 12 years.

The ERG flagged that the clinical trials used different age cut-offs for dosing than those in the marketing authorisation and that the starting and maximum dose of setmelanotide varied by country:

- In RM-493-012, 7 (47%) people were from Germany and 2 (13%) were from France. The starting dose in these countries was 0.25 mg in people under 18 years and the maximum dose was 2.5 mg in people 12 years and over.
- In RM-493-015, 4 (27%) people were from Germany and 6 (40%) people were from France. The starting dose in Germany was 0.25 mg in people under 18 years and the maximum dose was 2.5 mg in people over 12 years. The

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maximum dose in France in people over 12 years was initially 2.5 mg but was amended to 3.0 mg during the trial.

- In RM-493-022, only 7 people with POMC deficiency had published results. All were from Germany where the maximum dose in people over 18 years was 2.5 mg.

  The ERG noted that the dose titration schedule in the marketing authorisation involved steeper titrations and fewer steps than those used in the trials. Because of the discrepancy in dosing, it raised concerns over the generalisability of the results to anticipated UK use, particularly in the long term. Because almost all the reported data in RM-493-022 was based on the lower maximum dose used in Germany, the long-term efficacy and safety of setmelanotide at the maximum UK licensed dose of 3.0 mg is uncertain. The company explained that the steeper titration schedule had been found to be equally well tolerated during regulatory approval so had been included in the marketing authorisation. The committee acknowledged the differences between the dosing schedule used in the trials and that which would be used in the NHS but concluded that the results were still useful for decision making.

Outcomes in the clinical trial

3.10 Key secondary outcomes in RM-493-012 and RM-493-015 included changes in hunger, BMI, body fat, waist measurement and health-related quality of life (HRQoL) from baseline to 52 weeks. The secondary outcomes were analysed in the designated use set. This consisted of people with a weight loss of 5 kg or over (or 5% if body weight at inclusion was less than 100 kg) over the first 12-week open-label period and completed the placebo-controlled washout period. The company stated that there were no validated instruments for measuring hyperphagia in people with rare genetic disorders of obesity. So, RM-493-012 and RM-493-015 used a daily questionnaire for adults, which graded hunger on an 11-point Likert-type scale, ranging from 0 (no feeling of hunger) to 10 (extreme hunger). RM-493-022 measured hunger by asking Global Hunger Questions to people with LEPR or POMC deficiency or, in people aged 6 to 11, their carers. The index trials measured 'morning hunger', 'worst hunger in

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24 hours', and 'average hunger in 24 hours' in people 12 years and over. Reduction in mean daily highest hunger score from baseline was a secondary outcome. The clinical and patient experts explained that hyperphagia is a complex condition, and some aspects related to it, such as distress and obsession with food, may not be captured in the company's measurement of hunger score in the trials. The patient expert also raised concerns with the measurement of hunger on a binary scale. They stressed that, because people with the condition experience hyperphagia from birth, they would not have any perception of 'normal hunger'. So, the quantification of any reduction in hyperphagia would vary considerably between people. The committee understood that hunger scores measured in the trials may not have fully captured all aspects of hyperphagia in people with the condition.

Other key clinical outcomes

3.11 The committee noted that several outcomes included in the NICE scope had not been captured in the company's clinical trials. These were HRQoL for carers, mortality and several comorbidities, including cancer and cardiovascular events. The ERG stated that the exclusion of these outcomes meant that the psychosocial effect and full symptom burden of the condition may not have been captured in the clinical trial results. The committee acknowledged that the short follow up in the trials likely precluded collection of long-term outcomes such as mortality. But it agreed that the lack of data on key scoped outcomes increased the uncertainty about the clinical effectiveness of setmelanotide.

Clinical-effectiveness results

Obesity-related outcomes

3.12 In the full analysis set, 12 people (86%, 90% confidence interval (CI) 61 to 97, p <0.0001) in RM-493-012, and 8 people (53%, 90% CI 30 to 76, p <0.0001) in RM-493-015 had a weight loss of 10% or more from baseline to 52 weeks. People in both trials gained weight during the 8-week self-control withdrawal period but continued to lose weight when restarting setmelanotide. Reductions in the

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secondary outcomes of BMI, body fat and waist circumference were also seen for both index trials (exact results are academic in confidence and cannot be reported here). The committee noted that results appeared to suggest a greater response to setmelanotide in people with POMC deficiency compared with LEPR deficiency at 52-week follow up. However, it also noted the small numbers of people in the trials, single-arm study design, and a lack of clarity and consistency in the company's reporting of study outcomes and results. It concluded that setmelanotide may improve obesity-related outcomes in the short term, but that the results were associated with uncertainty.

Hunger

3.13 In RM-493-012 and RM-493-015, improvements in highest hunger score to 52 weeks were reported with setmelanotide for people in the pivotal cohort of the designated use set population:

- In RM-493-012, the mean reduction in highest hunger score from baseline was 27.1% (standard deviation 28.11, p=0.0005). Four people (50%) had a reduction in highest hunger score of 25% or more.
- In RM-493-015, the mean reduction in highest hunger score from baseline was 43.7% (standard deviation 23.69, p< 0.0001). Eight people (73%) had a reduction in highest hunger score of 25% or more.

  The ERG noted that the designated use set population only included people who had weight loss on setmelanotide. So, the results may have overestimated the effect of setmelanotide on hunger. The committee concluded that setmelanotide likely reduces hunger in people with the condition in the short term, but that the evidence is uncertain.

HRQoL

3.14 RM-493-012 and RM-493-015 reported statistically significant improvements from baseline in HRQoL, measured by the Impact of Weight on Quality of Life-Lite instrument in adults. For people 18 years and under, patients and carer-reported Paediatric Quality of Life Inventory (PedsQL) scores suggested similar

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improvements from baseline in children with POMC deficiency (exact results are academic in confidence and cannot be reported here). However, the ERG noted that no paediatric quality-of-life data was available for children with LEPR deficiency. The committee noted that there was no HRQoL collected from carers of people with the condition. It concluded that setmelanotide may improve HRQoL, but that the results are highly uncertain and there is no data in children with LEPR deficiency or their carers.

Long-term treatment effects

3.15 The company presented evidence from the RM-493-022 extension trial at different follow-up times during the first meeting, and the data suggested a plateau of weight loss. Compared with their weight when entering the extension study, people with LEPR deficiency had further weight loss of 2 kg (1%, standard deviation not reported) at 25 weeks. However, at 89 weeks, people with POMC deficiency had gained an average of 8 kg (9% of extension study baseline weight, standard deviation not reported). Also, people with POMC deficiency had a small increase in BMI at 37 weeks (exact results are academic in confidence and cannot be reported here). The clinical experts explained that, to some extent, a stabilisation of weight was expected and desired, especially for people with LEPR deficiency. This is because the deficient LEPR protein is not only found on the neurones that regulate the MC4R pathway, but also on other parts of the brain involved in food reward. So, setmelanotide only restores part of the mechanism driving the obesity, controlling about 50% to 60% of the hunger pathway in people with LEPR deficiency. However, in people with POMC deficiency, only the MC4R pathway is dysregulated, so setmelanotide restores most of the impaired function. These people may continue to lose weight because they no longer have hyperphagia and weigh less than before, making it easier to exercise and maintain a healthy lifestyle. So, people with POMC deficiency are expected to have a larger response to setmelanotide than people with LEPR deficiency. The clinical experts also explained that, in general, a plateau in weight loss could be seen as a positive outcome because hunger is controlled to a level at which people are eating a normal amount of food. The mean hunger score compared with the extension study baseline was maintained for people with LEPR deficiency at 25 weeks but worsened for people with POMC deficiency at 89 weeks. Only baseline HRQoL was reported for RM-493-022, so the long-term

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quality-of-life effect of setmelanotide is unknown. The committee noted the uncertainties in the evidence for setmelanotide's long-term treatment effect.

Maintenance of treatment effect

3.16 At consultation, the company stated that the observed weight gain and increase in BMI in the extension study was caused by normal growth in the population, which included people under 18 years. It also submitted evidence from a later data cut of the extension study which pooled data from people with POMC and LEPR deficiency. This showed that over half of adults had a reduction in BMI at their latest visit compared with their extension study baseline (exact figures are academic in confidence and cannot be reported here). Most children also had a BMI reduction, or a BMI increase lower than would be expected with normal growth over the course of the study. However, the ERG highlighted that the results in people with POMC deficiency alone showed that some young people and adults gained both weight and BMI compared with their extension study baseline. This suggested that growth in young people was not the primary cause of the increase seen in both outcomes. The clinical experts explained during the second committee meeting that, based on similar rare conditions of obesity, they anticipated that people starting treatment in childhood would see a better response than in the trials and would potentially be overweight or normal weight in the long term. They also highlighted that there was no biological reason for setmelanotide's treatment effect to diminish over time. The committee noted that there was no long-term evidence available that used the BMI z score, which is adjusted for age. It also noted the small number of people (particularly young people) included in the trial. The committee concluded that the company's results suggested some maintenance of treatment effect past 52 weeks but the evidence was uncertain.

Adverse events

3.17 The committee noted that the proportion of people with 1 or more treatment emergent adverse events was high across trials (exact results are academic in confidence and cannot be reported here). The most common adverse events reported in RM-493-012 and RM-493-015 were skin hyperpigmentation, injection

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site reactions (including erythema, pruritus, oedema and pain), nausea and headache. Injection site reactions, nausea and dry mouth were considered to be related to setmelanotide treatment. Upper respiratory tract infections, headache, nasopharyngitis and fatigue were also commonly reported in RM-493-022. However, the ERG noted that skin hyperpigmentation and injection site reactions had not been recorded as treatment emergent adverse events in the long-term extension study, despite the high levels in RM-493-012 and RM-493-015 at 52 week follow up (exact values are academic in confidence and cannot be reported here). A patient expert reported that skin hyperpigmentation may represent a benefit in the view of some people with the condition and their families. The committee noted that 1 person in RM-493-015 had been withdrawn from treatment because of an increased eosinophil count (a type of white blood cell) and 1 person had died in a car accident. However, the company explained that none of the serious adverse events reported in the clinical trials were believed to be related to setmelanotide (exact number of events is academic in confidence and cannot be reported here). During consultation, the company also stated that the later extension study data cut provided had identified no new safety issues. The committee concluded that the adverse events associated with long-term use of setmelanotide are uncertain but likely tolerable.

Stopping treatment

3.18 The committee was aware that the primary endpoint of the proportion of people having 10% or more weight loss in RM-493-012 and RM-493-015 was measured after 52 weeks of treatment (see section 3.6). The company stated that response to setmelanotide would be determined after 12 weeks of treatment. However, the ERG noted that results from week 12 had not been reported in the trials, and it was unclear if the rates from week 52 had been maintained from this timepoint. The clinical experts agreed that it was reasonable to assess response to treatment at 3 months. This was because a notable reduction in hyperphagia would be expected in people whose condition responded after 3 months of treatment. However, some people may not have lost 10% of their body weight by this timepoint. This is because, although suppression of hyperphagia is expected to cause weight loss, weight may be influenced by other factors, so a reduction in weight does not always immediately follow. In these people, clinicians may adjust the dosing and continue setmelanotide for a further 3 months after which

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setmelanotide would be stopped if there is little weight loss. The committee concluded that response would be assessed after a maximum of 6 months of setmelanotide in clinical practice.

The company's economic model

Company's modelling approach

3.19 The company developed a semi-Markov model to estimate the cost effectiveness of setmelanotide. Health states in the model included 7 BMI z classes (0 to 4 in increments of 0.5 and over 4) for children, 7 BMI classes (20 to 50 in increments of 5 and over 50) for adults and death. People with LEPR or POMC deficiencies entered the model having setmelanotide plus best supportive care. After 12 weeks, they transitioned between BMI class levels depending on condition response to setmelanotide. The company assumed a BMI drop for people whose condition responded to setmelanotide. People whose condition did not respond to setmelanotide were modelled to change to best supportive care only at 12 weeks. For these people, the company assumed an increase or maintenance of BMI. Children were assumed to have a BMI gain until 18 years. At this time, BMI z scores were mapped to the respective BMI score. People could transition to death from any BMI or BMI z score health state. The model cycle length was 1 year and used a lifetime time horizon. A disutility and cost associated with common obesity comorbidities was applied to each health state. The ERG was concerned that the maximum BMI and BMI z score health states might have been too low to fully capture the severity of obesity for people with LEPR or POMC deficiency. Also, the company's model was more complex than those used in NICE's technology appraisal guidance on naltrexone–bupropion for managing overweight and obesity and liraglutide for managing overweight and obesity. These were based on a systematic review by Ara et al. (2012). The company stated that the model by Ara et al. was granular for type 2 diabetes and cardiovascular diseases related to general obesity. But it did not fully capture some key MC4R-related comorbidities and the early mortality in this population. The committee concluded that the company's model structure based on BMI classes was acceptable for decision making.

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Modelling hyperphagia

3.20 The company modelled hyperphagia according to severity status (mild, moderate or severe), for each of which a utility multiplier was assigned to BMI health states. The company assumed that:

- setmelanotide's treatment effect on hyperphagia worked independently of its effect on BMI or BMI z score
- there was no interaction between change in BMI health states and hyperphagia.

The ERG was concerned that the company's approach did not explore the effect of any correlation between BMI and hyperphagia status. The clinical experts explained that the driver of hyperphagia is from the genetic defect, and the reduction in hyperphagia is not necessarily directly related to weight. But they noted that it was difficult to compare holistic gains from reductions in BMI and hyperphagia because of the complexity of obesity complications, including social and psychological aspects. They also noted that generally weight loss may plateau, but hunger is controlled by the treatment. At the second meeting, the clinical experts confirmed that a rapid reduction in hyperphagia was expected when taking setmelanotide, but the extent of this reduction would vary among individuals depending on response. However, hyperphagia was expected to stabilise at a markedly reduced level even in people whose condition showed only a partial response to treatment. The patient expert explained that in their experience, the feeling of hunger does not change either with higher or lower BMI. Setmelanotide quickly reduced the hyperphagia, and this benefit did not change with weight loss. Their motivation to eat while having setmelanotide is based on factors such as mood and energy levels rather than simply hunger. However, learnt food-seeking behaviours can be difficult to overcome, especially in people who have lived with the condition for a long time. The committee understood that hyperphagia is a multi-faceted state. Considering the rarity and complexity of the condition, the committee concluded that the company's approach to modelling hyperphagia was acceptable.

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Modelled population

3.21 The company's base case used the overall population, that is, it combined people with POMC and LEPR deficiency as well as adults and children. The committee agreed that the pooled population was appropriate for decision making during its first meeting. However, it noted that the baseline population distribution in the company's model concerning age and deficiency type did not reflect UK practice. In the company's original submission, the baseline distribution of children and adults in the company's model came from a conference abstract by Argente et al. (2019). The company updated this at consultation to include a lower proportion of children in the baseline population (exact proportions are academic in confidence and cannot be reported here). It stated this was a conservative assumption because it expected most people would start setmelanotide as children. The committee recalled that severe obesity usually presents within the first few years of life and the move towards earlier diagnostic testing (see section 3.2 and section 3.5). One clinical expert estimated that only 5% to 10% of people with the condition are diagnosed in adulthood, most of whom had not been living in the UK as a child. So, more people would be diagnosed as children in clinical practice than the company had modelled. For deficiency type, at the first committee meeting, the company assumed that one-third of people in the model had POMC deficiency and two thirds had LEPR deficiency based on a paper by Graves et al. (2021). One clinical expert stated that, in the UK, only a small number of people with biallelic POMC (including PCSK1) or biallelic LEPR deficiency had been diagnosed to date (number of people is deemed confidential and cannot be reported here). At consultation, the company updated its base-case assumptions to account for the distribution expected in clinical practice. The ERG agreed with the company's updated baseline distribution. The committee concluded that the company's baseline distribution was appropriate for decision making but noted that more people may start setmelanotide as children in clinical practice.

Modelling treatment effect on BMI

3.22 The distribution of people in each of the 7 BMI and BMI z score health states was based on the baseline characteristics from the index trials in the company's model. The response to setmelanotide at 12 weeks used the proportion of people who met the primary endpoint of 10% or more weight loss in these trials. During

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its first meeting, the committee noted that the 12-week response rates were assumed to be equal to results at 52 weeks and had not been reported in the company submission. In people whose condition responded in the model, the treatment effect of setmelanotide in the first year was based on the mean BMI reduction seen in the trials. After the consultation, the company updated its base case to assume that the post-trial BMI class was maintained, informed by longer-term data from the extension study. The ERG highlighted the uncertainty in these estimates and provided scenarios that varied BMI outcomes after the trial period. The committee recalled the uncertainty in setmelanotide's long-term treatment effect (see section 3.15 and section 3.16) and the lack of evidence on its comparative effectiveness relative to best supportive care. However, considering the entirety of the evidence, the rarity of the condition, and clinical expert opinions, the committee concluded that the company's assumptions about setmelanotide's long-term treatment effect on BMI in the model were acceptable for decision making but still associated with significant uncertainties.

Modelling treatment effect on hyperphagia

3.23 Because the effect of hyperphagia was not captured in the trials, hyperphagia's severity categories were defined according to a vignette study done by the company. In this study, health-state vignettes for no hyperphagia, and mild, moderate and severe hyperphagia were described. In forming the vignettes, the company considered literature and clinical expert input on hunger, food intake, distress and obsession with food. At consultation, both the company and ERG base cases were updated to assume all people have severe hyperphagia at baseline. The clinical experts supported this, stating that people with the condition would either have severe or extreme hyperphagia if they did not have treatment, depending on the extent of function remaining in the hunger pathway. One clinical expert informed the Likert scale cut-offs to relate hunger scores collected in the trials to hyperphagia severity status (exact values are academic in confidence and cannot be reported here). The company modelled setmelanotide's treatment effect on hyperphagia by mapping the change in daily worst hunger score from baseline to 52 weeks in the index trials to the relevant hyperphagia severity categories. The company applied this at the start of the first cycle. However, the committee noted the significant uncertainty in the modelling of hyperphagia and the long cycle length of 1 year. It recalled that clinicians

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would be likely to stop setmelanotide only if there was no significant weight loss after 6 months of treatment. So, it preferred to apply the change in hunger score from the trials as a half-cycle correction in the first cycle. At consultation, the ERG updated its base case to align with this but the company did not. The committee concluded that setmelanotide's treatment effect on hyperphagia should be applied after 6 months of treatment.

Stopping rate

3.24 At consultation, the company introduced a stopping rate of 1% for people whose condition responded to setmelanotide at 12 weeks. This was in line with the ERG and committee preference at the first meeting and based on the stopping rate from the pivotal trial in NICE's technology appraisal guidance on liraglutide for managing overweight and obesity. The patient and clinical experts confirmed that people would be unlikely to stop taking setmelanotide if their condition was responding. This was because there are no other options that control both weight and hyperphagia. However, it was possible that some people may stop taking the drug because of adverse events, mainly skin hyperpigmentation. This is caused by off-target interactions and tends to plateau with long-term use. One clinical expert estimated a compliance rate of at least 80% in people whose condition responded to setmelanotide. The clinical expert explained that clinicians may also choose to lower the dose of setmelanotide rather than stop setmelanotide completely. The patient expert explained that the feeling of hunger returned very quickly if doses of setmelanotide were delayed or stopped. The committee noted that in the longer-term data from the extension study, 1 person had not taken setmelanotide properly, but this was because of reasons other than adverse events or tolerability. The committee also noted that a weekly formulation of setmelanotide is being developed that will remove the need for daily injections. The committee considered that the rates of compliance for setmelanotide were likely to be high, but that a few people may stop treatment because of adverse events. It concluded that the assumption of a 1% stopping rate for setmelanotide was appropriate for decision making.

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Modelling mortality

3.25 The committee was aware that mortality had not been captured in the company's clinical trials for setmelanotide. For people whose condition responds to setmelanotide, the company assumed a mortality rate equal to that of people with general obesity of the same BMI. Because of the lack of natural history data in people with POMC or LEPR deficiency, the life expectancy of people having best supportive care is uncertain. So, the company used mean and maximum life expectancies estimated by 1 clinical expert for people whose condition did not respond to setmelanotide at 12 weeks. In its original base case, it transformed these values into probability distribution functions, which were applied in the model. However, the company updated this assumption after consultation to align with the ERG and committee's preferred modelling. This converted the company's life expectancy estimates to equivalent hazard ratios which were then applied to general population mortality. The committee concluded that modelling mortality in people having best supportive care using hazard ratios based on clinical expert life expectancy estimates was appropriate for decision making.

Utility values

Utility values for BMI health states and comorbidities

3.26 The committee was aware that quality-of-life data had been collected in RM-493-012 and RM-493-015. However, the company stated that the small sample size, inconsistent collection timepoints and lack of specific measure for hyperphagia made using the trial data inappropriate. Instead, it used utility values from the literature in the model. For each of the 7 BMI health states, utility values came from a US study of Short Form Survey (SF)-12 data by Alsumali et al. (2018). Utility values for the 7 BMI z health states came from Riazi et al. (2010). These values were mapped to EQ-5D-3L using a mapping algorithm from Khan et al. (2014). The ERG agreed that using literature values was reasonable given the limitations in the trial data. The committee noted that, because the utility values were derived in people with general obesity, few people may have had BMI or BMI z scores as high as people with POMC or LEPR deficiency. The company also considered common comorbidities in the model. For each of sleep apnoea,

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osteoarthritis, type 2 diabetes, non-alcoholic fatty liver disease and cardiovascular events, a disutility value was sourced from the literature. These were applied at differing prevalence rates in the model depending on BMI or BMI z score. The committee was concerned that, because the comorbidities were common to general obesity, their effects on quality of life may already be captured in the utility values for BMI health states. So, comorbidities would be double counted in the model. However, the clinical experts explained that rare genetic disorders of obesity have a higher comorbidity burden than general obesity because people's BMI is high from childhood. So, the company's values were likely conservative. The committee concluded that the company's utility values for BMI health states and comorbidities, while uncertain, are appropriate for decision making.

Utility values for hyperphagia

3.27 To account for the quality-of-life decrement caused by hyperphagia, the company applied a utility modifier for mild, moderate and severe hyperphagia to the utilities for BMI health states (values are academic in confidence and cannot be reported here). It derived the utilities from its vignette study. Time trade off interviews were done in 215 members of the UK general public using a 10-year time horizon to elicit utilities for each of the hyperphagia severity vignettes (see section 3.20). The committee recalled that hyperphagia is a multi-faceted state that would be hard for people with normal hunger levels to fully comprehend. However, it acknowledged that the rarity of POMC or LEPR deficiencies made doing the vignette in this population challenging. During its first meeting, the committee noted that the company's utility value for severe hyperphagia was extremely low. The committee was aware that hyperphagia is the driving force behind obesity and associated comorbidities, social stigma and psychological effects. So, a large quality-of-life increase from stopping hyperphagia is plausible. However, a disutility of -0.11 was used for presence of hyperphagia in NICE's highly specialised technologies guidance on metreleptin for treating lipodystrophy, a condition also affecting the MC4R pathway. In the metreleptin appraisal, the value of -0.11 was considered to underestimate the quality-of-life decrement for hyperphagia. So, the ERG provided a scenario analysis which used this value for mild hyperphagia. For moderate and severe hyperphagia, the ERG used double (-0.22) and triple this value (-0.33), respectively. During its first

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meeting, the committee noted that a disutility of -0.33 resulted in a utility multiplier of 0.603 for severe hyperphagia, considerably higher than the company's vignette study modifier. The committee considered that the true detrimental impact of severe hyperphagia on quality of life lay somewhere between the company's and ERG's utility multipliers. At consultation, the company highlighted that some 'responders' to the vignette study had rated severe hyperphagia as a negative utility, meaning they classed the condition as worse than death. The committee acknowledged that, while severe hyperphagia is debilitating (see section 3.2), the inclusion of negative values likely overestimated the quality-of-life decrement. It considered the company's scenarios, which:

- normalised negative vignette utility values to zero. This produced a utility modifier for severe hyperphagia slightly higher than what was originally derived from the company's vignette study without equalling negative values to zero
- normalised negative values to zero and assumed the same difference between moderate and severe hyperphagia as that for mild to moderate. This produced a utility multiplier for severe hyperphagia slightly lower than the ERG's value of 0.603 (exact values are academic in confidence and cannot be stated here).

  During the second committee meeting, the clinical experts explained that the hyperphagia associated with this condition is more severe than that in some other conditions because of the leptin deficiency and the nature of the fundamental pathway. They also noted that, once treated, hyperphagia would improve. There may be a dose response to treatment in relation to hyperphagia but this response varies among individuals. The ERG also flagged that because of the non-linear relationship across hyperphagia severities, it would prefer the company's first scenario. The committee recalled that in people whose condition responded to setmelanotide, hyperphagia would significantly reduce and some may resolve (see section 3.2). The committee concluded that the company's scenario which normalised the negative values from the vignette study to zero assuming a non-linear relationship across hyperphagia severity states was acceptable for decision making.

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Carer disutility

3.28 The committee was aware that there was a considerable mental and physical impact on carers of people with the condition (see section 3.2). To account for this, the company introduced a disutility of -0.0986 into its base case at consultation for people taking best supportive care. This was based on the value used in NICE's highly specialised technologies guidance on metreleptin for treating lipodystrophy. The ERG commented that it was unclear whether the disutility for lipodystrophy would be generalisable to people with POMC and LEPR deficiency, so it excluded a carer disutility from its base case. However, it noted that the company had placed a lower limit of zero for accrued quality-adjusted life years (QALYs; the sum of those from both carer and person with the condition) in the health states. The ERG removed this limit so negative QALY accruals could be accounted for in the incremental analysis. During the second committee meeting, the patient expert explained that full time care is needed for children with POMC or LEPR deficiency and highlighted the struggles for both parents and children to do daily activities from an early age. The committee acknowledged that the size of the disutility was uncertain because no data had been collected on the quality of life for carers in the setmelanotide clinical trials. Despite this, it considered that accounting for caregiver's disutility in the modelling was acceptable. It also agreed that, in the absence of further data, using the value from the metreleptin appraisal and allowing accrual of negative QALYs was appropriate for decision making.

Costs and resource use

Treatment costs

3.29 After consultation, the company and ERG's base cases used separate doses by age and deficiency and applied these to the model. This was because different doses of setmelanotide are used in the marketing authorisation for adults and children. The committee acknowledged the small number of people in the subgroups but concluded that separate doses by deficiency and age should be used in the model.

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Discount rate

3.30 NICE's interim process and methods of the highly specialised technologies programme 2017 states that a discount rate of 1.5% for costs and benefits may be considered by the evaluation committee. This is when it is highly likely that, on the basis of the evidence presented, the treatment is likely to restore people to full or near full health when they would otherwise die or have a very severely impaired life, and when this is sustained over a very long period (normally at least 30 years). In its original base case, the company used a discount rate of 1.5% for health benefits and 3.5% for costs. However, the committee noted that the NICE guide to methods of technology appraisal 2013 does not include using differential discount rates for health benefits and costs in the reference and non-reference case. It agreed that differential discounting was not appropriate. It also agreed that a discount rate of 1.5% could not be used for both health benefits and costs. This was because the short follow up in the trials meant that there was no long-term effectiveness data to support the mortality and quality-of-life gains in the model. After consultation, the company updated its base case to align with the ERG's preferred assumption, which used a 3.5% discount rate for health benefits and costs. The committee also considered the company's scenarios using the lower discount rate of 1.5% that incorporated longer-term effectiveness data from the extension study. It acknowledged that, by managing hyperphagia, setmelanotide would result in significant health benefits. These benefits would likely be greater if people started setmelanotide at a younger age when the level of obesity was less severe and regaining normal weight may be possible. However, the committee noted that only people aged 6 and over are included in the licence for setmelanotide, by which point food-seeking behaviours might be established. It also recalled that setmelanotide does not completely restore the pathways controlling hunger in people with LEPR deficiency, so some level of hyperphagia may remain in these people. Also, both LEPR and POMC deficiencies are associated with comorbidities that might prevent normal life expectancy (see section 3.1). Clinical experts explained that, although an improvement in comorbidities was plausible, there was no data to support this. The committee concluded that a discount rate of 3.5% should be used for both health benefits and costs.

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QALY weighting

Applying a QALY weighting

3.31 The committee understood that NICE's interim process and methods of the highly specialised technologies programme 2017 specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee noted that the undiscounted QALY gains for the scenarios incorporating its preferred assumptions met the criteria for applying a QALY weight. It acknowledged there was significant uncertainty in the cost-effectiveness estimates but agreed the extra health and quality-of-life benefits of setmelanotide are likely to be substantial.

Cost-effectiveness estimates

The company's and ERG's cost-effectiveness results

3.32 The company's base case showed that setmelanotide was associated with an ICER of £212,746 per QALY gained compared with best supportive care. The ERG's base case, which excluded a carer disutility, showed that setmelanotide was associated with an ICER of £324,925 per QALY gained compared with best supportive care. Both the company and ERG's base cases used the pooled population, with the prevalence of LEPR and POMC deficiencies expected in clinical practice and included the confidential discount for setmelanotide available to the NHS. The committee noted that the ICER was very sensitive to the choice of utility value for severe hyperphagia. Using its preferred utility multiplier that normalised negative values from the vignette study to zero and assumed a non-linear relationship between severity states increased the

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company's base-case ICER to £239,163 per QALY gained. However, the committee recalled that more people were likely to start setmelanotide as children in clinical practice than assumed by the company (see section 3.21). It also noted that increasing the proportion of children in the model might improve the ICER. So, the company's cost-effectiveness estimates were likely conservative. Considering the company and ERG's analyses, the committee's preferred assumptions included:

- using the pooled population combining deficiency type and age
- assuming BMI maintenance for people having setmelanotide after the first year of treatment
- applying setmelanotide's treatment effect on hyperphagia after 6 months of treatment
- using a 1% stopping rate applied from 12 weeks onwards
- converting life expectancy for people having best supportive care to equivalent hazard ratio multipliers
- using utility multipliers for hyperphagia from the company's vignette study for mild and moderate hyperphagia
- using the utility multiplier from the company's scenario that normalised negative values from the vignette study to zero and assumed a non-linear relationship across hyperphagia severity states for severe hyperphagia
- applying a carer disutility of -0.0986 and allowing the accrual of negative QALYs
- using separate doses of setmelanotide for adults and children and by deficiency
- applying a discount rate of 3.5% for both health benefits and costs.

The committee considered that, when using its preferred assumptions, setmelanotide was associated with an ICER of £194,630 per QALY gained compared with best supportive care. When applying a QALY weighting, this was within the threshold normally considered an effective use of NHS resources in a highly specialised technology.

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Impact of the technology beyond direct health benefits and on the delivery of the specialised service

Indirect benefits

3.33 The company stated that setmelanotide would result in benefits beyond those for the NHS and personal services. This was because rare genetic disorders of obesity result in the onset of obesity in infancy, which can significantly affect a child's social development and make them a target for bullying at school. The clinical experts explained that, by stopping hyperphagia and reducing weight, setmelanotide could indirectly improve education attainment, employment, the ability to find a partner and fertility of people with the condition. The patient expert also explained that obesity had a major effect on confidence and self-esteem as a child. People with the condition could find many social situations difficult and this may limit their ability to fulfil their full potential in society. The clinical experts noted that, in children who are growing, even maintaining a stable weight has a major effect on their mental health. The committee also recalled the burden of care needed for people with LEPR or POMC deficiency and the significant effect this can have on carers' mental health. Clinical experts also explained that by reducing hyperphagia, effective treatment with setmelanotide would substantially decrease the burden on carers and family members because it could:

- remove the need for constant supervision and extreme measures to control food-seeking behaviour
- reduce carer anxiety associated with a lack of control over food and exercise
- reduce the level of care needed for obesity-associated comorbidities.

The committee recalled that the company had applied a carer disutility only for people whose condition did not respond to setmelanotide in the model to account for these factors. It noted that, especially in people with LEPR deficiency, some hyperphagia would likely remain with setmelanotide. But this was expected to be mild and would be easier to manage, so the level of care needed would markedly reduce. The committee acknowledged that

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obesity caused by LEPR or POMC deficiency affects people with the condition beyond direct health benefits. It agreed that the company's model captured some of these but quantifying all the benefit was difficult. The committee considered this in its decision making.

Use in specialist centres

3.34 The clinical experts explained that NICE's guideline on overweight and obesity management recommends a tier-based system of obesity treatment. The company proposed that setmelanotide would be offered through specialist multidisciplinary weight management (tier 3) services plus a planned network of 14 commissioned paediatric centres. The clinical experts highlighted that referral to tier 3 services is poorly streamlined and access varies depending on location. They stressed the importance of people with rare genetic disorders of obesity having treatment by specialists with the expertise to make clinical decisions alongside a multidisciplinary team. Given the rarity of the condition, only a small number of high-level tier 3 clinics have the specialist knowledge to treat the condition. The representative from NHS England confirmed that, were setmelanotide to be recommended, it would initially be used in the 1 centre of excellence for rare genetic disorders of obesity in England, with potential to consider 1 or 2 further sites for access. The representative considered that, although genetic testing to confirm diagnosis is needed to have setmelanotide, this is already routinely commissioned. So, no additional investment would be needed to use setmelanotide in the NHS. The committee concluded that setmelanotide would be offered at a small number of specialist centres on the advice of a multidisciplinary team.

Other factors

Innovation

3.35 The company stated that it considered setmelanotide to be a step change in the treatment of LEPR or POMC deficiency. This was because there are no licensed treatments for the condition, and current options are hard to maintain and

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ineffective. The clinical experts agreed that setmelanotide is innovative because it is the first drug to treat the underlying mechanism of the obesity and, consequentially, hyperphagia. They also flagged the substantial weight loss seen with setmelanotide. The committee recalled that there is a high unmet need in this population. It also noted that setmelanotide significantly reduced weight, BMI and hunger levels in the single-arm trials, which quickly reversed when people stopped treatment. It concluded that setmelanotide may be innovative.

Equality issues

3.36 The committee noted that the population for which setmelanotide is indicated includes children and young people. It further noted the additional benefits beyond health the treatment may have for children and young people with the condition. The committee discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted the principles that guide the development of NICE guidance and standards. This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The committee acknowledged and considered the nature of the population as part of its decision making. The clinical and patient experts also noted that setmelanotide is administered as a subcutaneous injection every day, so people with vision problems, learning or physical disabilities and needle phobia might find this challenging. The clinical experts highlighted that the burden of administration would reduce significantly with the new weekly formulation. Also, support for these people should already be in place to manage other health needs. One clinical expert noted that biallelic, recessive disorders disproportionately affect people from ethnic backgrounds in which consanguineous marriage is more common. Because the committee had not been presented with clinical or economic evidence in these populations, it could not know whether setmelanotide's treatment effect reported in the clinical trials would differ for them. So, it could not make a recommendation in this subgroup. The committee concluded that all equalities issues for setmelanotide had been considered in decision making.

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Conclusion

Recommendation

3.37 The committee considered that there was uncertainty with the most plausible ICER for setmelanotide compared with best supportive care, but it was likely to be within the threshold normally considered an effective use of NHS resources in a highly specialised service. This was when considering QALY weighting and the fact that more people would start setmelanotide as children than currently modelled. So, it could recommend setmelanotide for routine commissioning to treat obesity caused by LEPR or POMC deficiency.

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4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a person has LEPR or POMC deficiency and the doctor responsible for their care thinks that setmelanotide is the right treatment, it should be available for use, in line with NICE's recommendations.

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5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Emma Douch
Technical lead

Yelan Guo
Technical adviser

Daniel Davies
Project manager

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Update information

Minor changes since publication

March 2025: Links were updated following publication of NICE's guideline on overweight and obesity management.

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