NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Setmelanotide for treating obesity caused by LEPR or POMC deficiency

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using setmelanotide in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of setmelanotide in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using setmelanotide in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 21st February 2022

Second evaluation committee meeting: 13th April 2022

Details of membership of the evaluation committee are given in section 7.

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1 Recommendations

1.1 The committee was minded not to recommend setmelanotide 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.

1.2 The committee recommends that NICE requests further information from the company, which should be made available for the second evaluation committee meeting. This should include exploratory analyses using the committee's preferred assumptions with the following:

- using the UK patient population distribution for the pooled population, as well as scenario analyses for sub-populations by deficiency type and age
- varying setmelanotide's long-term treatment effect on body mass index
- using alternative utility values for severe hyperphagia.

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. However, follow up in the trials is short, so the long-term effects of

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setmelanotide are uncertain. Also, it has not been compared with best supportive care.

There are uncertainties in the economic modelling, including:

- the proportion of people with the 2 different conditions in the model
- setmelanotide's long-term effect on BMI
- how setmelanotide affects hyperphagia
- the dosing of setmelanotide
- how long people having best supportive care live
- the stopping rate for setmelanotide
- quality-of-life values for severe hyperphagia
- what the discount rate for health benefits should be.

Because of the uncertainties in the clinical trials and the economic model, it is unclear whether the criteria for a quality-adjusted life-year weighting has been met (that is, extra health and quality-of-life benefits of setmelanotide are considered to be substantial). Also, the cost-effectiveness estimates are higher than what NICE usually considers acceptable for highly specialised technologies.

So, setmelanotide is not considered an appropriate use of NHS resources within the context of a highly specialised service and cannot be recommended.

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.'

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Dosage in the marketing authorisation

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

Price

2.3 The list price of setmelanotide is £2,376.00 per 10 mg/ml vial for injection (excluding VAT; company's evidence submission). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Rhythm Pharmaceuticals, the views of people with the condition and clinical experts, 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

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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.

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 the age of 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

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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 cupboards 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.

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.

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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 they 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.

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 clinical guideline on obesity and its identification, assessment and 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 disease (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

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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. They explained that the pathway for testing and knowledge of common genetic variants is well established both from established NHS services and a previous research programme. So, the number of new cases expected from the rollout of wider genetic testing would likely be minimal. The committee concluded 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.

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 mass index (BMI) of 30 kg/m^2 or more (or the ninety seventh 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

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deficiency are from week 37. Unpublished results for some outcomes are available up to week 89 for people with POMC and week 37 for people with LEPR deficiency.

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 support 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 have to consider this in its decision making.

Primary end point

3.7 The primary end point 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 end point 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 loss of 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.

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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 end point may have underestimated fat loss in children. The committee concluded that a weight loss of 10% or more is an appropriate end point 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 UK patients. 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. 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

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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

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2.5 mg in people over 12 years. The 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 then 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 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 a 11-point Likert-

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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 24 hours', and 'average hunger in 24 hours' in people 12 years and older. 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.

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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 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.

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The ERG noted that 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 (IWQOL)-Lite instrument in adults. For people 18 years and under, patients and carer reported Paediatric Quality of Life Inventory (PedsQL) scores suggested similar 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 committee noted that evidence from the extension study RM-493-022 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

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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 committee noted that, at the latest data cut there was a maximum follow up for setmelanotide of 32 months (2.7 years) for people with POMC deficiency and 17 months (1.4 years) for people with LEPR deficiency from the extension study, which are still relatively short follow-up times. The committee also noted that no BMI results from RM-493-022 were available for people with LEPR deficiency at the time of the first committee meeting. 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 quality-of-life effect of setmelanotide is unknown. The ERG stated that these results suggested a possible waning of treatment effect but noted the small number of people included in the extension study analyses. The committee noted these uncertainties in the evidence (see section 3.8) and concluded that setmelanotide's long-term treatment effect is uncertain.

Adverse events

3.16 The committee noted that the proportion of people with 1 or more treatment emergent adverse events was high across trials (exact results

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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 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 patients and 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). The committee concluded that the adverse events associated with long-term use of setmelanotide may be tolerable, but that the evidence is uncertain.

Stopping treatment

3.17 The committee recalled that the primary end point 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. 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

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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 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 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

3.18 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 disease 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 the age of 18. At this time, BMI-Z scores were mapped to the respective BMI score. People could transition to death from any BMI or BMI-Z 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 health states might have been too low

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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.

Modelling hyperphagia

3.19 The company modelled hyperphagia as a severity status and as a utility multiplier assigned to BMI health states. A severity status (mild, moderate or severe) was applied at the start of the first cycle and was assumed to be constant throughout a person's lifetime. So, 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

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the 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 was now 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 condition for a long time. The committee understood that hyperphagia is a multi-faceted condition. Considering the rarity and complexity of the condition, the committee concluded that the company's approach to modelling hyperphagia was acceptable.

Modelled population

3.20 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 baseline distribution of children and adults in the company's model came from a conference abstract by Argente et al. (2019). Based on a paper by Graves et al. (2021), the company assumed that one third of people in the model had POMC deficiency and two thirds had LEPR deficiency. One clinical expert stated that, in the UK, 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). The committee considered that the distribution of the company's baseline population may not reflect that seen in clinical practice. The ERG was concerned that the pooled population did not capture differences in treatment effect and disease progression between the different deficiency types. It also highlighted differences in related comorbidities and dosing schedules for adults compared with children. So, it preferred 4 separate subgroups by deficiency type (POMC and LEPR) and age (children and adults). The clinical experts explained that some comorbidities associated with the condition, such as diabetes, disproportionately affected adults. However there are also factors specific to children, including the effect on growth and educational development.

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The clinical experts were concerned that the ERG's use of subgroups by age would not capture the natural history of a condition that presented in children and considered the LEPR and POMC deficiencies similar enough to be considered as a whole population. They were also concerned that the subgroups may not be large enough to detect difference in people having setmelanotide. The committee acknowledged that condition severity and expectations of treatment response may differ by deficiency type (see section 3.8). It considered both the ERG and company's modelled populations uncertain but recalled that the ERG's subgroups included very few people. Considering these, the committee concluded that the pooled population should primarily be used in the model but noted that the company's baseline distribution of LEPR and POMC deficiencies did not reflect those seen in the NHS.

Modelling treatment effect on BMI

3.21 The distribution of people in each of the 7 BMI and BMI-Z health states was based on the baseline characteristics from the index trials. The response to setmelanotide at 12 weeks used the proportion of people who met the primary end point of 10% or more weight loss in these trials. The committee recalled 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 observed mean BMI reduction in the trials. Clinical expert opinion was used to predict treatment effect from 2 years onwards depending on deficiency type. The ERG highlighted the uncertainty in these estimates and provided scenarios that varied BMI outcomes after the trial period. The committee recalled the discussion about setmelanotide's treatment effect on BMI in people with POMC or LEPR deficiency (see section 3.15). It also recalled the uncertainties relating to setmelanotide's treatment relative to best supportive care (see section 3.6) and lack of evidence on long-term treatment effect (see section 3.15). Considering the evidence

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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 uncertain. It took this into account during decision making.

Modelling treatment effect on hyperphagia

3.22 Because 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. The baseline hyperphagia severity distribution was informed by 1 clinical expert. The same expert also informed the Likert scale cut-offs to relate hunger scores collected in the trials to hyperphagia severity statuses (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. Because response was measured at 12 weeks in the trials, the ERG preferred to apply the treatment effect on hyperphagia at the end of the first cycle in its base case. However, the committee noted the significant uncertainty in the modelling of hyperphagia and the long cycle length of 1 year. It recalled that clinicians would be likely to stop setmelanotide only if there was no significant weight loss after 6 months of treatment. So, it agreed that the treatment effect on hyperphagia should be applied as a half-cycle correction in the first cycle (after 6 months of treatment). The ERG also noted that NICE's technology appraisal guidance on metreleptin for treating lipodystrophy categorised hyperphagia based on presence or absence only. The committee recalled that the perception of a hyperphagia reduction would vary considerably between people with the condition (see section 3.10). It concluded that there was significant

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uncertainty around both the company and ERG's modelling of hyperphagia but that setmelanotide's treatment effect on hyperphagia should be applied after 6 months of treatment.

Stopping rate

3.23 The company did not include a stopping rate for people whose condition responded to setmelanotide at 12 weeks. This was because no serious adverse events seen in index trials were deemed related to setmelanotide. The ERG was concerned that the high side-effect profile of setmelanotide and burden of daily injections may lead to stopping treatment. It noted the relatively high stopping rates in the index trials and that 1 person stopped setmelanotide in RM-493-015 because of an adverse event. So the ERG included a stopping rate of 1% for people whose condition had responded at 12 weeks in its base case. This was 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 explained 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 chose 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 are delayed or stopped. The committee 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 few people

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may stop treatment because of adverse events. It concluded that the model should include a 1% stopping rate for setmelanotide.

Modelling mortality

3.24 The committee recalled 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, for people whose condition did not respond to setmelanotide at 12 weeks, the company used mean and maximum life expectancies estimated by 1 clinical expert. It transformed these values into probability distribution functions, which were applied in the model. The company assumed that life expectancy for people with POMC deficiency would be greater than that of people with LEPR deficiency. However, clinical advice to the ERG highlighted that the people with POMC deficiency had more comorbidities so mortality in this population would be higher than in those with LEPR deficiency. The ERG provided a scenario using alternative values for mean and maximum life expectancy. The ERG also stated that the company's use of alternative methodological approaches to model mortality for people having setmelanotide and best supportive care was inappropriate. To model mortality for best supportive care in its base case, the ERG preferred to convert the company's life expectancy estimates to equivalent hazard ratios which were then applied to general population mortality. The committee noted that, unlike the company's approach, the use of hazard ratios incorporated the expected pattern of deaths in the general population. It concluded that the ERG's approach to modelling mortality in people having best supportive care was appropriate for decision making.

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Utility values

Utility values for BMI health states and comorbidities

3.25 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, 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.

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Utility values for hyperphagia

3.26 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 3.22). The committee recalled that hyperphagia is a multi-faceted condition 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. It noted that the company's utility value for severe hyperphagia was relatively low. The committee recalled 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 technology appraisal guidance for 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. The committee noted that a disutility of -0.33 resulted in a utility multiplier of 0.603 for severe hyperphagia, considerably higher than the vignette study modifier. The committee considered that both the company's and ERG's utility multiplier values were likely to overestimate the detrimental impact of severe hyperphagia on quality of life. The committee recalled that there was a considerable mental and physical burden on carers of people with the condition (see section 3.2) and that a disutility for carers had not been applied in the

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company or ERG models. However, the committee recalled that hyperphagia and weight loss do not always align (see section 3.17 and 3.19). It was also concerned about the discrepancy on utility values applied for hyperphagia between the metreleptin appraisal and this topic, especially that for severe hyperphagia. The committee concluded that there was significant uncertainty in both company's and ERG's utility values for severe hyperphagia and this should be explored.

Costs and resource use

Treatment costs

3.27 The company pooled the average dose of setmelanotide in the index trials to calculate drug costs for setmelanotide. In its base case, the ERG preferred to separate the doses by age and deficiency and apply each to the respective subgroup in the model. It stated that the company's approach was inappropriate 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. However, it concluded that separate doses by deficiency and age should be used in the model.

Discount rate

3.28 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 base case, the company used a discount rate of 1.5% for health benefits and 3.5% for costs. The committee noted that the NICE guide to methods of technology appraisal (2013) does not include using differential discount

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rates for health benefits and costs in the reference and non-reference case. The company highlighted that a discount rate of 1.5% for benefits and 3.5% for costs had been accepted in NICEs technology appraisal on mifamurtide for osteosarcoma. However, the committee noted that mifamurtide is a short-term treatment, whereas setmelanotide would be used continuously over a person's lifetime. Also, this guidance was published in 2011, before the methods guide was updated. The committee agreed that differential discounting was not part of the reference case. It next considered if a discount rate of 1.5% could be used for both costs and health benefits. The company stated that a 1.5% discount rate for health benefits was appropriate because setmelanotide was associate with significant quality-of-life gains. Also, mortality was assumed to be comparable between people whose condition responded to setmelanotide and people with general obesity. However, the ERG highlighted the short follow up in the trials which meant that the long-term effectiveness of setmelanotide is unknown. So, mortality and quality-of-life gains in the model are not supported by evidence. The clinical experts also clarified that the goal of treatment was substantial weight loss but that a normal weight in people with POMC or LEPR deficiency would be difficult. This is because of the severity of obesity and likely plateauing of weight loss (see section 3.15). In its base case, the ERG used a discount rate of 3.5% for both health benefits and costs. The committee acknowledged that, by managing hyperphagia, setmelanotide would result in significant health benefits, but the duration of these benefits was unknown. 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. The committee concluded that the company's use of differential discounting was not appropriate and that a discount rate of 3.5% should be used for both health benefits and costs.

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Quality-adjusted life year (QALY) weighting

Criteria for applying a QALY weighting

3.29 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 some of the company and ERG's analyses showed QALY gains within this range. However, it recalled the uncertainties surrounding the modelling, including the long-term treatment effect of setmelanotide and utility values for severe hyperphagia. The committee concluded that it is unclear if the criteria for applying a QALY weighting is met.

Cost-effectiveness estimates

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

3.30 The company's base case showed that setmelanotide was associated with an ICER of £141,550 per QALY gained compared with best supportive care. This was in the pooled population, weighted by the prevalence of LEPR and POMC deficiencies specified in the literature. It included the confidential discount for setmelanotide available to the NHS. The ERG provided base cases by subgroup. In the population with POMC deficiency, setmelanotide was associated with an ICER compared with best supportive care of £218,390 per QALY gained in children and

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£242,240 per QALY gained in adults. In people with LEPR deficiency, the ICERs were £298,476 per QALY gained in children and £326,123 per QALY gained in adults. Considering the company and ERG's analyses, the committee's preferred assumptions included:

- using the pooled population combining deficiency type and age
- applying setmelantide'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 and exploring severe hyperphagia further
- 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 noted that it had not been presented with an ICER that included all its preferred assumptions. It agreed that it was not clear if the QALY weighting criteria was met, and noted that the company and ERG analyses were both above the threshold normally considered an effective use of NHS resources in a highly specialised technology. The committee concluded that both the company's and ERG's cost-effectiveness results were uncertain.

Uncertainties to explore further in the modelling

3.31 The committee recalled the high level of uncertainty surrounding some of the company's assumptions. It noted that the company should explore the following in the modelling:

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- using a UK patient population distribution for the pooled population with scenario analyses for sub-populations by deficiency type and age (see section 3.20)
- setmelanotide's long-term treatment effect on BMI
- alternative utility values for severe hyperphagia.

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

Indirect benefits

3.32 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 significant effect this can have on carer's mental health. It noted that setmelanotide 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

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- reduce the level of care needed for obesity-associated comorbidities.

The committee recalled that, especially in people with LEPR deficiency, some hyperphagia would likely remain with setmelanotide. So, these people would still need some support from carers. The committee recalled that the company had not applied a carer disutility in the model. However, it recalled the uncertainties associated with the utility value for severe hyperphagia (see section 3.26). The committee acknowledged that obesity caused by LEPR or POMC deficiency affects people with the condition beyond direct health benefits but that quantifying this was difficult. It concluded that the failure to capture carer disutilities added to the uncertainty in the QALY gains arising from that associated with utility values for hyperphagia.

Use in specialist centres

3.33 The clinical experts explained that NICE's clinical guideline on identification, assessment and management of obesity 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 being treated 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

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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

3.34 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 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.

Managed access agreement (MAA)

3.35 The committee discussed whether an MAA might address and resolve some of the clinical uncertainties. It noted that the open-label extension study RM-493-022 is due to complete in March 2023. This will provide further information on the long-term treatment effect of setmelanotide, including quality-of-life data. However, because most people in the extension study are from Germany, it will provide little further data on the clinical effectiveness of setmelanotide at the maximum dose of 3.0 mg that will be used in the NHS. The representative from the NICE managed access team explained that data collection in clinical practice could inform the proportion of LEPR and POMC deficiencies and dosing in the model. However, there are no existing registries to collect this data and bespoke

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data collection would be challenging in the timeframe of an MAA. Also, further data collection to provide clinically meaningful data on hyperphagia, BMI or mortality proportionate to address the clinical uncertainties would not be feasible. The committee understood that further data collection in an MAA might reduce some of the existing clinical uncertainties. However, data collection of important outcomes addressing the clinical uncertainties may not be feasible. Also, setmelanotide currently does not have plausible potential to provide value for money in the context of highly specialised technologies. The committee concluded that an MAA could not be considered.

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

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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.

Conclusion

Recommendation

3.37 The committee agreed that the most plausible ICER for setmelanotide compared with best supportive care was unknown but was likely to be above the threshold normally considered an effective use of NHS resources in a highly specialised technology. So, it could not recommend setmelanotide for routine commissioning to treat obesity caused by LEPR or POMC deficiency.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance when final results from the ongoing extension study should be available. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

January 2022

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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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