NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Setmelanotide for treating obesity and hyperphagia in Bardet-Biedl syndrome

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 NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders 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 clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: August 2023

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 stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using setmelanotide in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 24 August 2023
- Second evaluation committee meeting: 14 September 2023
- Details of the evaluation committee are given in section 4

Issue date: August 2023

1 Recommendations

1.1 Setmelanotide is not recommended, within its marketing authorisation, for treating obesity and hyperphagia in genetically confirmed Bardet-Biedl syndrome (BBS) in people aged 6 years and over.

1.2 This recommendation is not intended to affect treatment with setmelanotide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by them, their clinician, and their parents or carers.

Why the committee made these recommendations

BBS is a debilitating rare genetic condition that severely affects the quality of life of people with the condition, their families and carers. It causes early onset severe obesity and hyperphagia (characterised by a feeling similar to starvation), and affects many different parts of the body. These symptoms are managed with best supportive care, which includes dietary restrictions and lifestyle changes, including exercise.

Results from clinical trials suggest that setmelanotide may reduce weight and body mass index (BMI) in people aged 6 years and over. They also suggest that hunger scores and quality of life are improved with setmelanotide in the short term, although hunger scores may not reliably reflect changes in hyperphagia. Follow up in the trials is short, so the long-term effects of setmelanotide are uncertain.

In addition to the uncertainties in the clinical evidence, there are issues with the economic model. These include assumptions:

- that everyone has severe hyperphagia when they enter the model
- about setmelanotide's effect on BMI-Z in people aged under 18 years
- that all people whose condition responds to setmelanotide have mild hyperphagia
- on the quality-of-life values related to BMI

- about the effect on quality of life of BBS comorbidities not related to obesity
- on what the quality-of-life benefits are for carers of people whose condition responds to treatment.

This means that it is not possible to determine the most likely cost-effectiveness estimates. So, setmelanotide cannot be recommended and more data is needed.

2 Information about setmelanotide

Marketing authorisation indication

2.1 Setmelanotide (Imcivree, Rhythm Pharmaceuticals) is indicated for 'the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS)…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.

Price

2.3 The list price of setmelanotide is £2,376.00 per 10 mg/ml vial for injection (excluding VAT; BNF online, accessed July 2023).

2.4 The company has a commercial arrangement. This makes setmelanotide available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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.

3 Committee discussion

The evaluation committee considered evidence submitted by Rhythm Pharmaceuticals, a review of this submission by the external assessment group

(EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Bardet-Biedl syndrome (BBS)

3.1 BBS is a rare genetic disorder that results in obesity. It is caused by mutations in 1 or more of the BBS genes, of which 22 have been identified to date. 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. BBS is likely associated with increased death rates compared with general obesity because of renal failure and early onset of comorbidities related to severe obesity in childhood, such as diabetes and cardiovascular conditions. But this is uncertain. Other symptoms include learning difficulties, visual impairment, kidney problems, extra toes or fingers, and genital or hormonal problems. The committee concluded that obesity caused by BBS 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 living with obesity caused by BBS can be extremely poor. They emphasised that the associated hyperphagia can be debilitating and all-consuming. Without any signal of feeling full, people with BBS can show extreme food-seeking behaviours, such as taking food out of bins or hoarding food for later eating. A patient expert explained that, before taking setmelanotide, they thought about food constantly and never felt full. The resulting obesity affects mobility, sleep and concentration, and can make exercise challenging. Learning and communication difficulties may affect quality of life, and children and young people with the condition often need support at school. Visual impairment can also be challenging, both mentally and

physically, with blindness common by mid-teenage years. The committee understood that there is a significant psychological effect of living with BBS. For people with the condition, obesity can exacerbate feelings such as depression and anxiety. It is also often associated with stigma, especially considering associated learning difficulties. Carers are constantly worried about the level of obesity, resulting lack of mobility and strain on the body. One carer highlighted that hyperphagia is often misunderstood by healthcare professionals, who misinterpret the condition as general hunger. It can also be hard to access local support for related comorbidities. Siblings and the wider family are affected by the frequency of hospital visits, and the strict dietary measures needed to control hyperphagia. The committee concluded that BBS has a substantial impact on people with the condition, their families and carers.

Clinical management

Treatment options

3.3 There are no licensed treatments for obesity and hyperphagia caused by BBS. Best supportive care for obesity includes dietary advice to manage the hyperphagia and exercise modification. One patient expert highlighted that restricting calorie intake in a child with hyperphagia is extremely hard to manage. Carers face an “endless battle” over food and must take extreme measures, such as locking food cupboards, to limit intake. 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 the NICE scope also included bariatric surgery as a comparator, but that it was excluded from the company’s submission. The clinical experts explained that, although bariatric surgery has been used to treat BBS in the past, the outcomes are variable and

tend to be worse than outcomes for people living with general obesity. Hunger generally increases after surgery, and lifelong follow up with nutritional support is needed. So, bariatric surgery can exacerbate existing hyperphagia in people with BBS because the MC4R pathway remains disrupted. Also, even in people living with general obesity, only a small proportion have surgery because it is inappropriate for people with certain comorbidities. So, the committee agreed that bariatric surgery is rarely used in people with BBS. It noted that NICE's technology appraisal guidance on semaglutide for managing overweight and obesity had recently recommended semaglutide for treating general obesity in adults. The clinical experts explained that there was limited evidence on using semaglutide in people with BBS, Semaglutide is approved for use in the NHS for a maximum of 2 years and will likely not be used alone in people with BBS. But it may be considered in combination with other weight loss treatments in the future. The committee understood that, if recommended, setmelanotide would be used in addition to best supportive care with dietary and exercise interventions. So, it concluded that best supportive care without setmelanotide was the relevant comparator, and that bariatric surgery and semaglutide were not.

Decision problem

Company's population

3.5 The committee noted that the company had limited its population in the decision problem to only people with severe hyperphagia who would be expected to benefit most from setmelanotide. The EAG highlighted that there was no validated and standardised assessment tool to measure hyperphagia in people with BBS. It also noted that it was unclear how hyperphagia would be consistently and accurately categorised in clinical practice. Without a means of consistently identifying people with severe hyperphagia, it is possible that setmelanotide will be used in people with moderate hyperphagia. At technical engagement, the company explained that people with BBS have treatment at specialist centres with clinicians

experienced in the condition. The clinical experts agreed that severe hyperphagia would be identifiable by a person's weight, and by maladaptive and extreme food-seeking behaviour. This behaviour includes eating to the point of vomiting and taking food from bins. They highlighted that the extreme level of obesity in small children with severe hyperphagia makes BBS in them easy to identify. They noted that some of them will have sleep apnoea. A patient expert highlighted that a multidisciplinary team including clinicians, psychologists and nutritionists contribute to the diagnostic process. They build a relationship to establish the severity of eating habits for a particular person. One expert estimated that, in their experience, around 50% to 60% of people with BBS have severe hyperphagia in clinical practice. The committee considered the definitions of severe, moderate, and mild hyperphagia that had been provided by the company as part of a vignette to collect utility data (see section 3.18). But it noted some crossover between the description of activities associated with severe hyperphagia provided by the clinical experts at the meeting and the vignette definition of moderate hyperphagia. The committee was concerned that it is likely that some people with moderate hyperphagia will have setmelanotide in clinical practice. It thought this because there is no standardised severity scale, and identification relies on clinical judgement. They also recalled that severe hyperphagia was not an inclusion criterion in the clinical trials. The committee concluded that there was uncertainty about:

- the proportion of people with severe hyperphagia as envisaged in the company's decision problem, and
- whether it would be possible to identify these people in clinical practice.

So, it considered that the whole population in the marketing authorisation would likely be offered setmelanotide.

Clinical effectiveness

Data sources

3.6 The main clinical trial evidence for setmelanotide came from a phase 3 trial, RM-493-023, referred to as the 'pivotal trial' in this guidance. It has enrolled 44 people with BBS. The trial had 2 stages:

- Stage 1: this was a 14-week double-blind randomised placebo-controlled stage that enrolled people aged 6 years and over with a body mass index (BMI) of 30 kg/m^2 or over (or the ninety seventh percentile or more in people under 16 years). Twenty two people were randomised to placebo and 22 people to setmelanotide.
- Stage 2: this was an open-label treatment period of up to 52 weeks. Everyone in this stage of the trial (including people randomised to placebo in stage 1) had setmelanotide. Efficacy outcomes were assessed at 52 weeks of active treatment for each group (results assessed after 52 weeks for people randomised to setmelanotide; after 66 weeks for people randomised to placebo).

  People having setmelanotide in the trial had a maximum of 3 mg per day after dose escalation. The trial enrolled 2 separate cohorts:

- The pivotal cohort was the first 32 people enrolled in the study and informed the analyses at 52 weeks.
- The supplemental cohort included a further 12 patients, who could enter an open-label study from week 24, so only 14-week data was used for analyses.

  The company also provided evidence for setmelanotide from a phase 3 open-label extension study, RM-493-022. This is an ongoing long-term follow-up study of RM-493-023 and RM-493-014. RM-493-014 was a phase 2 single-arm open-label basket trial that enrolled 10 people with BBS as well as people with other rare genetic disorders of obesity. People in RM-493-022 will have a further 2 years of setmelanotide at the same dose as used in the index trials. Results are available up to week 89. No further data is expected for people with BBS. The committee concluded that RM-493-023 and RM-493-022 were the most

appropriate data sources to inform the clinical effectiveness of setmelanotide.

Generalisability

3.7 The committee noted that the company's clinical trials were small and included only 2 people from the UK. Because of this, the EAG highlighted that the population in the clinical trial may lack generalisability to the BBS population in clinical practice. It suggested comparing the trial baseline characteristics with people from the UK in the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS). But the company stated there were too few people with BBS from the UK enrolled in CRIBBS to provide useful data for comparison. The EAG also noted discrepancies between people with 52 weeks of follow up compared with people with less, and between people in the supplemental cohort compared with the pivotal cohort. The clinical experts stated that baseline characteristics for people with BBS were unlikely to differ by location and that the trial population was generalisable to the people they would expect to see in clinical practice. The committee recalled that the company's population included only people with severe hyperphagia (see section 3.5). The company explained that, because there was no validated or standardised instrument for measuring hyperphagia, severe hyperphagia was not an inclusion criterion in the clinical trials. It highlighted that people in the trial had a BMI of 30 kg/m^2 or over, a level of obesity suggestive of severe hyperphagia. But the committee was concerned that some people might have a BMI of this level without having severe hyperphagia. The clinical experts agreed that this was plausible because people living with general obesity (not associated with hyperphagia) may have a BMI of 30 kg/m^2 or over. So, the committee agreed that the company's clinical trial populations likely included a mixture of people with different levels of hyperphagia severity. But it recalled that setmelanotide would likely be used in people with a range of hyperphagia severities in clinical practice (see section 3.5). It concluded that RM-493-023 and RM-403-022 were likely generalisable to the BBS population in clinical practice.

Obesity-related outcomes

3.8 The primary outcome in the RM-493-023 study was the proportion of people having at least 10% weight loss with setmelanotide from baseline to 52 weeks. This was in people with BBS aged 12 years and over who were compared with an historical control rate of 10% from the CRIBBS registry (the results are confidential and cannot be reported here). It was assessed in the full analysis set in the pivotal cohort, defined as people who had at least 1 dose of setmelanotide and were evaluated at inclusion. The committee noted that the trial included people with BBS and Alstrom Syndrome, but only considered results in the BBS population. Results at 14 weeks showed a non-statistically significant difference between setmelanotide and placebo. The mean reduction in weight at week 52 in the BBS population in the pivotal cohort was 9.4 kg (8%). The company also presented subgroup analyses for the primary outcome in people aged 18 years and over. When compared with the CRIBBS historical control rate, 46.7% of people aged 18 years and over had a reduction in weight from baseline of 10% or more at week 52 (95% confidence interval [CI] 21 to 73, p=0.0003). For people under 18 years, the company preferred to use BMI-Z scores to characterise obesity. This is because BMI-Z scores are linked to sex and age, so account for natural growth in this population. In RM-493-023, 85.7% of people aged 6 years to 17 years (from here, referred to as children and young people) in the pivotal cohort (full analyses set) had a 0.2-point reduction in BMI-Z score or more at week 52. The EAG highlighted that the observed treatment effect was larger in children and young people then in adults. There was also variability in the size of the change, especially for children and young people. The committee concluded that setmelanotide may improve obesity-related outcomes in the short term, but that the results were associated with uncertainty.

Other key clinical outcomes

3.9 RM-493-023 also considered hunger and quality of life as key clinical outcomes. At week 52, there was a 31% improvement in worst hunger score for people aged 12 years and over without cognitive impairment in the pivotal cohort (standard deviation 26, p=0.0004). Of these, 57.1% had a reduction in their daily hunger score of 25% or more (p<0.0001). Improvements in quality of life were seen for the Impact of Weight on Quality of Life (IWQOL)-Lite scores in adults and Paediatric Quality of Life Inventory (PedsQL) scores for children and young people. EQ-5D-5L scores were also collected in RM-493-023 in people aged 12 years and over without cognitive impairment and showed improvements in the mean change score. The committee noted that quality of life of carers had not been collected in the trial, and that there were no results from 14 weeks reported in the company submission. It concluded that setmelanotide may improve hunger in and the quality of life of people with BBS in the short term, but the results are uncertain.

Potential bias in RM-493-023

3.10 The EAG highlighted that the week 52 results in RM-493-023 were not based on a randomised controlled comparison. Instead, people were compared with their baseline data. Because of this, it was concerned that the observed treatment effect may not have been caused by setmelanotide alone. It also noted that people in the placebo arm had a reduction in maximum hunger score and BMI during the titration and retitration periods. It highlighted that this may represent a regression to the mean or placebo effect. The company stated that weight, BMI and hunger scores were virtually unchanged in people on placebo during the 14-week randomised controlled period, so adjustment for regression to the mean was not needed. But the committee noted a larger treatment effect after 52 weeks of follow up in people initially randomised to setmelanotide than people initially randomised to placebo. The EAG stated that the treatment effect from the placebo arm between week 14 (when people swapped to setmelanotide) and week 24 (when people could enter the open-label extension study) would give an estimate of the

treatment effect accounting for any regression to the mean. The committee concluded that there was potential bias from a lack of randomised controlled data at week 52. It agreed that the effect of potential regression to the mean should be further explored, with 52-week outcomes (hunger score, BMI and BMI-Z) from the trial adjusted as appropriate.

Long-term treatment effects

3.11 The committee noted that evidence from the extension study RM-493-022 suggested that changes in weight and BMI were maintained from the pivotal study baseline (exact results are confidential so cannot be reported here). But the EAG highlighted that the results of the extension study were associated with considerable uncertainty. There were very few people with data available at the 36-week follow up. This was especially for weight loss when the company excluded children and young people because they were still growing. The committee also noted that hunger and quality of life had not been measured in the extension study. So, there were no results past 52 weeks of setmelanotide use for these outcomes. It concluded that the long-term treatment effects of setmelanotide were uncertain.

Stopping treatment

3.12 The company defined response to treatment after 52 weeks of setmelanotide as:

- a 10% or more reduction in weight in adults
- a 0.2 or more reduction in BMI-Z-score in children and young people.

The committee noted that the company's response criteria did not consider people for whom there was a reduction in hyperphagia but no reduction in weight. The clinical experts explained that, although BMI and hyperphagia were somewhat correlated, a small proportion may have reduced hyperphagia but limited weight loss. This may be caused by a change in eating habits or using other medications that promote

weight gain that is slower than the change in hyperphagia. Because reducing hyperphagia is likely to considerably increase quality of life, these people may want to continue setmelanotide. So, response was likely to be assessed as a change in the behaviours associated with severe hyperphagia (see section 3.5). While the company's response rates used data from week 52 of RM-493-023, it was uncertain as to when response to setmelanotide would be assessed in clinical practice. It concluded that behavioural changes are important markers of response to treatment. It also concluded that the criteria and timepoint for assessing response in clinical practice may differ from those used in the clinical trials.

Economic model

Company's modelling approach

3.13 The company developed a lifetime model based on UK life tables to estimate the cost effectiveness of setmelanotide. Health states in the model included 7 BMI-Z classes (0 to 1, over 1 to 2, 2 to 4 in increments of 0.5 and over 4) for children and young people, 7 BMI classes (25 to 50 in increments of 5 and over 50) for adults and death. People with BBS entered the model having setmelanotide plus best supportive care or best supportive care alone. After 14 weeks, they transitioned between BMI class levels depending on the clinical response to setmelanotide. The company assumed a BMI drop for people whose condition responded to setmelanotide. People whose condition did not respond changed to best supportive care alone at 14 weeks and immediately returned to their baseline BMI class. At 18 years, BMI-Z scores were mapped to the respective BMI score. People could transition to death from any BMI or BMI-Z health state. The committee concluded that the company's model structure based on BMI classes was acceptable for decision making.

Population in the model

3.14 In its base case, the company assumed that all people started setmelanotide as children (the model starting age was 6 years, in line with the marketing authorisation). It also provided subgroup analyses in which all people entered the model as adults and a mixed population in which 60% of the modelled population entered the model at age 6 years and 40% at age 18 years. The clinical experts stated that the company's mixed population may have overestimated the proportion of children with BBS in current clinical practice. But the company highlighted that, in future, it expected setmelanotide to be started when BBS is diagnosed, which would more likely be in childhood. The committee considered it preferable to use the scenario that best represented current clinical practice, while noting the uncertainty in the distribution of adults and children. So, it preferred the mixed population for decision making, but considered analyses in which people entered the model as children.

Baseline hyperphagia status

3.15 The company assumed that all people with BBS had severe hyperphagia at baseline, in line with its updated population (see section 3.5). The EAG provided a scenario in which, at baseline, 60% of people had severe hyperphagia and 40% had moderate hyperphagia. This was based on the proportion of people with severe hyperphagia in clinical practice estimated by the company's clinical experts. The committee recalled the challenges of differentiating between moderate and severe hyperphagia and its conclusion that some people with moderate hyperphagia would likely have setmelanotide in clinical practice (see section 3.5). It also recalled that a mixture of hyperphagia severities was likely included in the trial population (see section 3.7). It agreed that the modelled population should reflect setmelanotide's use in clinical practice. So, it preferred the EAG's scenario assuming a mixture of moderate and severe hyperphagia at baseline for decision making.

Modelling treatment effect on hyperphagia

3.16 At 14 weeks, the company assumed that all people whose condition responded to setmelanotide transitioned to mild hyperphagia independent of change in BMI-Z or BMI. This was based on feedback from people who met the primary outcome in RM-493-023. It was also based on the view that the extent of weight loss seen in the trial could only have been caused by a transition to mild hyperphagia and the resultant change in eating habits. One patient expert supported this assumption, stating that their hyperphagia, which was previously severe, had greatly reduced when having setmelanotide. The committee understood from the patient and clinical experts that hyperphagia is much more than hunger. So, it was concerned that the improvements in hyperphagia included in the model were based on assumptions alone, so making a large contribution to improvement in quality of life highly uncertain. The clinical experts explained that treatment response in obesity is complex, and that there is a lack of data to inform setmelanotide's effect on hyperphagia. Based on other weight loss interventions, they thought it likely that there would be varying degrees of response to treatment. The EAG highlighted the variation in BMI-Z and worst hunger score changes in RM-493-023. It explained that this suggested that some people remained at a moderate level of hyperphagia when their condition responded to setmelanotide (see section 3.8 and section 3.9). In its base case, the EAG modelled people with severe hyperphagia at baseline moving to both moderate and mild hyperphagia. Transitions were informed by the proportions in RM-493-023 moving 2 BMI-Z class levels for moderate hyperphagia and 1 BMI-Z class level for mild hyperphagia (exact proportions are confidential and cannot be reported here). The committee agreed that there was substantial uncertainty about the treatment effect on hyperphagia. While acknowledging the uncertain correlation between BMI and hyperphagia (see section 3.12), it preferred the EAG's scenario, which was based on trial data instead of assumptions. The committee also recalled its preference for a distribution of severe and moderate hyperphagia at baseline (see section 3.15). The EAG explained that the

model would not allow a variable treatment effect as well as a mixture of hyperphagia severities at baseline. The committee acknowledged that this was an important limitation of the modelling. It considered that people with moderate hyperphagia at baseline would have a smaller treatment response when moving to mild hyperphagia than people who started with severe hyperphagia. So, it thought that some variation in treatment effect would already be captured. Because of the modelling limitations, the committee only accepted the company's approach when combined with a mixed hyperphagia severity distribution at baseline.

Modelling treatment effect on BMI-Z in children

3.17 The company used data from RM-493-023 to inform the following model inputs:

- the distribution of people in each of the 7 BMI and BMI-Z health states at baseline
- the response rates for setmelanotide at 14 weeks (see section 3.12); the committee noted that the results from 52 weeks were used to inform response to setmelanotide at 14 weeks
- the size of the treatment effect on BMI, based on BMI or BMI-Z score reductions translated to shifts in modelled BMI class levels, with the most frequently seen class shifts applied to people whose condition responded to treatment.

  The EAG noted that children and young adults had a larger reduction in classes than adults (exact class drops are confidential and cannot be reported here). It highlighted that the BMI-Z class shift in children may have been overestimated. It noted that Forsythe et al. (2021) reported a mean change in BMI-Z score of -0.7 kg/m^2 for 9 children from RM-493-023. This translated to a class shift smaller than that modelled by the company. Based on this, in its base case, the EAG used a lower reduction in classes for children, equal to that in adults. The company highlighted that its chosen BMI-Z class cut offs had larger intervals at the extremities (less than 2 and over 4) than those used in the middle.

This may have underestimated the number of class changes in people with a baseline BMI-Z score of over 4. Also, RM-493-023 did not allow dietary and exercise modifications, which would likely be used in combination with setmelanotide in clinical practice and may convey some benefit. But the committee noted that a little over half the children in RM-493-023 had the modelled class reduction, with most others having a lower response. It recalled that the treatment effect reported in the trial may have been overestimated because of potential regression to the mean (see section 3.10). It also had concerns about using the BMI shift data in the model. It acknowledged the company had chosen the BMI class cut offs based on the available comorbidity data. But it noted that, by using this approach, the model had not captured the variability seen in the clinical trial for BMI-Z score changes. It would have preferred to see analyses that either applied the mean BMI-Z score shift (instead of the most frequent) or the actual BMI-Z score shift from individual trial participants to the baseline BMI-Z proportions. The committee concluded that the company's modelling of treatment effect on BMI-Z added uncertainty. It acknowledged the lack of alternative approaches and the variability in the results for children. But it preferred the conservative BMI-Z score shift used in the EAG base case for decision making.

Long-term treatment effect

3.18 After the initial response at 14 weeks, the company assumed that people in the model maintained their BMI or BMI-Z classes while on treatment. That is, there was no waning of treatment effect. As a proxy for treatment waning not leading to immediately stopping treatment, the company included an annual 1% stopping rate in people whose condition responded to setmelanotide. This was in line with NICE's highly specialised technology guidance for setmelanotide for treating obesity caused by pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiencies. But the EAG was concerned that more than 1% of people had stopped setmelanotide in RM-493-023 because of a lack of effect

(exact rates and confidential and cannot be reported here). So, it stated that the long-term stopping rates may be higher in clinical practice and included a stopping rate of 2% in its base case. The clinical experts explained that, based on their experience with glucagon-like peptide-1 receptor agonists such as semaglutide, some waning of treatment effect could be expected over time. But, without treatment, people with BBS steadily gain weight, so even a plateau of weight loss is beneficial. The ongoing treatment effect for setmelanotide is uncertain because it is a new class of drug with little available long-term data. High adherence to treatment is expected because reducing hyperphagia has a big quality-of-life benefit. But the need to self-inject every day may mean some people whose condition responds to treatment may stop setmelanotide. The committee recalled that the criteria for stopping treatment in the clinical trial may have differed from those used in clinical practice (see section 3.12). But, acknowledging the short follow up in the trials, it agreed that this should be informed by clinical data when possible. It concluded that the EAG's stopping rate of 2% should be used in decision making as a proxy for treatment waning.

Utility values

Source of obesity-related utility values

3.19 The committee was aware that quality-of-life data had been collected in RM-493-023. But the company stated that the quality-of-life instruments used in the trial (PedsQL, Impact of Weight on Quality of Life-Lite and EQ-5D) lacked the sensitivity to capture the full effect of hyperphagia. Instead, for hyperphagia, it used utility multipliers associated with severity status (mild, moderate and severe) from a vignette in the general public. For each of the 7 BMI health states, utility values came from a US study of Short Form Survey (SF)-12 utilities according to BMI 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 EAG highlighted that, although the

company's utility values had been accepted in NICE's highly specialised technology guidance for LEPR or POMC deficiency, Forsythe et al (2023) had recently published PedsQL results from RM-493-023. It preferred to use Forsythe et al. because it collected data from people with BBS instead of general obesity. At technical engagement, the company provided a scenario that mapped the PedsQL data from RM-493-023 to EQ-5D estimates. The EAG noted that the company scenario had not applied the mapping algorithm from Khan et al. correctly. The EAG suspected that this error likely applied to those values mapped from Riazi et al. in the company's base case as well. The EAG corrected the company's mapping from trial PedsQL values, which it preferred for its base case. The committee noted that the data from Riazi et al. was based on 96 children living with obesity, whereas the EAG's mapping was based on 5 people with BBS. One of these 5 informed the lowest BMI-Z health state (BMI-Z scores 0 to 1). The other 4 informed the highest (BMI-Z score over 4), with the utilities for the middle BMI-Z health states extrapolated. So, because there was only 1 person informing the lowest health state, any variation in baseline PedsQL score from the general BBS population could have biased the extrapolated values. The committee acknowledged that NICE's health technology evaluations: the manual specifies a preference for using trial-based utilities where available. But, given the uncertainty introduced by the small sample size from the trial available for mapping, the committee agreed that this constituted an exceptional circumstance. It concluded that utilities from the literature were most appropriate for decision making. But it agreed that the error in the company's mapping should be corrected.

BBS utility multiplier

3.20 To capture the impact of those features of BBS not related to obesity (such as visual impairment and learning difficulties), the company applied a multiplier of 0.8 to the utility values in the BMI health states of the economic model. This stopped people whose condition responded to setmelanotide having a quality of life equal to that of the general public.

The patient experts highlighted the considerable burden of non-obesity-related comorbidities. They stressed that learning and communication difficulties, and visual impairment significantly affect the quality of life of people with BBS (see section 3.2). But the committee was concerned that the company's BBS multiplier was based on an assumption instead of clinical evidence. The committee recalled its preference to use literature-based values from general obesity for baseline BMI health state utilities (see section 3.19). It considered the multipliers derived from PedsQL data in RM-493-023. It recalled the error in the company's mapping (see section 3.19). Also, it noted that only 1 person informed the EAG's mapped utility estimates from the PedsQL data in RM-493-023 for the lowest BMI-Z health state. It was concerned that, if this person had non-obesity-related comorbidities not typical of the condition, it would have skewed the extrapolated values. This meant that they might not have accurately represented the quality-of-life effect. Nevertheless, in this case, it considered the PedsQL derived multiplier values had some advantages because they were based on trial evidence and not an assumption. The committee acknowledged that the effect of non-obesity-related comorbidities on the quality of life of people with BBS was uncertain. But, when considering the analyses presented, it preferred the EAG's scenario using the corrected BBS multiplier based on PedsQL data from RM-493-023 for decision making.

Carer disutility

3.21 The company applied a disutility of 0.0986 for carers of people with BBS in its base case. It assumed an average 1.5 carers per child or young person with BBS. For adults, the number of carers was based on a survey by Bardet-Biedl Syndrome UK, which captured care for 121 adults with BBS. The EAG agreed it was appropriate to include a carer disutility. It also agreed that a lower care burden for adults was expected because carers generally have less control over diet and lifestyle at this point. It noted that the company had not provided the results of the BBS UK survey for verification, but used the estimate in its base case. The

committee agreed that a carer disutility was appropriate because of the high quality-of life-burden for carers of people with BBS (see section 3.2). But it was concerned that the company's carer disutility was applied at equal rates to carers of people having both setmelanotide and best supportive care. The patient experts explained that controlling diet and food-seeking behaviours constitutes a large proportion of the care needed for people with BBS. So, setmelanotide would likely improve quality of life for carers when hyperphagia was reduced in the person with BBS. The committee concluded that a quality-of-life benefit should be modelled for carers of people whose condition responds to treatment.

Costs and resource use

Ongoing monitoring of setmelanotide

3.22 The clinical experts explained that NICE's clinical guideline on identification, assessment and management of obesity recommends a tier-based system of obesity treatment. In its base case, the company assumed setmelanotide would be prescribed in specialist care (tiers 3 and 4) but monitored in primary care (tiers 1 and 2). The EAG stated that setmelanotide would likely be monitored in local weight management clinics in secondary care, supported by specialist BBS centres. It included the cost of secondary care weight management clinic visits in its base case. The clinicians at the committee meeting supported this, explaining that specialist centres would communicate with local tier 3 obesity clinics to coordinate the care of a person with BBS. They also highlighted that people with BBS often have limited mobility, so some level of local care is important to support with side effects and comorbidities. The committee concluded that ongoing monitoring for setmelanotide would likely take place in local tier 3 obesity clinics in secondary care. It concluded that the cost of additional visits should be included in the model.

Quality-adjusted life year (QALY) weighting

Criteria for applying a QALY weighting

3.23 The committee understood that NICE health technology evaluations: the manual (2022) 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's and EAG's analyses showed QALY gains within this range. So, it concluded that some of the criteria for applying a QALY weighting were likely met. It considered this in its decision making. But there were considerable uncertainties (see section 3.26) in the QALY gain estimates, so the committee was unable to conclude on the exact QALY weight to apply without further information.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.24 The company's base case showed that setmelanotide was associated with an ICER of £197,641 per QALY gained compared with best supportive care in the paediatric population. Considering a mixed population of children (60%) and adults (40%) increased the ICER to £204,894. When assuming all people enter the model as adults, the ICER was £229,614. These ICERs included the confidential discount for setmelanotide available to the NHS. In the EAG's base-case analyses, setmelanotide was associated with an ICER compared with best supportive care of:

- £203,784 per QALY gained in children
- £208,457 per QALY gained in the mixed population

- £222,857 per QALY gained in adults.

Acceptable ICER

3.25 Considering the company's and EAG's analyses, the committee's preferred assumptions included:

- using the mixed population (60% children and 40% adults)
- assuming a mixed baseline distribution of severe and moderate hyperphagia
- using the EAG's preferred treatment effect on BMI-Z score for children (while acknowledging the uncertainty)
- using a 2% annual stopping rate
- using utility values for BMI or BMI-Z class health states from the literature
- applying the BBS multiplier calculated by the EAG using corrected mapping from the PedsQL scores in RM-49--023
- assuming ongoing management of setmelanotide in local secondary care weight management clinics.

The committee noted that it had not been presented with an ICER that included all of its preferred assumptions. It noted that using BMI-Z health state utilities from the literature and assuming a mix of hyperphagia severities at baseline significantly increased the ICER. So, when using its preferred assumptions, the ICER was likely to be over the cost-effectiveness threshold, even when considering a QALY weighting.

Uncertainties to explore further in the modelling

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

- a reduction in carer disutility in people whose condition responds to setmelanotide

- corrected mapping of BMI-Z health state utilities from the literature
- alternative ways to model treatment effect on BMI-Z, such as applying the mean BMI-Z score shift (instead of the most frequent) or the actual BMI-Z score shift from people in the trial to the baseline BMI-Z proportions
- amendments to the model to allow a variable treatment effect on hyperphagia, as well as a mixture of hyperphagia severities at baseline
- the effect of potential regression to the mean for the 52-week outcomes (hunger score, BMI and BMI-Z) and adjusting for this as appropriate.

Managed access

Recommendation with managed access

3.27 Having concluded that setmelanotide could not be recommended for routine use, the committee then considered whether it could be recommended with managed access for treating BBS. It noted that the company had not submitted a managed access proposal, so it could not make a recommendation for managed access at this stage.

Other factors

Equality

3.28 The committee noted that the population for which setmelanotide is indicated includes children and young people. It further noted the additional benefits beyond health that 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 young people, 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 self-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 in a prefilled injector. The clinical experts also highlighted that 20% of people with BBS do not have identifiable pathogenic variants on genetic or genomic testing and are identified clinically. The committee noted that genetic confirmation was a requirement in the marketing authorisation for setmelanotide. So, some people with the condition would not be able to access the treatment. The committee considered that its recommendation applies to the full licensed population, and it could not make a recommendation outside of this. It concluded that all equalities issues for setmelanotide had been considered in decision making.

Innovation

3.29 The committee considered whether setmelanotide was innovative. The clinical experts stated that type 2 diabetes can often affect vision and kidney function. So, by improving obesity-related comorbidities, setmelanotide had the potential to indirectly affect the progression of comorbidities not linked to BMI. The committee noted that the utility decrement for non-obesity-related comorbidities applied equally to people whose condition did and did not respond to setmelanotide (see section 3.20). It also recalled the unmet need for BBS and that setmelanotide is the first treatment to address the underlying hyperphagia (see section 3.1). The committee concluded that setmelanotide may be innovative.

Conclusion

Recommendation

3.30 The committee noted that it had not been presented with an ICER that included all of its preferred assumptions (see section 3.25). But it concluded that the ICER 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 and hyperphagia in BBS. The committee concluded that the company and stakeholders should provide additional information for consideration at the next evaluation committee meeting (see section 3.25 and section 3.26).

4 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 being evaluated. If it is considered 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.

Chair

Peter Jackson

Chair, highly specialised technologies evaluation committee

NICE project team

Each 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

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