National Institute for Health and Care Excellence

Health Technology Evaluation

Setmelanotide for treating acquired hypothalamic obesity in people 4 years and over ID6542
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Rhythm Pharmaceuticals	We welcome the NICE evaluation of setmelanotide for treating acquired hypothalamic obesity.	Thank you for your comment.
	British Society for Paediatric Endocrinology and Diabetes BSPED	These are both appropriate.	Thank you for your comment.
	Neonatal and Paediatric Pharmacy Group	Appropriate.	Thank you for your comment.
Wording	Rhythm Pharmaceuticals	We request that the remit reflects the anticipated market authorisation wording and be defined as:	Thank you for your comment. The remit has been kept broad at

Section	Stakeholder	Comments [sic]	Action
		[redacted]	this stage. Setmelanotide will be evaluated in line with its marketing authorisation.
	British Society for Paediatric Endocrinology and Diabetes BSPED	This is appropriate.	Thank you for your comment.
	Neonatal and Paediatric Pharmacy Group	Appropriate.	Thank you for your comment.
	Kidney Research UK	Kidney Research UK uses the wording 'living with overweight and obesity', rather than 'People who are obese'; this aligns with wording used by the Obesity Health Alliance and other organisations.	Thank you for your comment. This wording has been amended.
Timing issues	British Society for Paediatric Endocrinology and Diabetes BSPED	Very urgent.	Thank you for your comment. This evaluation has been scheduled into the work programme.
	Neonatal and Paediatric Pharmacy Group	Urgent, given the paucity of interventions available to this subgroup of children with obesity.	Thank you for your comment. This evaluation has been scheduled into the work programme.

Section	Stakeholder	Comments [sic]	Action
	The National Kidney Federation	Urgent: Around 7.2 million people are living with kidney disease and around 30,000 adults and children rely on dialysis due to kidney failure. Without intervention the number of people living with chronic kidney disease (stage 3-5) is expected to increase by 2033 and the demand for dialysis this could be as high as 143,000 and 12,000 for transplantation. It is vital that there is a focus on early detection and intervention to slow the progression to kidney failure. (https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-summary-report_accessible.pdf)	Thank you for your comment. This evaluation has been scheduled into the work programme.
	Rhythm Pharmaceuticals	The urgency is high as there is a significant unmet need for patients living with acquired hypothalamic obesity (aHO) and their families due to there being no licensed treatment for treating rapid and severe weight gain and the control of hyperphagia and metabolic parameters associated with aHO. aHO should be considered as an indication entirely separate from that of general obesity. The underlying disease mechanism, clinical presentation, and therapeutic objectives are distinct. MC4R pathway-related obesity is an hypothalamic neuroendocrine clinical entity characterized by loss of satiety and reduced energy expenditure. This results in unique clinical symptoms such as hyperphagia and early-onset, severe obesity and requires targeted therapeutic strategies that address the root cause of the disorder, rather than conventional weight management approaches.	Thank you for your comment. This evaluation has been scheduled into the work programme.
Additional comments on the draft remit	The National Kidney Federation	Obesity along with diabetes and cardiovascular disease are factors that contribute to kidney disease and these are rising. There are limited treatment options for patients with kidney failure and early diagnosis, along with effective preventative medications and disease management can reduce the progression to kidney failure. Innovative medications must be optimised for effective management of kidney disease.	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Rhythm Pharmaceuticals	The background information does not fully consider acquired hypothalamic obesity (aHO) as a distinct neuroendocrine disorder, clearly differentiated from general obesity that arises primarily from lifestyle and environmental factors.[1,2] As NICE recognises, the hypothalamus is responsible for many important functions including energy balance, temperature and autonomic nervous system regulation, modulation of sleep and daily (circadian) rhythm, and control of pituitary hormones. aHO is a unique clinical entity characterised by disruption of the MC4R pathway.[1] α-MSH is a key neuropeptide naturally produced in the hypothalamus that activates MC4Rs in multiple locations, including the hypothalamus, brainstem, and spinal cord. MC4R activation by α-MSH controls hunger, food intake, and energy expenditure, all of which contribute to the regulation of body composition. Hypothalamic physical and functional damage may lead to decreased α-MSH production, impairing MC4R signalling and resulting in hyperphagia (pathological, insatiable hunger), decreased energy expenditure, and accelerated and sustained weight gain[1,2]. For younger patients with aHO, the early onset of obesity leads to an increased risk of comorbidities and cumulative adverse health effects. While 'feelings of excessive or insatiable hunger (hyperphagia)' are recognised, the significant impact on quality of life for these people and their caregivers/families because of hyperphagia is not. The quality of life in MC4R-related obesity for a similar indication (HST31) was described by a patient expert as "extremely poor", emphasising that "the associated	Thank you for your comments. The background section is intended to be a brief overview of the condition and available treatment options. The section has been amended to place greater emphasis on the neuroendocrinological nature of the condition and its impact on quality of life.

Section	Consultee/ Commentator	Comments [sic]	Action
		hyperphagia can be debilitating and all-consuming" with extreme food-seeking behaviours. The impact of aHO and hyperphagia on the quality of life of carers is also devastating, with one patient expert describing how carers face "endless battle" over food and must take extreme measures, such as locking food cupboards, to limit intake. Care for patients living with aHO typically involves more than one individual; although day-to-day responsibilities often concentrate on one or two primary carers (frequently parents in paediatrics), the wider caregiver unit including spouses, siblings, and other family members experiences significant and detrimental impacts on wellbeing, mood, sleep, family functioning, and daily life. In addition, families face direct and indirect financial consequences, such as costs linked to food-security measures and home adaptations, repeated travel to tertiary centres, and lost income from reduced working hours or job loss. In conclusion, aHO is a complex neuroendocrine disorder that is more complicated than general obesity. It is characterised by MC4R pathway disruption, hyperphagia and decreased energy expenditure. On this basis, the description of NICE guideline (NG) 245, the listed technology appraisals and the weight management medicines are inappropriate and more aligned with treatment strategies for people with general obesity who do not have MC4R dysregulation as the root cause of their condition. References: 1. Roth CL, McCormack SE. Acquired hypothalamic obesity: A clinical overview and update. Diabetes Obes Metab. Apr 2024;26 Suppl 2:34-45. doi:10.1111/dom.15530	

Section	Consultee/ Commentator	Comments [sic]	Action
		NIHR Innovation Observatory. Setmelanotide for treating acquired hypothalamic obesity in people 4 years and older: Health technology briefing. Newcastle upon Tyne: NIHR Innovation Observatory, Newcastle University; 2024 Jan. (NIHRIO ID: 31151).	
	British Society for Paediatric Endocrinology and Diabetes BSPED	The background information does not emphasise the differences between patients with acquired hypothalamic obesity vs obesity in the general population. Patients with hypothalamic obesity are treatment-resistant due to direct disruption of the hypothalamic-gut-adipose tissue circuitry and already have multiple complex morbidities associated with hypothalamic dysfunction (on top of obesity-related comorbidities), including hypopituitarism, hyperphagia, behavioural difficulties, temperature dysregulation and autonomic dysfunction (collectiverly known as hypothalmic syndrome). Therefore, in hypothalamic obesity, standard dietary, exercise and behavioural approaches do not lead to a reduction in weight or BMI. The final paragraph mentions that weight management medicines for children are only used in 'exceptional circumstances'. Children with obesity-related comorbidities are no longer exceptional cases. Prescribing GLP-1 agonists for children is therefore increasingly common within the NHS, with specialist services now using many of these medications as part of their standard of care.	Thank you for your comments. The background section is intended to be a brief overview of the condition and available treatment options. The section has been amended to include a reference to hypothalamic syndrome and the fact that aHO is resistant to dietary, exercise and behavioural approaches. GLP-1 agonists have been included in the list of comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
	Neonatal and Paediatric Pharmacy Group	The background mentions the marketing authorisation of setmelanotide for children, but does not mention the same level of detail for liraglutide and semaglutide for children. The latter have been studied extensively in children with obesity, have a UK marketing authorisation, and are in routine use within specialist paediatric centres in the NHS. Their use should not be marked as exceptional circumstances, which is the same descriptor for bariatric surgery in children.	Thank you for your comments. The background section refers to NICE technology appraisals and NICE guidelines for the relevant populations. The NICE committee can also consider comparators which are not recommended by NICE if they are established practice in the NHS. GLP-1 agonists and bariatric surgery have been included in the list of comparators for this appraisal.
	The National Kidney Federation	Kidney disease should be included as a condition at increased risk of development due to obesity.	Thank you for your comment. The background section has been amended to include the increased risk of kidney disease.
	Kidney Research UK	We also know that obesity is both directly and indirectly associated with increased risk of chronic kidney disease (CKD). Obesity and chronic kidney	Thank you for your comment. The background section has

Section	Consultee/ Commentator	Comments [sic]	Action
		disease: A current review - PMC therefore, any treatments should also consider risk reduction of CKD.	been amended to include the increased risk of kidney disease.
Population	British Society for Paediatric Endocrinology and Diabetes BSPED	Yes [population is defined appropriately].	Thank you for your comment.
	Neonatal and Paediatric Pharmacy Group	Yes [population is defined appropriately].	Thank you for your comment.
	Rhythm Pharmaceuticals	The population is defined adequately.	Thank you for your comment.
Subgroups	British Society for Paediatric Endocrinology and Diabetes BSPED	No [there are no subgroups that should be considered separately].	Thank you for your comment.
	Neonatal and Paediatric Pharmacy Group	No [there are no subgroups that should be considered separately].	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	The National Kidney Federation	People from lower socio-economic backgrounds may be less able to make changes to diet, exercise or access to regular support and equity of access to these interventions should be considered. People from lower socio-economic groups as well as some ethnic minority groups are more likely to develop kidney disease and progress faster to kidney failure. In addition, they face longer waits for transplantation. The impact of obesity on individual with kidney disease receiving dialysis and/or transplantation care should also be considered.	Thank you for your comment. The technology appraisal will take into account any equalities issues. No change to scope required.
	Kidney Research UK	It's possible some patients with Acquired hypothalamic obesity may already have an increased risk of CKD due to underlying conditions, so any medication for this subpopulation should both look to reduce risk factors for CKD (metabolic and neurohormonal changes) as well as ensure the medication itself does not lead to a decline in kidney function.	Thank you for your comment.
	Rhythm Pharmaceuticals	The two age subgroups (children and young people, age 4 years and above; adults, age 18 and above) are appropriate.	Thank you for your comment. This section has been amended to include consideration of potential subgroups based on age, the suitability of existing treatments (within and outside of their marketing authorisation) and previous treatments used.

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	Rhythm Pharmaceuticals	There are no licensed products with an indication for aHO. There is also no clinical evidence that treatments approved for weight management in general obesity are effective in addressing either the hyperphagia and the decreased energy expenditure that are hallmarks of MC4R associated obesity (including aHO), or the resulting rapid and severe weight gain and associated metabolic imbalance. The listed comparators are approved for the management of general obesity that arises primarily from lifestyle and environmental factors. While they have different mechanisms of action and do not target the MC4R pathway. Consequently, they cannot address the underlying pathophysiology of aHO. In contrast, setmelanotide - an MC4R agonist - is designed to re-establish the MC4R signalling pathway addressing the underlying cause of hyperphagia, decreased energy expenditure and the resulting severe obesity. **GLP-1 receptor agonists, including tirzepatide, semaglutide, liraglutide and orforglipron** • The only placebo-controlled randomised controlled trials of a GLP-1 receptor agonist in aHO was for exenatide, a product not currently recommended by NICE for weight management. They did not demonstrate a statistically significant improvement in BMI compared to placebo[2,3]. • GLP-1 receptor agonists that are recommended by NICE for managing overweight and obesity, such as tirzepatide, semaglutide and liraglutide, are not clinically proven in patients with aHO. Positive guidance is for use in adults only and with more stringent criteria than the label for aHO.	Thank you for your comments. The list of comparators has been amended to be broad and inclusive of all treatments that may be used for people with aHO in the NHS. This includes those that are used to treat people with general obesity, and which are sometimes used off-label in the paediatric population. The company may choose to exclude comparators it feels are not relevant in its evidence submission, with appropriate clinical justification. The committee will then consider if this is appropriate.

Section	Consultee/ Commentator	Comments [sic]	Action
		In addition, the guidance recommends use for a maximum of two years while aHO requires lifelong therapy. **Lipase inhibitors, including orlistat** • There is no data supporting the use of orlistat in aHO. **Surgical interventions, specifically bariatric surgery.** • Bariatric surgery is not recommended for patients with a disrupted MC4R pathway as the intervention does not address the underlying hyperphagia and decreased energy expenditure, and is even considered dangerous in patients with no satiety signals. Some studies of bariatric surgery have shown some weight loss in aHO. However, the effectiveness is significantly lower in aHO vs general obesity, and long-term data have demonstrated that weight regain is common due to persistent hyperphagia. Bariatric surgery has profound postoperative complications in patients living with aHO, as well as legal and ethical concerns in children. Notably, it has been disregarded as a comparator in similar appraisals (HST31) References: 1. Lambert F, Guillon E, Gatta-Cherifi B, et al. Effectiveness and safety of GLP-1 receptor agonists in craniopharyngioma patients with obesity: A multicentre real-world study. *Diabetes Obes Metab*. 2026;28(1):443-451. doi:10.1111/dom.70216 2. Gatta-Cherifi BM, K.; Cariou, T.; Poitou, C.; Touraine, P.; Raverot, G.; Brue, T.; Chanson, P.; Illouz, F.; Grunenwald, S.; Chabre, O.; Sonnet, E.; Cuny, T.; Bertherat, J.; Czernichow, S.; Frison, E.; Tabarin, A. Impact of exenatide on weight loss and eating behavior in adults with craniopharyngioma-related obesity: the CRANIOEXE randomized	

Section	Consultee/ Commentator	Comments [sic]	Action
		placebo-controlled trial. European Journal of Endocrinology. 01 Apr 2024;190(4):257-265. doi:https://dx.doi.org/10.1093/ejendo/lvae024 Roth CLP, F. A.; Whitlock, K. B.; Elfers, C.; Yanovski, J. A.; Shoemaker, A. H.; Abuzzahab, M. J. A phase 3 randomized clinical trial using a once-weekly glucagon-like peptide-1 receptor agonist in adolescents and young adults with hypothalamic obesity. Diabetes, Obesity and Metabolism. 01 Feb 2021;23(2):363-373. doi:https://dx.doi.org/10.1111/dom.14224	
	British Society for Paediatric Endocrinology and Diabetes BSPED	The comparators section does not state whether this specifically refers to patients with acquired hypothalamic obesity as well or patients with common obesity prevalent in the general population. I am presuming it refers to the former (ie patients with acquired hypothalamic obesity) which would be more appropriate. Liraglutide, semaglutide (and in the future, tirzepatide) should be comparators for the paediatric population as well. Despite having terminated NICE TAs, they are widely used by specialist paediatric services for obesity, and have been used in cases of hypothalamic obesity when no other alternative can be offered.	Thank you for your comments. The list of comparators has been amended to be broad and inclusive of all treatments that may be used for people with aHO in the NHS. This includes those that are used to treat people with general obesity, and which are sometimes used off-label in the paediatric population.
	Neonatal and Paediatric Pharmacy Group	GLP-1 agonists licensed for paediatric obesity should be included as comparators for children and young people. Data are available on use of liraglutide and semaglutide, both within RCTs and published UK observational studies in children. Some centres use dexamfetamine off-label.	Thank you for your comments. The list of comparators has been amended to be broad and inclusive of all treatments that may be used for people with

Section	Consultee/ Commentator	Comments [sic]	Action
			aHO in the NHS. This includes those that are used to treat people with general obesity, and which are sometimes used off-label in the paediatric population
Outcomes	Rhythm Pharmaceuticals	The outcomes are appropriate. However, the BMI z-score should be used in children and adolescents. Co-morbidities such as CV events and Type 2 DM will take years to develop, especially for children and adolescents, and cannot be evaluated as part of a regulatory trial. Thus, cardiometabolic parameters, including blood pressure, lipid profile, glycated haemoglobin (HbA1c), liver function and C-reactive protein, have been captured within the clinical trials and should also be included within the scope. Furthermore, metabolic indexes including lipid accumulation product (LAP), triglyceride-glucose waist circumference index (TyG-WC), visceral adiposity index (VAI), fatty liver index (FLI), and metabolic syndrome z-score (MetS z-score) after 52 weeks of therapeutic dose have been analysed in a post-hoc analysis and should also be included within the scope	Thank you for your comments. The list of outcomes is not intended to be exhaustive and focuses on the main outcome measures of interest. An additional outcome, other obesity-related complications, has been added to the scope. The company is invited to include data on additional outcomes in its evidence submission with appropriate clinical justification.
	British Society for Paediatric	In children, cardiovascular events are rare. Instead, other measures such as liver dysfunction (measured by liver function tests and potentially ultrasound	Thank you for your comment. Liver function

Section	Consultee/ Commentator	Comments [sic]	Action
	Endocrinology and Diabetes BSPED	scan of the liver with stiffness index) and obstructive sleep apnoea (measured accurately in sleep studies) are more common obesity-related co-morbidities.	and other obesity-related complications have been included as additional outcomes.
	Neonatal and Paediatric Pharmacy Group	Yes [the outcomes listed are appropriate].	Thank you for your comment.
	The National Kidney Federation	It is important to monitor the impact of the technology on the kidney and therefore Kidney function tests (eGFR or uACR) should be included as an outcome measure.	Thank you for your comment. Liver function has been included as an outcome.
	Kidney Research UK	We think kidney function is also an important outcome to consider as measured by eGFR and uACR tests. This will give a better picture of cardiorenal metabolic health and allow for monitoring to ensure kidney damage is not an emerging treatment side effect.	Thank you for your comment. Liver function has been included as an outcome.
Equality	Neonatal and Paediatric Pharmacy Group	Appropriate.	Thank you for your comment.
	Kidney Research UK	It's important to consider how the medication may affect patients of different ethnicities. People of a South Asian heritage, for example, face an increased risk of overwieght / obesity and assosiated complications. Weight gain leads to greater adverse metabolic responses in South Asian compared with white European men: the GlasVEGAS study | Nature Metabolism	Thank you for your comment. Potential equalities issues will be noted on the equalities impact assessment and

Section	Consultee/ Commentator	Comments [sic]	Action
		Access to medications should also be considered for people from lower socioeconomic groups, as well as access to affordable healthier foods alongside any medication options.	relevant issues will be considered by the committee as part of the evaluation.
Other considerations	Kidney Research UK	As above we advocate for the use of eGFR and uACR testing in people living with overweight and obesity to monitor kidney function in order to reduce the risk of developing CKD due to early intervention.	Thank you for your comment. No change to scope required.
Questions for consultation	British Society for Paediatric Endocrinology and Diabetes BSPED	Off-label medicines: Semaglutide and liraglutide have been used in children with obesity age 10-12 years in exceptional circumstances. Setmelanotide prescribing pathway: C. Prescribed in secondary care with routine follow-up in secondary care. For children, prescribing of GLP-1 agonists usually follows a similar pathway.	Thank you for your comments. Semaglutide and liraglutide have been included as comparators in the scope without reference to age restrictions on their use.
	Neonatal and Paediatric Pharmacy Group	Setmelanotide should be prescribed in secondary care with routine follow-up in secondary care. Note that the appraisal title mentions this is for children 4 years and older, but the questions for consultation ask about children 6 years and older.	Thank you for your comments. To clarify, this evaluation is for the treatment of acquired hypothalamic obesity in people 4 years and over.
	Rhythm Pharmaceuticals	*Where do you consider setmelanotide will fit into the existing care pathway for treating acquired hypothalamic obesity in people 6 years and over?* The scope of the assessment is people with aHO aged 4 years and over, so the question should be changed to ensure comments reflecting the labelled	Thank you for your comments. To clarify, this evaluation is for the treatment of acquired

Section	Consultee/ Commentator	Comments [sic]	Action
		patient population. If recommended, setmelanotide would be used in addition to best supportive care with dietary and exercise interventions as no aHO-specific treatment exist. *Please select from the following, will setmelanotide be:* We anticipate that setmelanotide will be prescribed at a very small number of specialist tertiary centres, with routine follow-up in tertiary care. Given this is a highly complex neuroendocrine disorder, it would not be managed in the same setting of care as general obesity *Would setmelanotide be a candidate for managed access?* We do not consider setmelanotide to be a candidate for managed access *Do you consider that the use of setmelanotide can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* Yes, as setmelanotide has the potential to have a life-changing impact on patients, caregivers and families.	hypothalamic obesity in people 4 years and over.
Additional comments on the draft scope	Rhythm Pharmaceuticals	Given the importance in understanding aHO as a complex neuroendocrine disorder, and the fact that this is the first time an aHO indication will be assessed by NICE, Rhythm Pharmaceuticals believe a Scoping Workshop is warranted to discuss the scope and to ensure there is an appropriate understanding of aHO as a distinct clinical entity. We do not believe it is appropriate to consider NICE recommendations on GLP-1's as related technology appraisals given the above comments on comparators.	Thank you for your comments. NICE invited a broad range of stakeholders to provide input on the scope, which has been reflected in the updated document. The comparators are kept inclusive at this stage to

Section	Consultee/ Commentator	Comments [sic]	Action
		In the section 'Technology', the technology was studied against placebo on top of BSC within the clinical trials.	allow committee to consider which comparators are established in practice, and are relevant to the decision problem. The technology section has been updated to clarify that the technology was studied against placebo on top of BSC within the clinical trials.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope