

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Metreleptin for treating lipodystrophy

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using metreleptin 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 metreleptin 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?

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 determination.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using metreleptin 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: 13 August 2018

Second evaluation committee meeting: 24 October 2018

Details of membership of the evaluation committee are given in section 6.

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

1 Recommendations

- 1.1 The committee was unable to make recommendations on metreleptin as an option for treating lipodystrophy.
- 1.2 The committee recommended that NICE requests further clarification and analyses from the company, which should be made available for the second appraisal committee meeting and include:
- comparator data, systematically identified, to support the relative clinical effectiveness of metreleptin compared with standard of care, and to include in the economic model (see sections 4.3 and 4.9)
 - results from the early access programme under the National Severe Insulin Resistance Service at Addenbrooke's (see section 4.4)
 - alternative, more plausible utility values, including those exploring the effects of hyperphagia on families and carers (see section 4.5)
 - the patient population likely to have metreleptin in clinical practice in England, with clear identification criteria (see section 4.6)
 - an alternative model structure based on established models for metabolic conditions, incorporating well-known risk indicators with additional consideration of fatty liver disease (see section 4.8)
 - full details about calculating the weighted average annual drug acquisition costs (see section 4.13).

Why the committee made these recommendations

Lipodystrophy is a rare and serious condition that severely affects the quality of life of people with the condition, and their families and carers.

Conventional therapy includes lifestyle modifications such as a low fat diet

and exercise, cosmetic surgery, and medication for diabetes and to lower lipids.

The company submission for metreleptin has limitations and the uncertainties mean that the size and nature of any clinical benefits compared with standard of care, and who would benefit from treatment, are highly uncertain.

There are also several important uncertainties in the economic model, so it is not possible to confidently identify a range of plausible cost-effectiveness estimates from which to make a decision. The cost-effectiveness estimates for metreleptin considered are much higher than what NICE considers acceptable for highly specialised technologies.

It is therefore not possible to make a decision on metreleptin as an option for treating lipodystrophy, and further clarification and analyses are needed from the company.

2 The condition

- 2.1 Lipodystrophy is a rare, heterogeneous group of syndromes characterised by complete or partial loss, or absence of, subcutaneous adipose tissue. Without sufficient adipose tissue, the hormone leptin can become deficient. This disrupts the body's system for regulating energy use and storage, resulting in lipid accumulation in abnormal sites such as the liver and muscle. Metabolic abnormalities often occur with lipodystrophy, including: insulin resistance with resultant hyperinsulinemia and diabetes; hepatic steatosis or steatohepatitis; and dyslipidaemia with severe hypertriglyceridaemia. Hyperphagia, muscle pain and female reproductive dysfunction also has a significant effect on quality of life. Lipodystrophy is often diagnosed late in the disease course or remains undiagnosed.
- 2.2 Lipodystrophy is generally classified based on the extent or pattern of fat loss (generalised or partial), and whether the disease is congenital or acquired. There are 4 major subtypes: congenital (inherited) and acquired

generalised lipodystrophy; and familial (inherited) and acquired partial lipodystrophy.

- 2.3 The prevalence of lipodystrophy depends on the subtype but is around 2.5 per 1,000,000 population overall, with partial lipodystrophy being slightly more common. It is estimated that there are around 200 people with lipodystrophy in England; a proportion of these people will be eligible for metreleptin treatment.
- 2.4 There are no licensed treatments in the UK for lipodystrophy. The condition is currently managed with: lifestyle modifications such as a low fat diet and exercise; cosmetic surgery; and medication to manage the metabolic disturbance associated with leptin deficiency, including lipid-lowering drugs (for example, fibrates and statins) and antidiabetic therapy (for example, metformin, insulin, sulphonylureas, and thiazolidinediones).
- 2.5 A single National Specialist Service for people with lipodystrophy was established in 2011 at Addenbrooke's Hospital in Cambridge. Treatment with metreleptin is currently provided there as part of an early access programme, under the National Severe Insulin Resistance Service at the hospital.

3 The technology

- 3.1 Metreleptin (Myalepta, Aegerion) is an analogue of the human hormone leptin, which is secreted into the circulation from adipocytes. It received a positive opinion from the Committee for Medicinal Products for Human Use in June 2018, but is yet to receive a marketing authorisation from the European Medicines Agency. Metreleptin is provisionally indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy:

- ‘patients with confirmed congenital generalized lipodystrophy (Berardinelli-Seip syndrome) or acquired generalized lipodystrophy (Lawrence syndrome) in adults and children 2 years of age and above
- or with confirmed familial partial lipodystrophy or acquired partial lipodystrophy (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.’

3.2 The most common treatment-emergent adverse events in metreleptin studies included weight loss, abdominal pain, nausea, hypoglycaemia, fatigue, alopecia, constipation, upper respiratory tract infection, urinary tract infection, anxiety and sinusitis.

3.3 Metreleptin is administered by subcutaneous injection. The price of metreleptin per 11.3 mg vial (10 mg dose) is £2,335 (excluding VAT; company’s evidence submission). The company has agreed a patient access scheme with the Department of Health and Social Care. If metreleptin had been recommended, this scheme would have provided a simple discount to the list price of the drug, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health and Social Care considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Aegerion, the views of people with the condition, those who represent them, clinical experts and NHS England, and a review by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, in particular, including the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Burden of disease

4.1 The patient experts explained the all-consuming nature of lipodystrophy. They highlighted that, other than the serious metabolic abnormalities caused by the condition, hyperphagia was a predominant debilitating feature. The company stated that this feeling of constant hunger was better described as starvation to convey the extent of its debilitating effects. The patient experts explained that eating does not relieve the hunger, so people with the condition are constantly looking for food, which results in physical, psychological and behavioural complications. For children, constant supervision is needed to ensure they do not eat inedible objects. The constant food seeking, and associated lack of concentration and fatigue, negatively effects social and professional life, and is a significant financial burden. The patient experts highlighted that, in the absence of treatment targeting lipodystrophy and hyperphagia, dietary advice is a mainstay of supportive treatment. They noted their frustration with this because dietary control is often impossible when overcome by a feeling of starvation. The committee acknowledged that lipodystrophy is a debilitating condition, and that hyperphagia results in very poor quality of life and has a far reaching effect on the lives of patients, and their families and carers.

Diagnosis

4.2 The clinical experts explained that lipodystrophy diagnosis may be delayed because it is not immediately recognised and is a rare condition. Diagnosing generalised lipodystrophy is easier because people typically present at between 1 to 2 years old, and develop diabetes and damage in 1 or more organs by the time they are 2 or 3 years old. However, partial lipodystrophy usually presents in adulthood, and symptoms are heterogeneous, which makes diagnosis at an early stage of the disease difficult. The clinical experts highlighted that an earlier diagnosis is

important to prevent disease progression. The company explained that some people may have a mutation that is unrelated to leptin deficiency but manifests with similar symptoms, emphasising that the right clinical diagnosis is critical for effective treatment. The clinical experts confirmed that patients are routinely genotyped as part of the NHS service at Addenbrooke's Hospital. The committee was satisfied that people with lipodystrophy can be accurately identified, but noted that diagnosis in some people with milder forms of partial lipodystrophy may be delayed.

Impact of the new technology

Clinical trial evidence

4.3 The committee discussed the clinical evidence submitted by the company.

- NIH 991265 was a pilot, dose-escalation study to determine the safety and efficacy of short-term leptin replacement (up to 8 months). After NIH 991265 ended, patients continued treatment in the extension study NIH 20010769 for long-term follow-up. All but 1 patient who completed NIH 991265 moved to NIH 20010769, so the studies were treated as 1 study continuously enrolling patients with generalised (n=66) and partial lipodystrophy (n=41) aged over 14 years.
- FHA101 was an open-label, single-arm, expanded-access study with 9 patients with generalised and 32 patients with partial lipodystrophy aged over 6 years.

Only 1 patient in these studies was recruited from the UK, but the clinical experts confirmed that the trial populations were generalisable to patients seen in clinical practice in England. The ERG highlighted that estimates of treatment effects were based on changes from baseline in single-arm metreleptin treatment studies, and no data for the comparator arm was presented within the clinical evidence. The ERG stated the submission did not include any search term for comparators, and that there was no attempt to do indirect comparisons to study the effects of established

clinical management. It also explained that a critical analysis of the GL/PL natural history study used to provide data for the comparator in the economic model was not provided in the clinical section, and included a population different to the metreleptin studies (see section 4.9). The committee recognised the limitations of generating evidence for an ultra-rare disease, but considered that the lack of a structured approach to identifying appropriate comparator data was unacceptable. It therefore concluded that the evidence presented to support the relative effectiveness of metreleptin was insufficient. The committee encouraged the company to systematically identify comparator data and present further evidence on the relative effectiveness of metreleptin.

HbA1c and triglyceride levels as surrogate endpoints

4.4 The primary outcomes measured in the clinical studies included actual change in HbA1c levels and percent change in fasting serum triglyceride levels from baseline at month 12. Metreleptin was associated with a statistically significant improvement in both primary outcomes compared with baseline in NIH 991265/20010769 (in the generalised lipodystrophy population: -2.2 , $p < 0.001$ and -32.1% , $p = 0.001$ respectively; and in the partial lipodystrophy population -0.6 , $p = 0.005$ and -20.8% , $p = 0.013$ respectively). However, decreases in HbA1c and triglyceride levels were not statistically significant in the FHA101 study. The committee was aware that HbA1c and triglyceride levels are surrogate outcomes. The company explained that they are commonly used important outcomes which show the effect of metreleptin. The clinical experts agreed that HbA1c and triglyceride levels are used in clinical practice and are considered to be predictive of clinical outcome, although possibly not to the same extent as in other disease areas such as diabetes. The clinical experts stated that, in general, people with lipodystrophy with lower HbA1c and triglyceride levels have a better prognosis than people with higher levels. They stated that many people are able to stop insulin completely after having leptin treatment. The company stated that long-term preliminary data from the

early access programme at Addenbrooke's Hospital were available and could be supplied. In the absence of comparator data, the committee asked about the likelihood of HbA1c and triglyceride levels falling without metreleptin. The clinical experts stated that, if people had not previously been given any dietary advice, it could result in improved levels but that the extent of improvement may be limited because of hyperphagia. The committee concluded that metreleptin may be effective in lowering HbA1c and triglyceride levels but that the extent of any effect was unclear. It requested that the company present data from the early access programme.

Clinical and patient-perceived outcomes

- 4.5 The committee was aware that the studies did not capture the effect of metreleptin on hyperphagia even though, as the patient experts explained, it is a defining characteristic of lipodystrophy with important physical and emotional consequences. The clinical experts agreed that treatment targeting hyperphagia is critical because eating less means the complications from lipodystrophy will improve. The ERG noted that the NIH study measured food intake (kcal) per day in a subset of patients and that, while intake decreased from baseline initially, it increased by the end of the year. The patient experts stated that, since starting metreleptin, they had experienced a feeling of fullness after eating and that this had dramatically altered their lives. The committee noted that no information was available about the range of experiences of hyperphagia or response to treatment. It also noted that, in the studies, a substantial number of patients stopped metreleptin treatment. The company explained that this could have been related to the need for injections in an area with no subcutaneous fat. The committee queried whether this was compatible with the far reaching symptomatic benefits described with reduced hyperphagia. The patient experts stated that it could take a few months for people to recognise the feeling of fullness. They suggested that, in the interim, discomfort from the injections could outweigh the benefits of

reduced hunger. The company stated that it intended to capture patient reported outcomes, including hunger scores, as part of its post-authorisation commitments. The committee considered that capturing the effect of metreleptin on hyperphagia was critical to assess the nature and magnitude of any clinical benefits. It encouraged the company to submit additional evidence to support this.

Subgroups

4.6 The committee queried whether, in line with the marketing authorisation, everyone diagnosed with lipodystrophy will be expected to have treatment with metreleptin. The clinical experts stated that most people with generalised lipodystrophy have hyperphagia and organ dysfunction, so would be expected to benefit from leptin treatment. Also, everyone diagnosed with generalised lipodystrophy had leptin treatment as part of the early access programme at Addenbrooke's Hospital. The experts explained that the effects of metreleptin in people with partial lipodystrophy vary, and those with lower leptin levels and higher hunger levels are likely to benefit more. Additionally, if there is no organ damage the extent of possible benefit will be limited. The clinical experts noted that around 70% of people with partial lipodystrophy will therefore not need leptin treatment. However, it is unclear how these people will be identified, for example, by thresholds of leptin, triglycerides or HbA1c levels or evidence of organ damage. The committee invited the company to present analyses on the population most likely to have metreleptin in clinical practice in England with clear identification criteria.

Adverse events

4.7 The committee noted that the proportion of patients in the main clinical trials who had a treatment-emergent adverse event (TEAE) was high:

- In the NIH study, around 89% of patients with generalised and 85% with partial lipodystrophy had an event, which was severe in 44% and

39% respectively, and caused 8% and 2% respectively to stop treatment.

- In the FHA101 study, around 78% of patients with generalised and 84% with partial lipodystrophy had a TEAE, which was severe in 67% and 28% respectively and caused 11% and 9% respectively to stop treatment.

The company commented that stopping occurred not only because of adverse events, but also because the studies included some patients for whom metreleptin was not effective because their condition was not related to leptin. Also, some patients stopped treatment because they were pregnant. The clinical experts suggested that adherence is likely to improve in practice as the benefits of metreleptin become clear. The company and clinical experts also noted that episodes of pancreatitis improved with metreleptin compared with baseline. A patient expert highlighted that she had gone from having frequent events of pancreatitis to no events since starting metreleptin treatment. The ERG noted that, in its submission, the company only included data for pancreatitis as an adverse event occurring after metreleptin withdrawal: 4 patients with generalised lipodystrophy and 2 patients with partial lipodystrophy had treatment-emergent pancreatitis across studies (1 patient died, 5 recovered). However, the ERG also noted that the NIH data indicated that patients had improvements in pancreatitis on metreleptin. The committee heard that the tolerability profile of metreleptin was likely to be acceptable, but noted that real-world data from the early access programme would be informative.

Cost to the NHS and value for money

Company's economic model

4.8 The company developed a patient-level Markov model comparing metreleptin with standard of care. It stated that the model structure was

based on natural history data and clinical expert opinion. However, the committee noted several concerns with the model:

- The health state of a patient was determined by a set of 13 attributes, which served as indicators of impairment. These included presence of organ dysfunction, biochemical measures and other attributes such as hyperphagia. The ERG highlighted that the formal selection criteria for the attributes modelled for each patient were not clearly explained in the company's submission. The clinical experts stated that presence of organ damage is not used to categorise patients in clinical practice, and that blood sugar levels are used as a measure of response (as in patients with diabetes). They also explained that people who decreased their food intake or their need for antidiabetic medications would be classed as 'responders'. The committee discussed whether well-known risk factors for organ damage in people with diabetes were applicable. The clinical experts agreed that this would be appropriate as long as fatty liver disease, more common in lipodystrophy, was also included.
- The ERG highlighted that all disease attributes were modelled or extrapolated independently of each other, whereas in other metabolic disease models (for example, diabetes) most disease attributes are interlinked. The committee agreed that assuming independence was implausible.
- The ERG noted that the model applied the extrapolation from different time points in the metreleptin and standard of care arms. For patients in the metreleptin arm, the extrapolation of disease progression was applied from the last observation point of the available real-world data for each patient until the end of the time horizon. However, for the patients in the standard of care arm, the extrapolation of disease was always applied from the baseline (since the natural history study did not provide these data). The ERG stated that this could have led to underestimating the uncertainty for patients having metreleptin.

- The ERG highlighted that in the company's model, in the standard of care arm, baseline laboratory values from the NIH Follow-up study were assumed to remain unchanged for the whole time horizon. In the metreleptin arm, data from the clinical trials were used and a last observed carried forward approach was used for extrapolating these attributes beyond data availability. The committee agreed with the ERG that it was unclear how laboratory results translated into long-term clinical outcomes.

The committee was concerned that the company had not adequately explained or justified its approach, and did not consider that there were advantages to moving away from established predictive models used in similar metabolic conditions. It concluded that using diabetes or fatty liver disease models as a basis could help to build a more reliable model.

Comparator data in the model

4.9 After discussing the lack of comparator data in the clinical evidence base, the committee discussed how the standard of care arm in the model was populated. The company incorporated data from a natural history study (the GL/PL natural history study), which was not discussed in the clinical section of its submission and had a different population from those included in the metreleptin studies. For example, patients in the GL/PL natural history study generally had lower levels of HbA1c and triglycerides than patients in the metreleptin studies. Also, around 50% of patients in this study were of Turkish ethnicity. So, the clinical experts stated that it was not clear whether the population was generalisable to patients in England, particularly because of potentially important dietary differences. The committee remained concerned that adequate comparator data had not been presented to allow a sufficiently robust comparison of metreleptin with standard of care.

Matching exercise

4.10 The company acknowledged that patients in the NIH Follow-up and GL/PL natural history studies were not comparable. It did a matching exercise so that the baseline characteristics of the patients from the 2 studies would be similar. This formed the basis for calculating transition probabilities between states with different numbers of organ impairment for standard of care. Pairs of patients were created from the NIH Follow-up and GL/PL natural history studies to create new organ impairment progression transition probabilities for the standard of care arm in the model. The ERG commented that this may have contributed directly or indirectly to a potential bias in favour of metreleptin treatment compared with standard of care, and highlighted several concerns with the matching exercise. It explained that the company had used a matching method outlined in NICE's [technical support document on methods for comparative individual patient data](#). However, the ERG disagreed with the company on the appropriateness of this approach. It described that, in the matching algorithm used by the company, for each patient who died or was censored in the GL/PL natural history study, pseudo patients that died or were censored were created. It was not clear to the ERG how these 'pseudo' patients were generated. Also, the ERG highlighted that the size of the untreated matched dataset (n=47) was around one-third of the treated dataset (n=112), which suggested that an untreated patient was matched to multiple treated patients from the NIH Follow-up study. Also, organ impairment transition probabilities for the treated and matched untreated datasets were estimated from different datasets independently. The ERG suggested that treatment effects estimated from a pooled dataset may have been more robust. The committee agreed with the ERG and concluded that the matching exercise was not sufficiently robust.

Mortality

4.11 The committee discussed the company's approach to incorporating mortality in the model and noted several concerns:

- Survival was assumed to be determined only by age, type of lipodystrophy and number of organs impaired over a time period. The type of organ impairment and time since damage was first detected had no effect on survival.
- The survival analyses included an extrapolation exercise for the survival of the patients having standard of care using parametric models and national life tables. This was followed by an estimation exercise for the relationship between organ abnormality and mortality. The ERG stated that the extrapolation exercise was done on data from patients in the NIH Follow-up study, while the estimation exercise was done on data from patients in the GL/PL natural history study. However, for consistency, the same data sets should have been used.
- The survival extrapolation for standard of care lacked face validity because some patients had a more favourable life expectancy than the general UK population. To correct this, the company implemented a cap. However, the ERG stated that this solution was artificial, and that the reasons underpinning the high survival outcomes had not been explored.

The company stated that it had explored including direct survival data and using a simple survival model and arrived at similar results. However, the committee was very aware that a transparent validation process had not been included in the company's submission to support its approach. It concluded that, based on all the limitations noted, including those associated with the structure of the model, there was a risk of exaggerating the scale of impact.

Utility values

- 4.12 The committee was aware that the metreleptin clinical trials did not collect any quality-of-life data. So, the company instead did a discrete choice experiment (DCE) on a large sample of the general population to estimate disutilities associated with key lipodystrophy attributes. The company explained that it identified a study, Dhankhar et al. (2015), which

estimated the average EQ-5D score for lipodystrophy to be 0.67. The company did not use this estimate because it considered that it did not fully represent the burden of lipodystrophy arising from disease attributes such as hyperphagia, female reproductive dysfunction or organ abnormality. Also, it included patients with milder disease and carers. The ERG agreed with the limitations of the Dhankhar study. However, it highlighted the significant methodological issues associated with using DCE to get disutility values for health states directly, which made the values highly uncertain. It also highlighted concerns around the face validity of DCE-based disutilities because, in the standard of care arm, 33.07 life years were accumulated, which translates into only 0.27 quality-adjusted life years (QALYs). The committee agreed that the results for the standard of care arm appeared unrealistically low and was concerned that the simple addition of utility decrements from multiple disease attributes may have overestimated the overall disutility. The company acknowledged this, but stated that it believed that the gain from leptin treatment of 0.338 per year was realistic. The committee remained concerned that this would not be reflective of the gain across the entire patient population eligible for metreleptin. It noted that the company's preferred scenario analysis doubled the level of disutility to account for hyperphagia having a major effect. The committee strongly disagreed with this, noting that doubling the value was entirely speculative. However, it understood and appreciated the burden of hyperphagia and encouraged the company to explore this further. The committee also noted that no specific carer-related utilities were included in the model, so encouraged the company to explore the effect of including carer utilities, including variation with age.

Costing

- 4.13 The committee discussed uncertainties around the costs incorporated in the model. It noted that metreleptin is available in 11.3 mg vials (a 10 mg dose), but that the company intends to apply for additional vial sizes of

5.8 mg (a 5 mg dose) and 3 mg (a 2.8 mg dose) within 3 months of the marketing authorisation being granted. The committee also noted that, based on the anticipated availability of multiple vial sizes, the company assumed weighted average annual drug acquisition costs of £434,633. This weighted average was based on the patients in Addenbrooke's Hospital expected to be treated with each vial size. The ERG commented that information on the characteristics of the patients in the early access programme were not provided. The committee acknowledged that, without these characteristics, the distribution of patients by age and weight (which determine the dosing) is unknown, and the acquisition costs of metreleptin have not been verified. It noted that incorporating multiple vial sizes had a substantial effect on costs and incremental cost-effectiveness ratios (ICERs). The committee decided that it could only factor in the currently available vial size in its deliberations because availability of additional vial sizes in the future was hypothetical and subject to change. Therefore, the issue of calculating acquisition costs based on multiple vial sizes was not an issue for its immediate decision-making. The committee noted that, if additional vial sizes become available during the course of this evaluation, it would take them into account. It encouraged the company to submit full details behind the method used for calculating the weighted average annual drug acquisition costs for metreleptin.

Application of QALY weighting

4.14 The committee understood that the [interim process and methods of the highly specialised technologies programme](#) (2017) specifies that a most plausible 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 magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It

understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee considered that it was not presented with a robust estimate of QALYs gained, therefore it could not assess whether QALY weighting would be applicable. The committee concluded that it was unable to make a decision about whether metreleptin would meet the criteria for applying a QALY weight.

Cost-effectiveness results

4.15 The committee discussed the cost-effectiveness results presented by the company and the results of the ERG's exploratory analyses. It noted that the most optimistic scenario presented by the company resulted in an ICER of £1,206,039. This was based on list prices, the 10 mg dose of metreleptin, and the assumption of double disutility with hyperphagia that the committee considered to be speculative. The ERG exploratory analyses resulted in ICERs of up to £5,898,649 per QALY gained. The biggest drivers of these ICERs included disease attributes other than organ impairment and laboratory values, and using different utility values. Taking into account its conclusions on the important gaps and uncertainties in the clinical evidence and economic model, the committee concluded that it was unable to arrive at a most plausible scenario based on the current evidence base. It noted that, even when the patient access scheme was incorporated, the ICERs were substantially higher than the range considered an effective use of NHS resources for highly specialised technologies.

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

4.16 The committee discussed the effects of metreleptin beyond its direct health benefits. It understood from patient experts that children with hyperphagia need considerable carer support, which can have a significant effect on families. In adults, hyperphagia and fatigue can comprise their social and professional lives. The committee concluded

that lipodystrophy affects patients beyond direct health benefits but that quantifying this was difficult. It concluded that it was highly unlikely that the effects would be sufficient enough to overcome its concerns about the substantial uncertainties in the clinical and cost-effectiveness evidence. The committee also concluded that the effects were unlikely to bring the most plausible ICERs to a level considered to be an acceptable use of NHS resources.

- 4.17 The committee noted that lipodystrophy is managed in an established specialist centre at Addenbrooke's Hospital Cambridge, so additional infrastructure or staff training is not expected to be needed to introduce metreleptin use in England.
- 4.18 The committee noted that the population for which metreleptin is indicated includes children and young people. It 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 NICE's [social value judgements: principles for the development of NICE guidance](#), which 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.

Conclusion

- 4.19 The committee acknowledged that lipodystrophy, and hyperphagia in particular, has a substantial effect on the quality of life of patients, and their families and carers. It noted that the clinical evidence suggested metreleptin may provide clinical benefits for some patients, but considered this to be highly uncertain because of important limitations in the nature and extent of the evidence. Also, because of the very significant uncertainties in the economic model, the committee was unable to identify a plausible range of ICERs or QALYs to underpin its decision-making. In addition, it considered that the ICERs presented in the company's base

cases and the ERG's exploratory analyses were all substantially above the range considered to be an appropriate use of NHS resources for highly specialised technologies. The committee was therefore unable to make a decision on metreleptin as an option for treating lipodystrophy. The committee recommended that NICE requests further clarification and analyses from the company, which should be made available for the second appraisal committee meeting, and should include:

- comparator data, systematically identified, to support the relative clinical effectiveness of metreleptin compared with standard of care, and to include in the economic model (see sections 4.3 and 4.9)
- results from the early access programme under the National Severe Insulin Resistance Service at Addenbrooke's (see section 4.4)
- alternative, more plausible utility values, including those exploring the effects of hyperphagia on families and carers (see section 4.5)
- the patient population likely to have metreleptin in clinical practice in England, with clear identification criteria (see section 4.6)
- an alternative model structure based on established models for metabolic conditions, incorporating well-known risk indicators with additional consideration of fatty liver disease (see section 4.8)
- full details about calculating the weighted average annual drug acquisition costs (see section 4.13).

5 Proposed date for review of guidance

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. 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

June 2018

6 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 appraisal.

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

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