NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final evaluation document

Metreleptin for treating lipodystrophy

1 Recommendations

1.1 Metreleptin is recommended, within its marketing authorisation, as an option for treating the complications of leptin deficiency in lipodystrophy for people who are 2 years and over and have generalised lipodystrophy.

1.2 Metreleptin is recommended as an option for treating the complications of leptin deficiency in lipodystrophy for people who are 12 years and over, have partial lipodystrophy, and do not have adequate metabolic control despite having standard treatments. It is only recommended if they have an HbA1c level above 7.5%, or fasting triglycerides above 5.0 mmol/litre, or both.

1.3 This recommendation is not intended to affect treatment with metreleptin 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. This decision should be made jointly by the clinician, the child or young person and their parents or carers.

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. For children and young people with the condition, it may also shorten their life expectancy. Conventional

therapy includes lifestyle modifications such as an extreme low-fat diet and exercise, cosmetic surgery, and medication for diabetes and to lower lipids.

There is no trial directly comparing metreleptin with standard care. Results from clinical studies suggest that metreleptin appears to improve hyperphagia and reduces HbA1c and triglyceride levels in people with lipodystrophy. An indirect comparison with standard care also suggests that metreleptin is more effective at improving HbA1c, triglyceride and liver enzyme levels at 12-month follow up. However, metreleptin's long-term effect and several assumptions in the economic modelling are uncertain. Despite this, metreleptin is likely to provide important clinical benefit and improve quality of life for people, parents and carers. It also provides value for money within the context of a highly specialised service. So, it is recommended for use in the NHS.

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 there is disruption of the body's system for regulating energy use and storage. This results 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. The associated lack of leptin, particularly in people with generalised lipodystrophy, leads to symptoms such as hyperphagia. It may also contribute to the metabolic abnormalities. Hyperphagia, muscle pain and female reproductive dysfunction also have 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 of the 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, 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, Amryt) is an analogue of the human hormone leptin, which is secreted into the circulation from adipocytes. Metreleptin has a UK marketing authorisation under 'exceptional circumstances' as 'an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

- with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above
- with confirmed familial partial LD or acquired partial LD (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 Metreleptin is administered daily by subcutaneous injection. For people weighing 40 kg or less, the starting daily dose is 0.06 mg/kg. Dose adjustments of 0.02 mg/kg are allowed up to a maximum daily dose of 0.13 mg/kg. For men and women weighing over 40 kg, the starting daily dose is 2.5 mg and 5 mg respectively. For people weighing over 40 kg, dose adjustments of 1.25 mg to 2.5 mg are allowed up to a maximum daily dose of 10 mg.

3.3 The most common treatment-emergent adverse events in metreleptin studies included weight loss, hypoglycaemia, fatigue, injection site reactions, neutralising antibodies, decreased appetite, nausea, headache, abdominal pain, menorrhagia and alopecia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 The price of metreleptin per 11.3 mg vial (10 mg dose) is £2,335 (excluding VAT; company's evidence submission). The company has a commercial arrangement (simple discount patient access scheme). This makes metreleptin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

4 Consideration of the evidence

The evaluation committee (see section 8) considered evidence submitted by Amryt, the views of people with the condition and those who represent them, clinical experts and NHS England, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

History of the evaluation

4.1 Previously, 2 committee meetings were held for the evaluation of this topic. After the second committee meeting (12 February 2019), a final evaluation determination was drafted of the committee's considerations

and conclusions based on the evidence presented. NICE received 2 appeals against that final evaluation determination. The appeal hearing did not take place because Aegerion (the marketing authorisation holder at the time) requested reconsideration of this topic (in line with the highly specialised interim methods and process guide). This was granted and the final evaluation determination was withdrawn. For reconsideration of the topic, the company also agreed to address the concerns outlined in the drafted final evaluation determination by presenting additional evidence and doing further analysis. Amryt, the company that is now the marketing authorisation holder, submitted the additional evidence and new analyses for reconsideration. The resubmission went through a technical engagement process in August 2020.

4.2 Concerns raised by the committee during the second meeting (reported in the final evaluation document that was withdrawn) included:

- Lack of evidence on relative effectiveness of metreleptin on disease progression or important outcomes such as hyperphagia:
  - The systematic literature review may have missed some studies.
  - There was no evidence on change in patient experience and disease progression for people who did not have metreleptin.
  - Early access programme results did not improve the committee's understanding of metreleptin's relative effectiveness in the short or long term because they did not include long-term data or patient-reported outcomes (such as hyperphagia).
- The economic model focused on mortality and did not capture important aspects of the condition; it oversimplified its underlying progression. The committee's suggestion that using a model structure with established diabetes or fatty liver disease models to capture some important aspects of disease progression was not followed.
- Starting and stopping criteria were not included in the economic model.

- Rescaled utility estimated from the discrete choice experiment was more plausible than the original discrete choice experiment, but there were still uncertainties.
- Carer utility decrement was based on literature and only applied to the standard care arm.

4.3 The evaluation committee was aware that 1 issue (issue 5) was resolved during the technical engagement stage. It agreed that yearly rates of stopping treatment (8.93% in year 1, 5.63% in years 2 to 9 and 2.04% in year 10 onwards) were a good reflection of treatment stopping seen in the first year of the National Institutes of Health (NIH) trial and the decline in how many people stopped treatment over time. It agreed that it was better than applying a single stopping rate only based on those who chose to stop metreleptin in each population (1.5% for generalised lipodystrophy and 3.86% for partial lipodystrophy) from NIH trials.

4.4 There was 1 remaining area of uncertainty associated with the analyses presented (see technical report, issue 11, page 10). The committee took this into account in its decision making. It discussed issue 1, issues 2 and 3 together; issue 4, issue 6, issue 7, issue 8, issue 9, and issue 10, which were outstanding after technical engagement. When forming the recommendations, the committee took into account the full range of factors that might affect its decision, in particular, 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

4.5 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 affects social and professional life, and is a significant financial burden. The patient experts highlighted that, in the absence of specific 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 patient experts also noted that caring for a child with lipodystrophy is a substantial burden, affecting parents and carers both emotionally and financially. The committee acknowledged that lipodystrophy is a debilitating condition, and that hyperphagia has a significant effect on quality of life, which affects patients, parents and carers. For children and young people with congenital generalised lipodystrophy, the condition may also shorten their life expectancy. The committee recognised that there is a significant unmet need for an effective treatment option.

Diagnosis

4.6 The clinical experts explained that lipodystrophy diagnosis may be delayed because it is not immediately recognised and is a rare condition. Diagnosing generalised lipodystrophy, particularly when congenital, 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 later, 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 patient experts supported the view of the clinical experts, stating that partial lipodystrophy can progress and become severe if undiagnosed and untreated. 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

4.7 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. This meant 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 during the first and second committee meetings. The committee noted that there was a lack of evidence on metreleptin's relative treatment effect. In its resubmission, and in response to committee's concerns at the second meeting (see section 4.2), the company updated its systematic literature review. It used a new search strategy to include search terms

for comparators and did a new indirect treatment comparison using 3 methods. The ERG noted that the new systematic literature review addressed its previous critiques on searching. The committee concluded that it was satisfied with the company's attempt to identify evidence on comparators in its updated systematic literature review.

Early access programme

4.8 One of the committee's concerns was the lack of evidence on metreleptin's long-term effect in people who have treatment (see section 4.2). In its resubmission, the company provided additional clinical evidence with 36-month follow up from the metreleptin early access programme (n=31, including all patients who had treatment since the start of the programme) at Addenbrooke's Hospital. Data were collected retrospectively, with clinicians entering patient data on baseline characteristics, organ damage and complications, laboratory values and metreleptin dose. The ERG noted that the additional data showed persistence of changes with metreleptin treatment up to 36 months, with a reduction in HbA1c and triglycerides (see section 4.11). But, there were no patient-reported outcomes or measures of patient experience (including hyperphagia) presented, despite some people having treatment for 10 years or more. The company explained that when the early access programme was set up in 2005 there was no pre-specified data collection protocol, so the only data available were from a review of patient medical records. In addition, clinical experts noted that the treatment eligibility criteria currently used were not in place when the programme was set up. Because the criteria were only introduced 2 years ago, not all people with partial lipodystrophy in the programme had poor enough metabolic status at baseline to be eligible for the treatment under the current criteria. For example, people with high level of triglycerides and low level of HbA1c were enrolled at the time. The clinical experts also stated that the programme had a small sample size, and there were very few data on generalised lipodystrophy's response to metreleptin. This meant that no conclusion on efficacy could be made from the early access programme.

The committee welcomed the company's attempt to gather additional clinical evidence to supplement the sparse evidence base. It agreed that the new evidence indicated that metreleptin treatment improves metabolic outcomes at 36-month follow up. But, the committee did not substantially improve its understanding of the relative effectiveness of metreleptin. It concluded that evidence from the early access programme itself was not sufficient to address the gaps in the clinical evidence base.

Representativeness of the NIH follow-up study and the indirect treatment comparison

4.9 In response to the committee's concerns about the lack of evidence on metreletpin's relative effectiveness (see section 4.2), the company did an indirect treatment comparison. This used 3 methods (inverse probability weighting, multi-regression analysis, and naïve comparison) to estimate the treatment effect of metreleptin relative to standard care for key clinical outcomes. Data used to inform the indirect treatment comparison were from the NIH 991265/NIH 20010769 study (metreleptin arm) and the GL/PL natural history study (standard care arm), respectively. Outcomes assessed included change from baseline in HbA1c, triglycerides and liver enzyme (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels, the incidence of acute pancreatitis and all-cause mortality. The results of the indirect treatment comparison showed statistically significant difference in favour of metreleptin on HbA1c, triglycerides, liver enzymes and reducing the risk of pancreatitis at 12-month follow up. It also suggested that survival was worse with metreleptin compared with standard care, but the difference was not statistically significant.

4.10 The committee agreed in a previous meeting that the NIH follow-up study was representative of people with lipodystrophy in the UK and appropriate to be used for treatment comparison. However, with additional evidence available from the early access programme, the ERG raised 2 concerns related to the indirect treatment comparison. These were the representativeness of the NIH follow-up study used to inform the indirect

treatment comparison compared with the early access programme, and the selection of covariates used to adjust for differences between patient cohorts in the indirect treatment comparison. The ERG noted differences in the effects of metreleptin treatment (particularly for changes in triglyceride levels) between the early access programme (see section 4.8) and the NIH follow-up study (see section 4.7). For example, for people with generalised lipodystrophy, the 12-month change was -3.5 mmol/litre (based only on people for whom both baseline and 12-month data were available) in the early access programme, compared with -10.54 mmol/litre in the NIH follow up. The ERG noted that the early access programme estimate is closer to that of the GL/PL natural history study estimate of -4.43 mmol/litre. The change in HbA1c at 12 months was also lower in the early access programme (-1.5% for those with generalised lipodystrophy) than in the NIH follow-up study (-1.94% for all patients). Given these differences and the fact that people enrolled in the early access programme are from the UK, the ERG stated that the early access programme should be used in the indirect treatment comparison instead of the NIH follow-up study. The company explained that the early access programme had a much smaller sample size (n=31) and started over a decade ago. The eligibility criteria have evolved along with the growing evidence base for people with lipodystrophy. The clinical experts highlighted the limitations of the early access programme data, namely that people did not have poor enough metabolic status at baseline when they were enrolled in the programme (see section 4.8). They added that the early access programme was not a research study, it was based on 'compassionate use' rather than formal clinical criteria. One of the clinical experts involved in the early access programme explained that recent outcomes are becoming more and more aligned with those of the NIH study follow up. This is because of the application of recent clinical inclusion criteria (see section 4.8). The clinical experts stated that the indirect treatment comparison would be better informed by the NIH follow-up study. The ERG was also concerned about the limited covariates adjusted for in the indirect treatment comparison. This is because

important prognostic covariates such as baseline HbA1c and triglyceride levels are not controlled for in the analysis. The company argued that these were not confounding factors because they were not related to treatment allocation. The company also explored using additional covariates in a sensitivity analysis. But, it stated that this analysis was not feasible because of small sample size, the high proportion of missing data and the large number of potential covariates. The company explained that there was more than 90% of missing data and, despite a small sample number (n=31), the 3 methods it used to adjust for cofounders (inverse probability weighting, multi-regression analysis, and naïve comparison) showed consistent results with statistical significance. The company added that its approach was driven by clinical opinion and statistical principles. The committee recognised the limitation of the company's indirect treatment comparison. However, it understood the challenges in generating evidence for ultra-rare diseases given the availability of the data. The committee concluded that, despite the limitations, it was broadly satisfied with the company's methods for the indirect treatment comparison.

HbA1c, triglycerides and liver enzymes levels as surrogate end points

4.11 The primary outcomes measured in the clinical studies included absolute change in HbA1c levels and percent change in fasting serum triglyceride levels from baseline to 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 this was -2.2, percentage point (pp), $p<0.001$ for HbA1c levels and -32.1%, $p=0.001$ for triglyceride levels. In the partial lipodystrophy population this was -0.6 pp, $p=0.005$ for HbA1c and -20.8%, $p=0.013$ for triglyceride levels. Decreases in HbA1c and triglyceride levels were not statistically significant in the FHA101 study. Additional data from the early access programme (at 36-month follow up) that became available for the resubmission also suggested that metreleptin reduced HbA1c in both people with generalised and partial lipodystrophy (-1.2% and -1.6%,

respectively) and fasting triglyceride levels (-23.9% and -19.9%, respectively). No statistical significance was reported. The company also presented evidence on metreleptin's treatment effect on the liver enzymes, ALT and AST. This showed treatment effect in favour of metreleptin at 12-month follow up (see section 4.9).

4.12 The committee discussed HbA1c, triglyceride and liver enzyme levels as surrogates because changes in these outcomes were used to adjust long-term transitions between states in the modelling. As part of their resubmission, the company held a Delphi panel involving 10 international clinical experts (3 of whom were clinical experts from Addenbrooke's Hospital). The Delphi panel reached a consensus that HbA1c is a good predictor of diabetes-related complications including cardiovascular disease, kidney disease, retinopathy and neuropathy in people with lipodystrophy. The company explained that the relationship between HbA1c and long-term clinical outcomes based on 30-year follow up in diabetes studies is established and widely accepted. The clinical experts explained that triglyceride levels were strongly linked to pancreatitis but that the association was harder to capture mathematically. The clinical experts agreed that HbA1c and triglyceride levels are used in clinical practice and are considered to be reasonably predictive of clinical outcomes. However, the relationship may not be identical to that in other disease areas such as diabetes. For example, the risk of early death is greater for people with lipodystrophy compared with people with type 2 diabetes and metabolic syndrome. They stated that, in general, people with lipodystrophy with lower HbA1c and triglyceride levels have a better prognosis than people with higher levels. They also noted that the effects of HbA1c and triglycerides were broadly correlated but there may be differences between individuals with lipodystrophy depending on other independent factors, for example, genetic factors. They added that HbA1c can predict for complications of the eye and nervous system, as in type 2 diabetes, but differently for other organs complications such as complications of the kidney, liver and heart. They also stated that many

people can stop insulin completely after starting leptin treatment. The committee also considered the merit of liver enzymes as a surrogate outcome for liver complications. Clinical experts explained that these are poor predictors of liver disease. The company stated that, because it knew liver enzymes were not a good surrogate, it sought the opinion of clinical experts (through the Delphi panel) on the likely effect of metreleptin on liver disease. 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, that giving it at the start of treatment could result in improved levels. But, the extent of improvement may be limited because of hyperphagia. In fact, they stated that without treatment, HbA1c levels are likely to reverse to their baseline values over 6 to 12 months, or sooner. The committee noted that evidence showed that metreleptin is effective in lowering HbA1c and triglyceride levels. Evidence also showed that metreleptin may affect liver enzymes but their correlation with the progression of liver disease is less clear. The committee concluded that using HbA1c to predict diabetes-related complications in people with lipodystrophy is acceptable but the relationship between liver enzymes and liver disease is uncertain.

Clinical and patient-perceived outcomes

4.13 The clinical studies did not include an objective measure to 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 some complications of lipodystrophy will improve. The clinical experts also explained that hyperphagia is caused by a deficiency in the hormone leptin (see section 2.1). They also noted that it was hard to predict the impact of metreleptin effect on hyperphagia and quality of life, because there is no simple relationship between eating less and quality of life. The committee acknowledged the expert comments and agreed that any

improvements in hyperphagia would be important, but difficult, to capture when considering the clinical benefits of metreleptin. The ERG noted that the NIH study measured food intake (kcal) per day in a subset of patients. This showed that, while intake decreased from baseline initially (4-month assessment), decreases were not statistically significant at the end of the year. Results from the NIH follow-up study showed that 99% of people who had metreleptin reported improvements in hyperphagia. The ERG highlighted that improvements were assessed in a review of medical notes and, although results suggested metreleptin improved hyperphagia, these judgements were not made using an objective measure. 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. One patient expert also noted that, before their daughter started metreleptin, they had to lock cupboards because her intense hunger led her to search for food. But, since starting the drug her hunger had reduced, and food seeking had stopped. The clinical experts agreed that metreleptin reduces hunger and food seeking. They also noted that children with congenital leptin deficiency could continue benefiting from metreleptin when having treatment for over 20 years, including avoiding obesity and related comorbidities. The committee queried whether there was any continued effect of metreleptin if patients stop the treatment. Clinical experts stated that symptoms of hyperphagia will return after a few days once metreleptin is stopped. The committee noted that, in the studies, a substantial number of patients stopped metreleptin treatment. The clinical experts explained that this could be because metreleptin only treats leptin deficiency and does not correct problems associated with loss of adipose tissue. The company explained that some patients who were seen as stopping treatment had remained on metreleptin but moved to local treatment centres where treatment was provided through compassionate use programmes. It stated that it intended to capture patient-reported outcomes, including hunger scores, as part of its post-authorisation commitments. The committee agreed that any additional information (qualitative or quantitative) about the experience of

hyperphagia in people with lipodystrophy, and the effect metreleptin has on it, could substantially improve its understanding of the potential clinical benefits. It concluded that capturing the effect of metreleptin on hyperphagia could be challenging but was important to assess the nature and magnitude of any clinical benefits of metreletpin while patients are on treatment, and also after stopping treatment.

Starting and stopping criteria

4.14 The committee queried whether all people diagnosed with lipodystrophy and covered by the marketing authorisation would 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. The committee was also aware that everyone diagnosed with generalised lipodystrophy had leptin treatment as part of the early access programme at Addenbrooke's Hospital.

The marketing authorisation for partial lipodystrophy (for people aged 12 and over) was not restrictive. But, the committee was aware that several different subsets of people with partial lipodystrophy had been presented in the company evidence:

- NIH studies 991265/20010769 included leptin level criteria in their definition of people with partial lipodystrophy (used for the indirect treatment comparison):
  - NIH 2001769: below 12.0 ng/ml in women, below 8.0 ng/ml in men, and below 6 ng/ml in children between 6 months and 5 years
  - NIH 991265: 8.0 ng/ml and below in women and 6.0 ng/ml and below in men
  - HbA1c 6.5% or more or triglycerides 5.65 mmol/litre or more, or both.
- A subgroup of people with partial lipodystrophy from the NIH study with baseline HbA1c 6.5% or more, or triglycerides 5.65 mmol/litre or more, or both (used for model inputs for the economic analysis, including

baseline levels of metabolic surrogates and changes from baseline of HbA1c). The company considered that this subgroup of people with partial lipodystrophy represents a more severe group compared with the overall population of people with partial lipodystrophy in the NIH study. This is because they are more at risk of organ damage and this best reflects the licensed indication.

- The early access programme included people with partial lipodystrophy with baseline leptin below 12 ng/ml and HbA1c 6.5% or more, or triglycerides 5.65 mmol/litre or more, or both (used by the company for baseline patient distribution in the model). The early access programme also included people with partial lipodystrophy who did not meet these criteria (see section 4.8).
- After the technical engagement, the company suggested further restricting the group of people with partial lipodystrophy from their original definition (HbA1c 6.5% or more, or triglycerides 5.65 mmol/litre or more, or both), to baseline HbA1c above 7.5%, or fasting triglycerides above 5.00 mmol/litre, or both. But, they accepted the HbA1c could be lower in cases of extreme hyperphagia or intolerance to standard diabetes treatment, or both. The company explained these restrictive criteria were developed based on the clinical evidence from the NIH studies 991265/20010769, UK clinical expert experience and consensus from European lipodystrophy centres.

The ERG pointed out that there was no clinical or economic evidence for this further restricted subgroup of partial lipodystrophy proposed by the company. It was concerned that the effect on the population size eligible for treatment was unknown given the lack of information on the number of people who would actually fulfil these criteria, including the exceptions. It noted that the narrower population would cause issues around application of the various data sources to UK clinical practice. The clinical experts explained that response to metreleptin is greater in people with lipodystrophy and with more severe metabolic status (that is, HbA1c and triglyceride levels) at baseline. They further explained that the criteria of

'HbA1c above 7.5%' was based on the recommended value for a person with diabetes to target in clinical practice. The criteria of 'fasting triglycerides above 5.00 mmol/litre' was based on the value above which people with diabetes are at risk of pancreatitis. The committee understood the rationale for choosing the further restricted criteria for the subgroup of people with partial lipodystrophy. It acknowledged the ERG's concerns, but agreed that partial lipodystrophy with more severe metabolic status (that is, HbA1c above 7.5%, or fasting triglycerides above 5.00 mmol/litre, or both) may benefit more from metreleptin. Because the subgroup of people with partial lipodystrophy included in the economic model had less severe metabolic status (HbA1c 6.5% or more, or triglycerides 5.65 mmol/litre or more, or both), the estimated cost effectiveness for metreleptin was likely to be too high. The committee concluded it would take this into account in its decision making.

Adverse events

4.15 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. This was severe in 44% and 39% of patients, 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. This was severe in 67% and 28% of patients, respectively, and caused 11% and 9%, respectively, to stop treatment.

The company commented that stopping happened 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 company added that TEAEs happened over a long

period of time, more than 3 years in the NIH study and over 2 years in the FHA101 study, and that several reported TEAEs (such as decreased appetite and weight, and hypoglycaemia) were consistent with metreleptin's mechanism of action. 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 original submission, the company only included data for pancreatitis as an adverse event happening 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 company noted that TEAEs were not reported in the data collected from the early access programme. The ERG highlighted that this contradicted the company's comments from the first evaluation committee meeting that additional adverse event information could be provided. The committee agreed that additional real-world data on adverse events would be informative. But, based on what it had heard from the experts, it concluded that the tolerability profile of metreleptin was likely to be acceptable.

4.16 In NIH 991265/20010769 and FHA101 studies, 88% of people developed antibodies to metreleptin, and 4% developed neutralising antibodies to metreleptin. This raised concern that developing neutralising antibodies could affect metabolic control and immune function. The company explained that neutralising antibodies are only reported in 4% of people. Therefore, it did not anticipate this affecting a significant proportion of people or affecting outcomes such as HbA1c and triglyceride levels in the long term. Clinical experts stated that neutralising antibodies are rare, and although relevant to some people, do not seem to be a frequent problem

in clinical practice. The same issues are seen in other metabolic diseases, but it does not affect the efficacy of the drug. They noted that neutralising antibodies should still be monitored. The committee concluded that neutralising antibodies did not seem to be a significant issue, but this should still be monitored in the future.

Cost to the NHS and value for money

Company's economic model

4.17 The company developed a de novo individual patient level model addressing previous committee concerns (see section 4.2). The model consists of 6 Markov sub-models. These simulate the progression of disease on distinct organ systems affected by lipodystrophy, capturing the key lipodystrophy-related complications that affect health-related quality of life, costs and mortality over the lifetime of people with lipodystrophy. The 6 organ sub-models are: pancreas, liver disease, cardiovascular disease, kidney, neuropathy (nerves) and retinopathy (eyes). In each cycle (which lasted for 1 year), a person is simultaneously in a single discrete health state in each of the 6 independent organ sub-models. A person can die during each cycle, in which case they are removed from all sub-models into the death state.

- Pancreas sub-model starts in the 'no pancreatitis' state when a person is at risk of developing pancreatitis.
- Liver sub-model is based NICE's guideline on non-alcoholic fatty liver disease (NAFLD). People transition through health states, from having no or asymptomatic fibrosis, to advanced fibrosis, to compensated and then decompensated cirrhosis.
- Cardiovascular sub-model: people start in the 'no cardiovascular disease' state, when they are at risk of experiencing cardiovascular complications (stroke, angina, congestive heart failure, and myocardial infection).
- Kidney sub-model is based on structure of the Sheffield diabetes model. People start in the 'no chronic kidney disease' state, when they

can transition through microalbuminuria and macroalbuminuria to the end-stage renal disease (ESRD) health state. From ESRD, people can transition to receiving a kidney transplant (tunnel state), moving to the post-transplant state in the following cycle.

- Neuropathy sub-model: people start in the 'no peripheral neuropathy' and can progress to peripheral neuropathy, peripheral arterial disease with amputation, moving to the post-amputation in the following cycle.
- Retinopathy sub-model: people start in the 'no retinopathy' state and can progress to blindness either directly, or by progressing through various retinal diseases such as background retinopathy, proliferative retinopathy and macular oedema.
- People are at risk of death in all states.

The ERG noted that the company's model structure is an improvement from previous submissions (see section 4.2). This is because it is better structured to account for the potential progression of complications related to lipodystrophy over time. However, it relies on the assumption that people with diabetes or elevated triglyceride levels, because of lipodystrophy, will follow a similar course to people with similar metabolic abnormalities but different aetiology. It stated that this was an area of considerable uncertainty. The company explained that its choice to follow a diabetes framework for its model structure was in response to the committee's previous suggestion (see section 4.2). The model is based on the structure on the diabetes-related complications seen in the Sheffield diabetes model, and the established model structure from NICE's guideline on NAFLD to reflect liver disease progression. It chose the Sheffield diabetes model, among others, because it considered it the most robust, and it was previously used in a multiple technology assessment for diabetes. The committee was satisfied with the company's attempt to capture the disease progression using sub-models for each relevant organ. It was aware that there are uncertainties as to what extent people with lipodystrophy will follow a similar course to people with diabetes and fatty liver disease. However, given the scarcity of evidence in

lipodystrophy, the committee concluded that the model structure is appropriate for decision making.

Transition probabilities adjusted by HbA1c for sub-models

4.18 The company used published literature for baseline transition probabilities for 4 of the sub-models that are diabetes-related complications: cardiovascular, kidney, neuropathy and retinopathy. Baseline transition probabilities were then adjusted according to the absolute change in HbA1c level from baseline to 12 months from NIH 991265/20010769, to generate probabilities for people having metreleptin. For the liver sub-model, the baseline transition probability for liver disease was derived from the model in NICE's guideline on NAFLD, and then adjusted using reduction in risk estimated from the Delphi panel (company's base case) or changes in liver enzymes from the indirect treatment comparison (company's scenario analysis). For the pancreas sub-model, the baseline transition probability for pancreatitis was directly sourced from the GL/PL natural history study. It was then adjusted using odds ratios estimated from the indirect treatment comparison (see section 4.9).

4.19 For the 4 diabetes-related sub-models, the ERG noted that the company did not adjust the transition probabilities based on triglycerides, because of lack of data in the literature. The company explained that it meant that the transition probabilities were underestimated in cases when hypertriglyceridaemia contributes to the risk of a complication, such as cardiovascular disease. The committee noted that using only HbAc1 to adjust the transition probabilities in the 4 diabetes-related sub-models could either under or overestimate metreleptin's treatment effect on those organ complications. But, the exact magnitude of that is unlikely to be quantified because of limited evidence. It agreed that, qualitatively, HbA1c has value as a surrogate for clinical outcomes in the cardiovascular, kidney, neuropathy and retinopathy sub-models. It was generally satisfied with the approach taken by the company to model transition probabilities. The ERG preferred using the change in liver enzymes (trial-based data) estimated from the indirect treatment comparison (rather than the risk

reduction estimate directly obtained from the Delphi panel) to adjust the baseline transition probability for the liver in their base case. The committee recalled that liver enzymes are a poor predictor for liver complications (see section 4.12). It agreed that the Delphi panel, based on clinical experts' judgement, would be an appropriate source to inform the liver transition probabilities in this case. It was also aware that the choice between liver enzymes and the Delphi panel estimates only had a minor impact on the cost-effectiveness estimate. The committee concluded that it was generally satisfied with the company's approach to modelling transition probabilities.

Utility decrements for organ complications

4.20 The committee was aware that the clinical trials of metreleptin did not collect any quality-of-life data. In its resubmission, the company did a systematic literature review to identify sources of utility values from the literature. The utility decrement for pancreatitis was based on the discrete choice experiment (DCE) from the original submission. The DCE was done for a large sample of the general population, to estimate utility decrements associated with key lipodystrophy attributes. The utility decrements for the other organs were taken from published sources and those previously used and accepted in NICE appraisals of type 2 diabetes and fatty liver disease. The committee agreed with using utility decrements from other conditions than lipodystrophy, given the scarcity of data for this condition. Also, to capture specific symptoms not already accounted for in the sub-models (that is, hyperphagia, polycystic ovary syndrome, inability to work and impaired physical appearance), the company's model applied a utility differential (compared with standard care) of 0.12, based on the rescaled DCE from the original company submission (see section 4.2). The committee recalled it had had concerns relating to the validity of the utility values estimated from the DCE (see section 4.2). The company acknowledged the limitations but stated that no alternative value could be sourced from the literature. The patient expert explained that people with lipodystrophy with organ damage may also

have fertility issues, pain and fatigue, so those should be taken into account in the model. The clinical expert added that, even when including the utility differential of 0.12, there could be other symptoms or factors not accounted for. The committee concluded it was generally satisfied with the approach to include a utility differential to account for symptoms not captured by estimates of utility related to organ damage.

Carer utility

4.21 The company recalled that the committee had concerns about how it had modelled carer utility in its previous submission (see section 4.2). In its resubmission, the model also included a utility decrement to account for the burden on carers of -0.0986. This decrement was estimated as the difference between the mean value for carers in the Lipodystrophy Caregiver Burden Survey (done by the company to explore carers experience in the UK) and the general population norm, obtained from the EQ-5D. The committee was satisfied with the company's approach to model carer utility.

Number of carers

4.22 The company assumed that each patient had 2 carers. This was the median and the rounded value of the mean of 1.67 carers, based on the Lipodystrophy Caregiver Burden Survey. The company argued that the median is more likely to be representative of the number of carers in UK clinical practice and was validated by UK patient experts. The ERG used the mean of 1.67 in their base-case model as is usual in health economic modelling. The committee agreed with using 1.67 carers from the ERG because not all people with lipodystrophy will have 2 carers. It concluded that it was satisfied with the ERG's approach.

Long-term effect of metreletpin on HbA1c, liver, quality of life, and patient-reported outcomes such as hyperphagia after stopping treatment

Metreleptin's treatment effect on HbA1c after stopping treatment

4.23 Although there is no evidence on metreleptin's effect on HbA1c after stopping treatment, the company's model assumed that metreleptin's treatment effect on HbA1c will be maintained for lifetime after stopping treatment. In the model, when people start metreleptin, their HbA1c level is fully reduced (in the first cycle), based on the change from baseline to 12 months from the NIH 991265/20010769 studies. In subsequent cycles, people have a yearly rise of 0.15% in their HbA1c level, regardless of whether they have or have not stopped metreleptin, or have standard care. The yearly increase of 0.15% in HbA1c level was assumed from NICE's technology appraisal of canagliflozin in combination therapy for treating type 2 diabetes. It is intended to reflect disease progression in people with diabetes. This yearly rise continues up to a ceiling of 12%, which represents people whose diabetes is poorly controlled (based on clinical opinion from the Delphi panel). The ERG considered this persistence of effect after stopping treatment unrealistic. During technical engagement, the company explained that complications associated with diabetes develop over many years at a rate and extent that is related to the adequacy of glucose control. Therefore, a slow-offset period of treatment effect would be expected after stopping treatment. This is because the benefit of controlling blood glucose with metreleptin would decline at a similar rate to benefit accruing. The ERG argued that there is no evidence for this. It noted that the company assumed the lag between glucose control (marked by HbA1c) and the effect on risk of complications in the model after stopping treatment. But, this lag was not modelled at the start of the treatment when people are at increased risk because of previous poor glucose control. It therefore removed this assumption (lifetime HbA1c benefit) in their base case so that HbA1c returned to baseline within the year after stopping metreleptin. The ERG also excluded the annual drift of 0.15% after stopping treatment, as was

modelled in NICE's technology appraisal of canagliflozin in combianation therapy for treatment type 2 diabetes. The clinical experts stated that HbA1c level is likely to revert to baseline levels over 6 to 12 months after stopping treatment (see section 4.12) and agreed that the ERG's base case best reflected this statement. The committee concluded that the likely delayed onset of treatment effect compared with the slow offset of treatment effect does not have a substantial impact on modelling. This is because the lag is only about 1 year and any delay would happen at the beginning and end of treatment. This means they, in part, would cancel each other out. The committee was satisfied with the company's approach of modelling HbA1c level while on treatment. But, it agreed that the duration after which HbA1c reverts to baseline levels (6 to 12 months) after stopping treatment should be reflected in the model.

Metreleptin's treatment effect on liver disease after stopping treatment

4.24 Similarly, although there is no evidence of an effect of metreleptin on liver complications after stopping treatment, the company assumed (in their base case) that the liver benefit would remain for a lifetime after stopping treatment. This was based on clinical experts' opinion stating that residual liver benefit will be retained and that it would take several years to return to a baseline level of risk. Additionally, the company applied the persisting lifetime liver benefit in addition to the period of treatment effect after stopping treatment. Therefore, the experts' statements were not reflected in the model appropriately. The clinical experts explained that some sustained slowing of liver damage may be maintained for months when metreleptin is stopped. The ERG remained uncertain of the true period and level of benefit when metreleptin is stopped. However, in their base case, the ERG included the 1-year efficacy after stopping treatment to reflect the possibility that there may be some residual benefit to the liver. The committee concluded that the ERG's analysis was appropriate and consistent with the clinical experts' views.

Metreleptin's treatment effect on quality of life and patient-reported outcomes such as hyperphagia after stopping treatment

4.25 The committee discussed how the utility differential and carer utility (see sections 4.20 and 4.21) are modelled when metreletpin is stopped. The company assumed, in its base-case model, that 50% of the 0.12 differential and 50% of benefit to carers would be maintained over the patients' lifetime after stopping treatment. The ERG's base case removed the assumption of the 50% continued lifetime treatment benefits. This is because including it would suggest continued absence of hyperphagia and continued ability to work, but there is no evidence to support this. During the technical engagement, the company explained that the utility differential accounted not only for hyperphagia but also other symptoms not captured in the organ damage sub-models. The ERG noted that hyperphagia and inability to work accounted for about 80% of the utility differential according to the company's rescaled DCE. However, it recalled that the symptoms of hunger would return within days after stopping metreleptin (see section 4.13) and ability to work is not in NICE's reference case for consideration. The committee asked how much weight hyperphagia accounted for in the utility differential. The company explained it was not a primary driver but still had a weight of about 25%. The committee considered it appropriate to account for specific symptoms not related to organ damage separately, some of which may not return fully after stopping treatment, as a utility differential. But, it concluded that the ERG's approach of removing the assumed lifetime maintenance of 50% utility differential to both patients and carers is preferred.

Stopping rule

4.26 The company's model structure for metreleptin included a stopping rule for people with partial lipodystrophy. At 9 months after the start of metreleptin treatment, a specialist service review will see whether treatment should be stopped if the following metabolic criteria have not been met: an HbA1c reduction of at least 0.75% from baseline, or a fasting triglyceride reduction of at least 50% from baseline. A clinical

expert stated that there was a consensus in European lipodystrophy centres to stop metreleptin at 6 to 9 months if the person did not take the treatment properly or did not engage with appointments, or there was no HbA1c reduction of at least 0.5% from baseline or a fall in fasting triglycerides of at least 50% from baseline. The clinical expert can apply their own judgement and agree to continue to treat the lipodystrophy even if the criteria are not met. The committee noted that the company's stopping rule did not match the one from the clinical experts, but the rule proposed did incorporate significant clinical discretion.

Application of quality-adjusted life year (QALY) weighting

4.27 The committee understood that NICE's interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude 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 between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee considered that although there was uncertainty, the undiscounted QALY gains for the scenarios incorporating its preferred assumptions did not meet the criteria for applying a QALY weight.

Cost-effectiveness results

4.28 The company's base case showed that metreleptin was associated with an ICER of £60,611 per QALY gained for the overall population. The ICER for generalised lipodystrophy was £46,000 per QALY gained, and the ICER for partial lipodystrophy was £81,584 per QALY gained. The

total costs and QALYs are considered by the company to be commercial in confidence and so cannot be reported here.

4.29 The ERG's base case showed that metreleptin was associated with an ICER of £110,460 per QALY gained for the overall population. The ICER for generalised lipodystrophy was £92,593 per QALY gained, and the ICER for partial lipodystrophy was £130,334 per QALY gained. The total costs and QALYs are considered by the company to be commercial in confidence and so cannot be reported here.

4.30 Considering both the company and ERG's scenario analyses, the committee's preferred assumptions were:

- using the estimate directly obtained from the Delphi data to adjust transition probabilities in liver model (rather than liver enzymes, see section **Error! Reference source not found.**)
- reversing HbA1c to baseline level after stopping treatment (excluding 0.15% drift, see section 4.23)
- maintaining liver benefit for 1 year when metreleptin is stopped (see section 4.24)
- removing assumed lifetime maintenance of 50% of quality-of-life treatment differential and carer utility gain after stopping metreleptin (see sections 4.25 and 4.22)
- correcting number of carers to 1.67 (rather than 2 in company base case, see section **Error! Reference source not found.**4.22).

The committee's preferred assumptions were associated with an ICER of £108,267 per QALY gained (for the overall population). The ICER for generalised lipodystrophy was £87,545 per QALY gained, and the ICER for partial lipodystrophy was £133,606 per QALY gained.

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

4.31 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. It noted that the treatment may have benefits beyond health in children and young people with generalised lipodystrophy. They may account for a minority of the patient population, but the treatment may have important implications for their schooling, interactions with their parents, and social life. This could lead to profound psychosocial benefits for individuals. In adults, hyperphagia and fatigue can compromise their social and professional lives. The committee acknowledged that lipodystrophy affects patients beyond direct health benefits but that quantifying this was difficult. However, it concluded that the effects are qualitatively accounted for in its decision making.

4.32 The committee noted that lipodystrophy is managed in an established specialist centre at Addenbrooke's Hospital in Cambridge. This means that additional infrastructure or staff training is not expected to be needed to introduce metreleptin in England.

4.33 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 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.

Other factors

4.34 The committee discussed the nature of the condition and to what extent the severity of lipodystrophy was comparable to other ultra-rare conditions. It understood that hunger was a particular aspect of the condition which caused substantial impact on quality of life for people with lipodystrophy and was likely to associated with other comorbidities.

4.35 It also noted that response to metreleptin is heterogenous between people with general lipodystrophy and partial lipodystrophy. Evidence showed that metreleptin was associated with greater benefits in people with general lipodystrophy (sees section 4.14) and children with congenital leptin deficiency may keep benefiting from metreletpin after a long period of treatment (see section 4.14). The heterogeneity is more obvious in partial lipodystrophy and people with more severe partial lipodystrophy are likely to benefit more from the treatment. This was the basis for the company's suggestion of further restricting the metabolic status of partial lipodystrophy subgroup to HbA1c above 7.5%, fasting triglycerides above 5.00 mmol/litre, or both (see section 4.14). The committee noted that, because the more severe partial lipodystrophy subgroup was associated with greater benefit, including it in the cost-effectiveness model was likely to lower the cost-effectiveness estimates. But, the magnitude of that was difficult to quantify.

Conclusion

4.36 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 provides clinical benefits by reducing blood sugar, triglycerides and liver enzymes in people with lipodystrophy. The indirect treatment comparison results presented by the company during the resubmission also indicated that metreleptin was associated with greater improvement in metabolic outcomes compared with standard care.

However, there are uncertainties in metreleptin's treatment effect on clinical outcomes in the long term.

4.37 The committee was generally satisfied with the company's modelling approach in the resubmission, which was based on established diabetes and fatty liver frameworks. It was aware that there are uncertainties about transition probabilities (see section 4.18) and utility values (see section 4.20) sourced from other disease areas, transition probabilities adjusted by change in HbA1c (see section 4.19), and metreleptin's assumed treatment effect on organ damage and quality of life after stopping treatment (see sections 4.23, 4.24 and 4.25). It also noted that metreleptin did not meet the criteria for a QALY weighting to be applied. The committee acknowledged the uncertainties and took into account the impact of metreleptin beyond direct health benefits (see section 4.31) and the likely overestimated cost-effectiveness results (see sections 4.14 and 4.35). It agreed that the ICER of £108,267 per QALY gained would lower to an acceptable range for metreleptin to be an effective use of NHS resources. Therefore, the committee concluded that metreleptin can be considered a cost-effective use of NHS resources for highly specialised technologies, and recommended metreleptin as an option for treating the complications of leptin deficiency in lipodystrophy for people who are either 2 years and over with generalised lipodystrophy, or 12 years and over with partial lipodystrophy with HbA1c above 7.5%, or fasting triglycerides above 5.0 mmol/litre, or both.

5 Implementation

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

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

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has lipodystrophy and the doctor responsible for their care thinks that metreleptin is the right treatment, it should be available for use, in line with NICE's.

6 Review of guidance

6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
January 2021

7 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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