SMC2559

metreleptin powder for solution for injection (Myalepta®)

Amryt Pharmaceuticals DAC

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The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: 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.
- 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.

Key points:

- Lipodystrophy is a very rare, serious and heterogeneous, inherited or acquired condition. It is characterised by variable loss of adipose tissue and is associated with severe metabolic abnormalities, which can result in significant morbidity and mortality in affected patients.
- After 12 months of treatment in a single-arm, open-label study, metreleptin significantly improved the co-primary outcomes of change from baseline in HbA1c and percent change in fasting triglycerides.
- The co-primary outcomes are surrogate outcomes of metabolic control and there are no data on the effect of metreleptin on clinically relevant longer term complications.
- There are no controlled data and limitations in the indirect comparison with supportive care make the size of the metreleptin treatment effect unclear. Furthermore, evidence was confounded by a lack of restriction or control of background diet and supportive treatment, which may have affected metabolic control.
- No patient-reported outcomes or quality of life data were collected during the main study and the impact of metreleptin on these outcomes is unknown.

- The cost of metreleptin in relation to its health benefits remains high and the evidence used in the economic model is highly uncertain; including no direct evidence on long term effectiveness, impacts on morbidity and mortality, no utility evidence for patients, and limited primary resource use data for a population of lipodystrophy patients.

Chair
Scottish Medicines Consortium

SMC ultra-orphan designation

Metreleptin has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of lipodystrophy is estimated to be ≤1 in 50,000 (or around 100 people in Scotland).
- Metreleptin has GB orphan designation for the treatment of each of the four main types of lipodystrophy included in the licensed indication and this was maintained at the time of marketing authorisation.
- Lipodystrophy is chronic and severely disabling in patients, particularly those with generalised lipodystrophy, who have serious metabolic complications leading to early morbidity and mortality associated with diabetes, cardiovascular and liver disease.
- This condition requires highly specialised management.

1. Clinical context

1.1. Background

Metreleptin is a recombinant human leptin analogue which acts by binding to and activating the human leptin receptor belonging to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway. Leptin acts via multiple mechanisms to decrease triglyceride and other lipid intermediates in lipodystrophy patients, reducing their accumulation in tissues such as liver and muscle, and ameliorating severe insulin resistance, thereby improving hyperglycaemia and hypertriglyceridaemia.[1]

Metreleptin is administered by daily subcutaneous injection. The recommended daily starting dose is 0.06mg/kg for patients weighing ≤40kg, 2.5mg for male patients weighing >40kg and 5mg for female patients weighing >40kg. Based on clinical response, the dose may be decreased or increased to a maximum daily dose of 0.13mg/kg in patients weighing ≤40kg and to 10mg in patients (male or female) weighing >40kg.[1, 2]

1.2. Nature of condition

Lipodystrophy is a very rare condition, characterised by variable loss of adipose tissue, mainly subcutaneous fat, that leads to very low levels of the adipocyte-secreted hormone leptin. Leptin is important for regulating energy homoeostasis, fat and glucose metabolism, reproductive capacity as well as other physiological functions. Patients with lipodystrophy, and leptin deficiency, experience an inability to regulate hunger and energy, as well as glucose and fat metabolism leading to severe metabolic abnormalities such as such as premature diabetes and atherosclerosis. This can result in high morbidity, with multi-organ damage of the liver, kidneys and pancreas, impaired quality of life and premature death.[1]

Lipodystrophy varies in severity and is a heterogeneous condition with four main categories, depending on level of adipose deficiency (generalised or partial) and whether it is congenital or acquired. Generalised lipodystrophy is more severe and is diagnosed at an earlier age. Although there is considerable heterogeneity in the level of morbidity in patients with

generalised and partial disease, the symptoms and metabolic abnormalities are very similar. The complications associated with partial and generalised lipodystrophy can be severe and require aggressive management over the course of the patient's life. This can have a substantial physical and psychological impact on patients and carers affecting their activities of daily living and ability to work or go to school.[1]

There are no other medicines currently licensed for the treatment of patients with lipodystrophy. Patients receive supportive care to manage the metabolic abnormalities including antidiabetic and lipid-lowering medicines.[1]

Clinical experts consulted by SMC considered that metreleptin fills an unmet need offering a specific licensed treatment for lipodystrophy.

2. Impact of new technology

Comparative efficacy

2.1. Evidence for the licensed indication under review

The main evidence comes from a dose-escalating pilot study (NIH 991265) which assessed the short term efficacy and safety of metreleptin for up to 8 months and a longer term, phase II/III efficacy and safety study (NIH 20010769). Patients in NIH 991265 were allowed to roll-over into study NIH 20010769, along with recruitment of new patients. These studies have been integrated and presented together as one final analysis with results for patients with generalised and partial lipodystrophy.[1, 3, 4]

Table 2.1 Overview of relevant study/studies[1, 3, 4]

Criteria	NIH 991265 (pilot study) and NIH 20010769 (phase II/III study)
Study design	Open-label, single-arm pilot study (n=9) leading on to open-label, single-arm, phase II/III study (n=107)
Eligible patients	• Patient age: NIH 991265: >5 years (modified from >14 years). NIH 20010769 ≥6 months (modified from >5 years). • Investigator-assessed clinically significant lipodystrophy. • Leptin level: NIH 991265: ≤8 nanograms/mL in females and ≤6 nanograms/mL in males (modified from <4 nanograms/mL and <3 nanograms/mL respectively). NIH 20010769: <12 nanograms/mL in females and <8 nanograms/mL in males and <6 nanograms/mL in patients aged 6 months to 5 years. • Presence of at least one of the following metabolic abnormalities: - diabetes according to the American Diabetes Association criteria - fasting insulin >30 microunits/mL - fasting hypertriglyceridaemia defined as fasting triglycerides of >200mg/dL (>2.26 mmol/L) or NIH 20010769 when fasting not

	possible, postprandial elevated triglycerides >500mg/dL (>5.65 mmol/L)
Treatments	NIH 991265: target metreleptin daily dose was 0.04mg/kg in females aged ≥18 years, 0.03mg/kg for females aged <18 years and 0.02mg/kg for males split into two equal SC doses. The daily dose started at 50% of target then increased at monthly intervals to 100% and 200% which was continued to end of study. NIH 20010769: dosing was initially the same as above but was modified to minimise titration and dosing frequency changed to once daily. In females aged ≥5 years, the modified starting dose was 0.08 to 0.10mg/kg/day, in females <5 years of age and all males, the starting dose was 0.06mg/kg/day. The dose of metreleptin could be increased after the 6-month follow-up. Dose escalations were capped at 0.24mg/kg/day for any patient without prior approval. If patients did not tolerate a higher dose level, they could continue the study at the next lowest tolerated dose.
Randomisation	Not applicable
Primary outcome	There were two co-primary outcomes, assessed at month 12: • change from baseline in HbA1c • percent change from baseline in fasting triglycerides
Secondary outcomes	Key secondary outcomes included the proportions of patients who, at month 12, achieved : • ≥1% decrease in HbA1c or ≥30% decrease in fasting triglycerides • ≥1.5% decrease in HbA1c or ≥35% decrease in fasting triglycerides • ≥2% decrease in HbA1c or ≥40% decrease in fasting triglycerides actual and percentage change from baseline in fasting plasma glucose levels.
Statistical analysis	Statistical analysis was performed to compare values at baseline and 12 months for the two co-primary outcomes in the FAS, which included all patients who received at least one dose of study medicine and had either primary efficacy parameter measured at baseline and at least one post-baseline visit.

SC=subcutaneous; HbA1c=glycated haemoglobin; FAS=full analysis set

The key results of studies NIH 991265/20010769 are presented in Table 2.2.

Table 2.2 Results for co-primary and key secondary outcomes of NIH 991265/20010769 study in the FAS[1, 3-5]

	Generalised lipodystrophy	Partial lipodystrophy[A]
Co-primary outcomes		
Change from baseline in HbA1c		
Baseline, mean, %	(n=62) 8.6	(n=39) 8.0
Month 12, mean, %	(n=59) 6.4	(n=36) 7.5

Mean change from baseline, % (95% CI), p-value	-2.2 (-2.7 to -1.6) p<0.001	-0.6 (-1.0 to -0.2), p=0.005
Percent change from baseline in fasting triglycerides		
Baseline, mean, mmol/L	(n=61) 14.7	(n=39) 12.5
Month 12, mean, mmol/L	(n=58) 4.5	(n=36) 5.4
Mean percentage change from baseline, % (95% CI), p-value	-32% (-51% to -13%) p=0.001	-21% (-37% to -4.6%) p=0.013
Secondary outcomes		
≥1% decrease in HbA1c or ≥30% decrease in fasting triglycerides at month 12	80% (47/59)	51% (19/37)
≥1.5% decrease in HbA1c or ≥35% decrease in fasting triglycerides at month 12	75% (44/59)	38% (14/37)
≥2% decrease in HbA1c or ≥40% decrease in fasting triglycerides at month 12	66% (39/59)	32% (12/37)
Change from baseline in fasting plasma glucose levels		
Baseline, mean, mmol/L	(n=62) 10.2	(n=40) 8.8
Month 12, mean, mmol/L	(n=59) 7.0	(n=37) 7.5
Mean change from baseline, mmol/L (95% CI), p-value	-3.0 (-4.2 to -1.7)	-1.2 (-2.1 to -0.3)
Mean percentage change from baseline, % (95% CI), p-value	-20% (-29% to -10%)	-6.1% (-16% to 3.8%)

[A] in the FAS excluding one outlying patient for the co-primary outcomes. FAS=full analysis set; HbA1c=glycated haemoglobin; CI=confidence interval

Changes to concomitant supportive medication were allowed during the study and sensitivity analyses were performed for the co-primary outcomes in patients in the FAS who had controlled concomitant medication use (CFAS), described as no change or a decrease in baseline concomitant medications (antidiabetic or lipid lowering medicines) before 12 months. Results for the co-primary outcomes were generally similar in these patients.[1, 3, 4]

After 12 months of metreleptin treatment, there were also reductions in secondary outcomes of total cholesterol, LDL-cholesterol and liver enzymes in patients with generalised lipodystrophy; improvements were smaller in patients with partial lipodystrophy. Results suggest reductions in liver volume in 71% (15/21) of patients with generalised lipodystrophy and in 50% (4/8) patients with more severe partial lipodystrophy who had assessments at baseline and after treatment.[1]

Patient-reported or health-related quality of life outcomes were not assessed in study NIH 991265/20010769.

Supportive data were provided from further retrospective, longer term follow-up of the NIH 991265/20010769 study, from an expanded access programme (FHA 101) and from real-world evidence from the UK specialist treatment centre. These data support the treatment effect of

metreleptin on HbA1c and triglycerides but improvements appeared smaller than observed in the NIH study.[1, 6]

In the absence of direct evidence comparing metreleptin with supportive care, the submitting company presented an indirect treatment comparison of metreleptin (using data from the NIH study follow-up) with supportive care (using data from a natural history study in patients with lipodystrophy) (Table 2.3).[6, 7] This has been used to inform the incidence of pancreatitis in the economic base case and other outcomes in economic scenario analyses.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Indirect treatment comparison using three methods: inverse probability weighting, multivariate regression analysis and naïve comparison.
Population	Pooled population of patients with a diagnosis of generalised or partial lipodystrophy.
Comparators	Supportive care.
Studies included	Two single-arm, retrospective cohorts: NIH 991265/20010769 follow-up and lipodystrophy natural history study.[6, 7]
Outcomes	Change in HbA1c, triglycerides and liver enzyme (ALT/AST) levels from baseline to 12 months; incidence of pancreatitis and all-cause mortality.
Results	The average treatment effect results using the inverse probability weighting method show that metreleptin +/- SC compared with SC alone reduced actual HbA1c by 1.52%, lowered triglyceride levels by 915mg/dL, lowered levels of ALT by 44 units/L and AST by 28 units/L at month 12 from baseline. Metreleptin +/- SC was also found to decrease the odds of a pancreatitis episode by 6%, rising to 7% when missing values were imputed. Risk of mortality was greater in the metreleptin with or without SC group and the company have noted this result may not truly reflect the benefits associated with metreleptin due to the low number of patients and events available. Results presented using the multivariate regression analysis and naïve comparison were generally fairly consistent.

SC=supportive care; HbA1c=glycated haemoglobin; AST=aspartate aminotransferase; ALT=alanine aminotransferase

Comparative safety

No comparative safety data are available. Refer to the summary of product characteristics (SPC) for details.

In the NIH 991265/20010769 study, mean overall exposure to metreleptin was 62.5 months in patients with generalised lipodystrophy and 48.1 months in patients with partial lipodystrophy.[1, 3, 4]

In patients with generalised lipodystrophy, any treatment-emergent adverse event (AE) was reported by 89% (59/66) of patients and these were considered treatment-related in 48%. A serious AE was reported by 35% of patients and these were treatment-related in 4.5%. Metreleptin was discontinued due to an AE in 7.6% of patients.[1, 4]

In patients with partial lipodystrophy, any treatment-emergent AE was reported by 85% (35/41) of patients and these were considered treatment-related in 20%. A serious AE was reported by 24% of patients and none were considered treatment-related. Metreleptin was discontinued due to an AE in one patient (2.4%).[1, 3]

In patients with generalised lipodystrophy, the most frequently reported treatment-emergent AEs of any grade were: decreased weight (26%), abdominal pain (17%), hypoglycaemia (15%), decreased appetite (12%) and headache (12%). In patients with partial lipodystrophy, the most frequently reported treatment-emergent AEs of any grade were: hypoglycaemia (17%), abdominal pain (15%) and nausea (15%).[3, 4]

Severe hypertriglyceridaemia can result in acute episodes of pancreatitis and in the NIH 991265/20010769 study, 27% of patients with generalised lipodystrophy and 37% of patients with partial lipodystrophy had a history of pancreatitis at baseline. During the study, four patients with generalised lipodystrophy and two patients with partial lipodystrophy had treatment-emergent pancreatitis reported as an AE. These patients had a history of pancreatitis and hypertriglyceridaemia and in two patients interruption or non-compliance of metreleptin may have increased the risk of further acute events.[1, 2]

Antidrug antibodies have been reported in the majority of patients (88%) treated with metreleptin but no patient had total failure of efficacy.[1, 2]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- Lipodystrophy is a rare, heterogeneous condition that can be severe and associated with reduced morbidity and mortality. Metreleptin is the first medicine licensed for treating lipodystrophy and acts as a replacement therapy for leptin; patients would otherwise only receive supportive care to control metabolic abnormalities, which are often difficult to control even with high doses of currently available treatments. Clinical experts consulted by SMC have confirmed that there is a high unmet need in this setting.[1]
- In the main NIH 991265/20010769 study, metreleptin significantly improved metabolic control from baseline after 12 months, as assessed by change in HbA1c and fasting triglycerides in patients with generalised and partial lipodystrophy. Reductions in HbA1c and triglycerides were -2.2% and -32% respectively in the generalised lipodystrophy patients and -0.6% and -21% respectively in the partial lipodystrophy patients. The treatment effects in patients with generalised lipodystrophy were considered clinically meaningful. The results were considered conservative since not all patients in the full analysis set had abnormal levels of HbA1c and triglycerides at baseline.[1, 3, 4]
- The results of co-primary outcomes were supported by improvements from baseline in secondary outcomes on plasma glucose, lipid parameters and liver enzymes. In addition, a proportion of patients were able to reduce or discontinue their use of antidiabetic or lipid-lowering medicines while receiving metreleptin. In patients with generalised lipodystrophy, 41% (16/39) were able to discontinue insulin, 22% (7/32) discontinued oral antidiabetics

and 24% (8/34) lipid-lowering medicines. Few patients with partial lipodystrophy discontinued supportive medication.[1, 3, 4]

Key uncertainties:

- The main evidence to support the use of metreleptin in patients with lipodystrophy is limited to open-label, uncontrolled data in small numbers of patients after 12 months of treatment.[1, 3, 4]
- The key outcomes assessed are surrogate outcomes which are used in clinical practice and indicate improved metabolic control but effects on longer term, clinically relevant complications are lacking. Although HbA1c is a well-established surrogate for diabetes-related complications, it is unclear if this completely translates to lipodystrophy.[1, 3, 4]
- The study did not assess the effects of metreleptin on patient-reported outcomes, including effects on hyperphagia, and quality of life [1, 3, 4]
- Study patients did not follow a specific diet or calorific intake and were able to take concomitant medication as needed. Sensitivity analysis was performed in the CFAS in patients whose use of concomitant medication either reduced or stopped during the 12 months period and improvements in outcomes were generally similar to analysis in the FAS. However, differences in background care leads to uncertainty in the magnitude of treatment effect due to metreleptin.[1, 3, 4]
- Metreleptin is not licensed for use in patients with partial lipodystrophy aged <12 years due to a lack of data possibly related to the later diagnosis in these patients. In generalised lipodystrophy, the treatment effect of metreleptin appeared to be smaller in children which may reflect the natural and progressive history of the condition. Despite this smaller effect, the regulator considered treatment of generalised lipodystrophy in patients ≥2 years may help to prevent or delay the development of complications.[1]
- In terms of safety, metreleptin was generally well-tolerated. However, safety data are uncontrolled and involve a small number of patients and long-term safety is limited. The SPC recommends caution on abrupt withdrawal to minimise the risk of pancreatitis. There is a risk of hypoglycaemia in patients who are also receiving insulin or other antidiabetic medicines and close monitoring of blood glucose is recommended. Further evidence is to be collected on the development of antidrug antibodies and their clinical significance.[1, 2]
- As noted, the data for metreleptin are uncontrolled and the company presented indirect comparisons with supportive care. The company concluded that metreleptin with or without supportive care resulted in greater improvements from baseline to 12 months in HbA1c, triglycerides and liver enzymes and reduced the incidence of pancreatitis. The company also note that the results should be reviewed with caution in line with a number of limitations. These limitations include the uncontrolled and retrospective nature of the data and the pooling of both types of lipodystrophy. There was a high level

of missing data in the natural history population which limited the use of covariates and possible comparisons. Patients in the natural history cohort appeared to have less severe disease. There was a lack of control or definition of supportive care which led to heterogeneity within and between the cohorts. The indirect comparison did not include any safety or quality of life outcomes. Despite these limitations, the company's conclusions seem reasonable but given the available data and heterogeneity, the magnitude of the improvements associated with metreleptin are highly uncertain.

Metreleptin has received marketing authorisation under exceptional circumstances (it does not have a conditional marketing authorisation). The European regulator has included a number of obligations (a disease registry, a study to provide further information on the effect of metreleptin in patients with partial lipodystrophy on poor metabolic control once background therapy has been maximised and further analysis of immunogenicity). There is an ongoing phase III study (METRE-PL) comparing metreleptin with placebo in patients aged ≥12 years with partial lipodystrophy; this is not expected to complete until January 2026. The Medicines and Healthcare products Regulatory Agency will review any additional information annually and update the SPC as necessary.[1, 2, 8]

3. Impact beyond direct health benefits and on specialist services

Metreleptin may improve metabolic control and reduced complications in patients with lipodystrophy allowing them to live a more normal and independent everyday life. In some patients, it may be possible to reduce or discontinue concomitant treatments used as symptomatic/supportive management for example insulin, oral antidiabetics, lipid-lowering medicines. The availability of an effective treatment for lipodystrophy has the potential for a profound positive effect on lifestyle opportunities and the quality of life of patients including ability to work and study.

Metreleptin is administered by subcutaneous injection and after supervised initiation in a specialist centre is expected to be given by the patient or their carer, therefore requiring no additional facilities or infrastructure. There are no additional tests required for selecting or monitoring patients above the currently existing treatments.

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Lipodystrophy UK, which is a charitable incorporated organisation.
- Lipodystrophy UK has received 96% pharmaceutical company funding in the past two years, including from the submitting company.
- Lipodystrophy is an ultra-rare, life-limiting disease, which has an extremely detrimental impact on quality of life. Many experience a degree of pain and discomfort that

prevents them being able to carry out daily tasks easily. Most make significant distressing dietary changes to try to manage their lipodystrophy. Families and carers are likewise severely impacted by lipodystrophy. Some patients require constant care, particularly children. The daily regime of pills, injections, blood glucose monitoring and control, physical comfort/mobility issues, body confidence and self-esteem make managing lipodystrophy, or caring for someone who has lipodystrophy, a full-time job.

- There is a significant unmet need for an effective treatment option. Currently available treatments only work to mitigate the multiple side effects of lipodystrophy. They are restricted in their ability to effectively treat patients due to the highly treatment-resistant nature of lipodystrophy.
- Metreleptin is a specific treatment for leptin deficiency in lipodystrophy patients who are resistant to conventional diabetes/lipid lowering therapies. Many patients have reported that metreleptin has been the only effective treatment, allowing them to live a more normal life. Early intervention is key to living a healthy life and substantially reducing the risk of life threatening complications. It may be possible that with metreleptin treatment, conditions such as fatty liver disease may be reversed, or even prevented, before it develops into cirrhosis.

5. Value for money

5.1. Economic case

The submitting company provided an economic case, as described in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime time horizon
Population	Confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above. 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.
Comparators	Standard of care which includes diet and exercise, conventional therapies for hyperglycaemia and hypertriglyceridemia.
Model description	De novo individual patient-level model consisting of six independent Markov sub-models reflecting the main complications of lipodystrophy. The model consists of over 30 health states, across six sub-models - liver disease, cardiovascular disease, kidney disease, neuropathy, retinopathy, and pancreatic disease. The six sub-models were independent and the patient was simultaneously in a discrete health state in each of the six sub-models during each cycle. A patient could die during each cycle, in which case the patient was removed from all models into a death state. A cohort of 3,000 patients was modelled for the base case.

	The clinical effectiveness of metreleptin was expressed in terms of changes in HbA1c associated with treatment in 4 out of the 6 sub-models. Based on a difference in HbA1c between metreleptin and standard care, patients receiving metreleptin were assigned reduced transition probabilities. This meant that patients moved more slowly to more severe disease states. Clinical effectiveness in the liver sub-model was driven by a relative risk reduction, applied to transition probabilities, obtained from a Delphi panel of clinicians. In the pancreatitis sub-model, results from the indirect treatment comparison (ITC) were applied to obtain a risk reduction associated with metreleptin, compared to standard care alone.
Clinical data	Clinical data are included for six complications (sub-models) in the model. • The clinical efficacy data used to inform the cardiovascular, kidney, retinopathy and neuropathy sub-models comes from the single arm open label NIH studies 991265/20010769. Treatment effect is based on the change in HbA1c from baseline to 12 months, which was -2.2% and -0.6% for patients with generalized LD and partial LD respectively. • Efficacy data for the pancreas sub-model was sourced from an ITC of the NIH studies 991265/20010769 with the generalised lipodystrophy/partial lipodystrophy natural history study. Treatment effect is based on the change in HbA1c from baseline compared with standard of care. The ITC obtained an odds ratio of 0.94, suggesting a 6% reduction in the risk of a pancreatitis episode with metreleptin, compared to standard of care. • Efficacy data for the liver sub-model was obtained from a Delphi panel of clinical experts surveyed by the company. The Delphi Panel estimated a 77% and 25% relative risk reduction in liver complications for generalized and partial lipodystrophy patients treated with metreleptin.
Extrapolation	The extrapolation assumes a treatment effect until discontinuation, and the HbA1c treatment effect diminishes over time due to a 0.15% HbA1c drift per cycle until a maximum HbA1c level of 12% is reached. Treatment benefit is applied at the outset of the model, via a reduction in HbA1c, reduced relative risk of liver complications and reduced odds of a pancreatic episode for the metreleptin arm. A stopping/discontinuation rule is applied for patients who are non-compliant or have no meaningful improvement by 6 months (defined as 0.5% HbA1c reduction and / or 15% reduction in triglycerides after 6 months of initiating treatment). For those who have treatment discontinuation (due to intolerance or no difference) partial treatment effects beyond discontinuation are maintained for only the liver sub-model. In the base case, upon treatment discontinuation of metreleptin, HbA1c reverts to the baseline HbA1c level (excluding the 0.15% annual drift), such that the HbA1c level is the same as per cycle 0.
Quality of life	No primary quality of life data were used in the economic model, utility values for all 30 health states were obtained from previously published literature and from NICE clinical guidelines for the various health states, yet appear to be reasonable. The company propose a base case analysis including carer disutilites, rather than considering this as a sensitivity analysis in line with SMC guidance.
Costs and resource use	No primary resource use data were presented within the health economic analysis. All cost estimates used in the model were obtained from previously published cost-effectiveness analyses or from NICE clinical guidelines. The model included treatment costs, routine monitoring costs and the cost associated with each health state included in the model. Adverse event costs were not included because they were anticipated to have minimal impact

	on costs as they are mild or moderate in their severity and occur at a low frequency. SMC clinical experts agreed with these assumptions.
PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

5.2. Results

Base case analysis results are shown in Table 5.2.

Table 5.2. Life years, QALYs and ICER (PAS PRICE) SMC base case results

	Total life years	Incremental life years	ICER (£) per QALY
Standard care	25.61	-	-
Metreleptin	27.96	2.36	191,234

QALYs: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio

5.3. Sensitivity analyses

A deterministic one-way sensitivity analysis (OWSA) was undertaken using a cohort of 200 patients including the PAS, for the respective upper and lower bounds of the relevant parameters. The intervals do not have a major impact on the ICER and appeared reasonably tight. The main drivers in the model from the OWSA were decrease in HbA1c, relative risk of liver complications, carer disutility, and the proportion of patients not requiring a dose escalation of metreleptin.

A range of scenario analyses were also performed (Table 5.3), exploring alternative HbA1c reductions, discount rates, utility decrements, mortality risks and alternative time horizons. These had minimal impact on the base case ICER, with inclusion of carer disutilities having the greatest impact. The company's preferred scenario, which included carer's utilities and multiple, lower discount rates than the 3.5% recommended rate, resulted in an ICER of £110,503.

Table 5.3 Selected sensitivity analyses with PAS

Scenario assumption	Base case assumption	SMC Base Case: ICER (£)
Base case	N/A	**191,234**
1: Patient and carer utility, at 3.5% discount rate	Patient only utility (no carer disutility), at 3.5% discount rate	**117,493**
2: Apply a disutility for carers in metreleptin arm (50% of disutility in the standard care arm)	Disutility in standard care arm only	**150,846**

3: Alternative HbA1c reduction: 1.52%	-2.2% and -0.6% for patients with generalised lipodystrophy and partial lipodystrophy, respectively	**183,030**
4: Additive disutility	Multiplicative disutility	**184,687**
5: Largest single utility decrement	Multiplicative disutility	**207,162**
6: Shorter time horizon - 30 years	Lifetime horizon	**206,564**
7: Societal perspective - including employment	NHS and social care perspective	**107,378**
8a: Treatment effect • No continued liver disease benefit, • HbA1c restored to baseline with no drift accumulated.	One-year treatment effect continuation for liver disease only Baseline HbA1c level is restored at discontinuation with no drift applied	**192,850**
8b: Treatment effect • No continued liver disease benefit, • HbA1c restored to baseline with drift accumulated.	One-year treatment effect continuation for liver disease only Baseline HbA1c level is restored at discontinuation with no drift applied	**199,582**
9: Company's preferred case – including carers' utilities and multiple (lower) discount rates	SMC preferred base case required no carers' utilities and a discount rate of 3.5%	**110,503**

5.4. Key strengths:

- There is a lack of previous cost-effectiveness analyses of treatment options for lipodystrophy in a UK population. This submission has presented a de novo cost-effectiveness model which seeks to model the natural history of disease among lipodystrophy patients. The analysis incorporates evidence from a range of sources to estimate the costs and consequences associated with the six main complications of lipodystrophy.

5.5. Key uncertainties:

- The main weakness of this analysis is the lack of any direct clinical effectiveness data comparing metreleptin with standard of care.
- The treatment effect of metreleptin on cardiovascular disease, kidney disease, retinopathy and neuropathy was obtained from a single arm open label study (NIH

991265/20010769). This type of study makes it difficult to attribute effects to metreleptin or other causes.

- The treatment effect of metreleptin on pancreatitis was obtained from an indirect treatment comparison of metreleptin (from the NIH 991265/20010769 studies) and standard care (from the lipodystrophy natural history study). The natural history study was not based on a UK population (it included 230 patients in the US, Turkey and Brazil), and therefore introduced limitations with regards to patient heterogeneity and generalisability of findings.
- Treatment effect for four out of the six complications (excluding liver disease and pancreatitis) was based on a surrogate outcome – the change in HbA1c from baseline to 12 months, which was clinically validated as suitable indicator of disease progression, rather than a definitive clinical outcome.
- The HbA1c treatment effect of metreleptin is assumed to continue until discontinuation, and an annual 0.15% HbA1c drift is applied in both arms until a maximum HbA1c level of 12% is reached, such that patients receiving metreleptin eventually have a HbA1c level equivalent to that of patients receiving standard of care. However, evidence from the NIH 991265/20010769 study demonstrated treatment benefit up to 48 months. Therefore, any assumption regarding treatment benefit beyond this time point is uncertain and not based upon study evidence. The company justified this assumption on the basis of the NIH follow-up study which showed continued HbA1c reduction up to 48 months from baseline. However, the data at 12, 24 and 36 months seem to suggest a reduction in treatment effect over time. Furthermore, the estimates are based on very small sample sizes, which further increases the uncertainty associated with the lifetime benefit of metreleptin. The company refused to provide results for scenario analyses exploring alternative lifetime assumptions. A reduction in treatment effect over time could increase the ICER substantially.
- The company submitted a base case analysis which used annual discount rates for costs and benefits of 1.5% in years 0-30, 1.29% in years 31-75, and 1.07% in years 75 onwards in the base case, rather than the 3.5% for all ages recommended by SMC. The company also included the health utility of carers in the base case, rather than as a separate scenario analysis as recommended by SMC. Therefore, a revised base case, based on a discount rate of 3.5% and excluding carers' utilities was requested and has been presented. Inclusion of carer utilities have been included as a scenario analysis in Table 5.3, and show that this doubles the QALY gain.
- No primary quality of life data were presented within the health economic analysis. All utility values used in the model were obtained from previously published cost-effectiveness analyses or from NICE clinical guidelines and are highly uncertain.
- The data sources for resource use are mostly taken from published cost-effectiveness studies and NICE clinical guidelines. As such, the data sources are acceptable, however,

primary resource use data obtained from a population of lipodystrophy patients would have been preferable. The cost of metreleptin itself is obtained directly from the company and the cost of routine monitoring is obtained from the NIH 991265/20010769 studies.

*Other data were also assessed but remain confidential.**

6. Costs to NHS and Personal Social Services

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

An international consensus guideline was published in December 2016: "The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline."[9]

8. Additional information

8.1. Product availability date

24 February 2021

8.2. Summary of product characteristics

See the SPC for further information including dosing and safety. Metreleptin 3mg, 5.8mg and 11.3mg powder for solution for injection (Myalepta®)

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
metreleptin	**Maximum recommended dose for adults weighing >40kg: 10mg daily by subcutaneous injection** **Maximum recommended dose patient weighing ≤40kg: 0.13mg/kg daily by subcutaneous injection**	**For 70kg adult: up to 849,940** **For 20kg child: up to 212,485**

Costs from BNF online on 6 March 2023. Costs calculated based on maximum dose for patient weighing >40kg and for child weighing 20kg using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

References

1. European Medicines Agency (EMA). European Public Assessment Report. Metreleptin (Myalepta®). 31/05/2018, EMEA/H/C/004218/0000. www.ema.europa.eu.
2. Amyrt Pharmaceuticals DAC. Metreleptin 3mg, 5.8mg and 11.3mg powder for solution for injection (Myalepta®), summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc Last updated 11 April 2022.
3. Oral EA, Gorden P, Cochran E, Araújo-Vilar D, Savage DB, Long A*, et al.* Long-term effectiveness and safety of metreleptin in the treatment of patients with partial lipodystrophy. Endocrine. 2019;64(3):500-11.
4. Brown RJ, Oral EA, Cochran E, Araújo-Vilar D, Savage DB, Long A*, et al.* Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. Endocrine. 2018;60(3):479-89.
5. Aegerion Pharmaceuticals L. Clinical study report: Protocol 991265 AND 20010769 Metreleptin Long Term Efficacy and Safety of Leptin Replacement in the Treatment of Patients with Lipodystrophy. 2016.
6. Tuttle E. Technical Report: Morbidity and Mortality Outcomes in Patients with Lipodystrophy Receiving Leptin Replacement Therapy: a Longitudinal Medical Chart Review Study. 2018.
7. Akinci B, Oral EA, Neidert A, Rus D, Cheng WY, Thompson-Leduc P*, et al.* Comorbidities and Survival in Patients With Lipodystrophy: An International Chart Review Study. J Clin Endocrinol Metab. 2019;104(11):5120-35.
8. ClinicalTrials.gov. A 12-month randomized, multicenter, double-blind, placebo-controlled phase 3 study to evaluate the safety and efficacy of daily subcutaneous metreleptin treatment in subjects with partial lipodystrophy. Last updated 15 December 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05164341.
9. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. J Clin Endocrinol Metab 2016; 101: 4,500-11.

This assessment is based on data submitted by the applicant company up to and including 13 April 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment

Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.