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Dr Rebecca Sanders
Chair and Co-founder
Lipodystrophy UK
29 Collington Way
Abingdon OX13 5GP
Registered Charity Number 1175462
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Mr Tim Irish
Vice Chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Mr Irish,

Re: Final Evaluation Determination – Metreleptin for treating lipodystrophy [ID861]

The main cruxes in NICE's decision not to approve metreleptin focus on the inadequate model presented by Aegerion, which was lacking in details regarding the natural history of the disease and co-morbidities beyond hyperphagia, and the shortage of corroborating evidence from both the company and the clinicians to bolster the case for treatment effectiveness.

However, there is plenty of evidence available and patients shouldn't have to pay the price for these failures. Leptin has been shown to lower HbA1c by ~2% in patients who already had access to all conventional therapies (Chan *et al.* 2011, Brown *et al.* 2017, Brown *et al.* 2018, Gu *et al.* 2008, Park *et al.* 2007). It also substantially reduced triglycerides (up to 66% - Brown *et al.* 2017, Gu *et al.* 2008), whereas nothing else has been shown to do so. These data led to metreleptin approval in the US, Japan and the EU. There are data

regarding efficacy of metreleptin in providing metabolic improvement (reviewed in Brown *et al.* 2016) – as supported by the EMA decision – eligible patients' quality of life without therapy would be a lot worse due to comorbidities including diabetes complications, pancreatitis, fatty liver disease and cardiovascular disease. There are also natural history studies to support this, documenting disease progression without metreleptin treatment (Akinci *et al.* 2016, Ajluni *et al.* 2017).

The current FED is unfair as there is too much emphasis on hyperphagia and not enough on the other metabolic factors which would affect quality of life and for which clinical trial evidence exists.

Before listing the specific grounds for appeal, Lipodystrophy UK would like to highlight the following relevant information:

1. This is a specific treatment for leptin deficiency in lipodystrophy patients who are resistant to conventional diabetes/lipid lowering therapies;

2. There is evidence from trials that metreleptin is efficacious in patients with lipodystrophy and this has been confirmed by the positive opinion from the EMA/FDA/Japanese regulators;

3. Quality of life/life expectancy is highly likely to be improved by a reduction in metabolic complications;

4. As there is no other alternative therapy, comparator data will always be difficult to collect and it would not be ethical to perform a placebo controlled trial;

5. Withdrawal of therapy from patients currently taking metreleptin and denial of therapy for patients deemed likely to benefit by specialist clinicians, especially young children, is unethical.

Lipodystrophy UK would like to appeal against the Final Evaluation Determination for the above-mentioned highly specialised technology on the following grounds:

Ground one: In making the assessment that preceded the recommendation, NICE has:

a) failed to act fairly

Ground two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Ground 1: In making the assessment that preceded the recommendation, NICE has: (a) failed to act fairly

1a.1 Page 1-2, Section 1.2
"these studies do not include any objective measure of hyperphagia or any comparison of metreleptin with other treatments. Therefore, the relative treatment benefit of metreleptin is unclear"

It is unfair to reject the application based on the lack of data for comparative treatments, when no such comparative treatments exist. All therapeutic options available to patients only manage the symptoms of disease; none target a root cause – which is why metreleptin is so important. Furthermore, objective measures of hyperphagia do not exist. LDUK is frustrated both with Aegerion and the clinicians for not developing a method or recording the level of hyperphagia in patients, with the corresponding impact of metreleptin on this. It is procedurally unfair to seek to compare the relative treatment benefit of metreleptin against a dataset that simply does not exist. Patients should not be punished for the failure of the company and clinicians to produce a suitable comparative data set.

1a.2 Page 2, Section 1.2
"There is a lack of real-world data outlining how lipodystrophy progresses in people who have not had metreleptin, so underlying progression of the condition is unclear"

This statement is fundamentally flawed. As detailed for appeal point 1a.1, given the ultra-rare status of lipodystrophy, patient numbers are extremely small and the assessment should be adjusted to reflect this. However, there are natural history studies available, which outline disease progression (Akinci *et al.* 2016, Ajluni *et al.* 2017).

1a.3 Page 2, Section 1.2
"even with an appropriate model, any benefits attributed to metreleptin would be highly uncertain because of the substantial uncertainties in the clinical evidence."

Again, as detailed for appeal points 1a.1, and 1a.2, the ultra-rare nature of lipodystrophy means sufficient patient numbers and comparative data are difficult to achieve. These criteria are inherently biased as they are unachievable for such a small patient community.

1a.4 Page 3. Section 3.1
"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"

'Exceptional circumstances' authorisation by the EMA is "granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is a rare disease or because collection of full information is not possible or is unethical" (EMA website[1]). Again, as detailed for appeal points 1a.1, 1a.2 and 1a.3, when requesting further efficacy data, NICE are failing to recognise the ultra-rare nature of the condition. Furthermore, the benefits of treatment have been such that clinicians have treated wherever possible, as it is unethical not to do so when such improvements to health and long-term well-being are observed (Chan *et al.* 2011, Brown *et al.* 2017, Brown *et al.* 2018, Gu *et al.* 2008, Park *et al.* 2007). This is another reason why comparison data was not available (treated *vs.* untreated). The EMA authorisation evidences and reflects the difficulties in presenting comprehensive efficacy and safety data given the ultra-rare nature of the condition. Notwithstanding such limited data, the EMA appreciated the efficacy of treatment based on the limited data available.

1a.5 Page 5. Section 4.1
"The committee acknowledged that lipodystrophy is a debilitating condition, and that hyperphagia is associated with very poor quality of life which affects patients, parents and carers. It recognised that there is a ***significant unmet need*** *for an effective treatment option."*

The decision, therefore, not to recommend metreleptin is in complete contradiction to this statement.

1a.6 Page 6-7. Section 4.3
"The ERG highlighted that estimates of treatment effects were based on changes from baseline in single-arm metreleptin treatment studies, and no data for the comparator arm were presented within the clinical evidence. It stated that the submission did not include any search term for comparators,

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta

and that there was no attempt to do indirect comparisons to study the effects of established clinical management."

Again, as stated above for appeal points 1a.1, 1a.2, 1a.3 and 1a.4, the ultra-rare nature of lipodystrophy means sufficient patient numbers and comparative data are difficult to achieve, particularly if patients are split into treated and untreated populations. Furthermore, it is unethical not to treat people who have no other effective treatment options, when significant improvements to health and long-term well-being are observed (Chan *et al.* 2011, Brown *et al.* 2017, Brown *et al.* 2018, Gu *et al.* 2008, Park *et al.* 2007). As such, clinicians worldwide have treated patients wherever possible. As stated in appeal point 1a.4, the EMA decision deemed fit to grant authorisation notwithstanding the limited efficacy data.

1a.7 Page 9. Section 4.6
"without understanding the experience of people whose disease is managed without metreleptin, any estimates of relative effectiveness would be highly uncertain"

Again, as detailed for appeal points 1a.1, 1a.2, 1a.3, 1a.4 and 1a.6, the ultra-rare nature of lipodystrophy precludes the availability of robust data sets. We respectfully suggest that in its appraisal of metreleptin, NICE has sought to give unfair significance to data that is not currently available due to the ultra-rarity of the condition.

1a.8 Page 10. Section 4.7
"The clinical experts also explained that hyperphagia is caused by a deficiency in the hormone leptin (see section 2.1), so any improvements in hyperphagia signal improvements in underlying lipodystrophy"…"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."

Again, there is clear evidence of the impact on hyperphagia, yet the burden of evidence is too high for such an ultra-rare disease. Surely, 99% leaves no room for doubt. Patients should not be penalised for poor study designs. (See appeal points 1a.1, 1a.2, 1a.3, 1a.4, 1a.6, 1a.7 and 2.7).

1a.9 Page 15. Section 4.10
"It recalled concerns about the lack of comparator evidence (see sections 4.3, 4.5 and 4.6), and the uncertainty surrounding metreleptin's effect on improving hyperphagia (see section 4.7)."

Again, as detailed for appeal points 1a.1, 1a.2, 1a.3, 1a.4, 1a.6, 1a.7 and 1a.8, comparator data is unavailable due to the ultra-rare nature of the condition. It is unfair to hold rare diseases to the same data burden as other,

more prevalent diseases. Plus, the results from the NIH follow-up study and anecdotal evidence relating to improved hyperphagia should leave the committee in no doubt as to the efficacy of metreleptin on the available data.

1a.10 Page 16. Section 4.11
"The committee had concerns about the generalisability of the GL/PL natural history study population to the population of people with lipodystrophy in England" … "The committee concluded that it had not been presented with adequate comparator data to allow a sufficiently robust comparison of metreleptin with standard of care."

Again, as detailed for appeal points 1a.1, 1a.2, 1a.3, 1a.4, 1a.6, 1a.7, 1a.8 and 1a.9, too much weight is given to the need for comparator data and any available data should be considered, regardless of study/patient geographical location, due to the ultra-rare nature of the condition.

1a.11 Page 18. Section 4.13
"The committee agreed that the matching exercise did not address its overall concerns relating to the lack of relative effectiveness evidence for metreleptin."

Again, as detailed for appeal points 1a.1, 1a.2, 1a.3, 1a.4, 1a.6, 1a.7, 1a.8, 1a.9 and 1a.10, too much weight is given to the need for comparator data.

1a.12 Page 21. Section 4.16
"The ERG highlighted that the small sample size was a concern."

Again, as detailed for appeal points 1a.1, 1a.2, 1a.3, 1a.4, 1a.6, 1a.7, 1a.8, 1a.9, 1a.10 and 1a.11, the ultra-rare nature of the condition precludes large patient cohorts.

1a.13 Page 27. Section 6.1
"The committee discussed whether its concerns about the clinical and economic uncertainties in the evidence could be addressed by an 'only in research' recommendation or in the context of a managed access agreement. It recalled not only the lack of evidence in the submission but more importantly that there was no reliable framework on which to base an opinion on metreleptin's cost effectiveness. The committee did not believe this was an issue that could be addressed by further interventional research. Therefore, neither data collection as part of a managed access agreement nor an 'only in research' recommendation were considered appropriate."

We implore you to give us an opportunity to collect the relevant data for reassessment.

1a.14 Metreleptin funding has been approved for congenital leptin deficiency, despite being unlicensed for this condition. While we agree that it should be

used for these patients, it is grossly unfair that people with lipodystrophy don't have access to the same treatment when they often have similarly undetectable leptin levels; lipodystrophy patients deserve the same access to this medication. The committee has acknowledged that lipodystrophy is a debilitating condition, and that hyperphagia is associated with very poor quality of life, which affects patients, parents and carers. It recognised that there is a significant unmet need for an effective treatment option for lipodystrophy patients. We respectfully contend that approval of metreleptin goes a long way to meeting that unmet need.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 Page 1, A. Section 1.2
"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. For a child or young person, the decision should be made jointly by them and their parents or carers, and their clinician."

The above statement is illogical. Patients currently on treatment are not being funded via the NHS – Aegerion is providing the drug free of charge on compassionate grounds. Without an agreement to fund metreleptin via the NHS, all patients will be withdrawn from treatment. Addenbrooke's has already contacted patients receiving metreleptin to this effect. Therefore, whilst NICE's recommendation is not intended to impact current patient recipients, the reality is that all patients will lose access to metreleptin as a direct result of this decision.

2.2 Page 1, Section 1.2
"Lipodystrophy is a rare and serious condition that severely affects the quality of life of people with the condition, and their families and carers."

That "lipodystrophy severely affects the quality of life of people with the condition" is a woeful underestimation of the impact of this disease. Lipodystrophy kills people. It shortens life expectancy and sentences patients to a life of pain and distress. LDUK is concerned that the gravity of this condition has not been recognised by the committee, which is perpetuated by inaccurate interpretation of the evidence. When a child of 7 years old presents with liver cirrhosis as a direct consequence of lipodystrophy, this disease cannot be described as a quality of life issue, but a life or death issue. Early intervention is key to living a healthy life and substantially reducing the risk of life-threatening complications. With metreleptin treatment, conditions such as

fatty liver disease may be reversed before it develops into cirrhosis. If left untreated, the inevitable development of cirrhosis cannot be reversed.

2.3 Page 2, Section 1.2
"metreleptin is not considered to provide value for money within the context of a highly specialised service, and is not recommended in the NHS as an option for treating lipodystrophy."

In such a small patient community, the cost of the treatment dwarfs in comparison to the lifelong treatment of chronic and acute medical emergencies. Cost-effectiveness estimates may be made based on diabetic complications, organ failure, chronic pancreatitis and acute hospitalization (Akinci *et al.* 2016, Ajluni *et al.* 2017).

2.4 Page 2. Section 2.1
"Lipodystrophy is often diagnosed late in the disease course or remains undiagnosed."

That is true for partial lipodystrophy. However, generalised lipodystrophy is often picked up at a very young age (Brown *et al.* 2017). Early treatment intervention for both populations is critical.

2.5 Page 3. Section 2.3
"It is estimated that there are around 200 people with lipodystrophy in England; a proportion of these people will be eligible for metreleptin treatment"

If the population of England is approximately 55.62 million (2017, ONS UK), then at a prevalence of around 2.5 per 1,000,000 population, 140 people with lipodystrophy is a more accurate estimate.

2.6 Page 4. Section 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"

It is untrue that weight loss and decreased appetite are adverse effects of metreleptin treatment. In fact, these outcomes are a large part of the reason metreleptin is a successful therapy for lipodystrophy patients. Weight loss is mainly attributable to the reduction of visceral fat packed around organs. This not only improves the health of multiple vital organs but also improves insulin sensitivity. This increased sensitivity to insulin is the reason for hypoglycaemia, and why patients are closely managed to reduce injected insulin doses (where applicable). This reduction in insulin requirements is also a positive effect of metreleptin treatment and has knock-on effects including further weight loss, better diabetic control and improved acanthosis nigricans. Having recognised that hyperphagia is a major factor in untreated patients;

the committee in contradiction state that decreased appetite is an adverse effect. Surely it can be recognised that this outcome is a major benefit for patients? The results from the NIH follow-up study (99% of people treated with metreleptin reported improvements in hyperphagia – appeal point 1a.8), and the patient testimonies at the committee meeting, assure the benefits to satiety are unequivocal.

2.7 Page 10. Section 4.7
"The clinical experts also explained that hyperphagia is caused by a deficiency in the hormone leptin (see section 2.1), so any improvements in hyperphagia signal improvements in underlying lipodystrophy"..."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."

Again, there is clear evidence of the impact on hyperphagia (NIH follow-up study and Brown, *et al.* (2016)), yet the burden of evidence is too high for such an ultra-rare disease. An improvement in 99% of patients is compelling evidence. Patients should not be penalised for poor study designs (see appeal point 1a.8).

2.8 Page 17-18. Section 4.13
"The model showed that metreleptin was associated with a 71.9% reduced mortality risk (hazard ratio 0.281; p=0.017)."

Why then, with such a marked reduction in mortality risk, has metreleptin been rejected? Given the reduction in mortality risk, we respectfully suggest that NICE's recommendation cannot reasonably be justified from the evidence presented to the committee.

2.9 Page 19. Section 4.14
"In its preferred analysis, the ERG assumed that the survival of people with partial lipodystrophy who had and had not had metreleptin were equivalent ... It concluded that, because of the limitations associated with the structure of the model, any modelled survival benefits needed to be plausible. Therefore, it agreed that the adjustments made by the ERG were appropriate."

While we agree that the model submitted by the company was insufficient, this assumption by the ERG is fundamentally flawed and the reasons for making survival between treated and untreated partial patients equivalent are not outlined in this report.

2.10 Page 20. Section 4.16
"[The ERG] also noted that asking clinicians to score people who had not had treatment could have caused confusion, implying that they had nothing rather than standard of care."

By making this statement the ERG are assuming that the standard of care without metreleptin improves utility values. They have not shown any data to support this.

Conclusion

The lipodystrophy community is devastated by the FED recommendation against funding metreleptin via the NHS. This is the only therapy available to directly treat lipodystrophy, and patients deserve health equality in treatment. We believe that it is procedurally unfair to seek to compare the relative treatment benefit of metreleptin against, and give weight to, a comparator dataset that simply does not exist. We also consider that NICE's recommendation cannot reasonably be justified from the evidence presented to it, when these data led to metreleptin approval by the EMA, FDA and Japanese regulators. The world is watching and further recommendations in Europe and America may also be influenced by this decision, meaning implications may reach patients across the globe. Lipodystrophy UK will continue to advocate for excellent care and improved treatment options for people with Lipodystrophy.

Lipodystrophy UK wishes this appeal to proceed at an oral appeal.

Yours truly,

Dr. Rebecca Sanders PhD
Chair and Co-founder
Lipodystrophy UK

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APPENDIX

Further evidence related to this appeal

Selected references

Ajluni *et al.* (2017) **Spectrum of Disease Associated with Partial Lipodystrophy (PL)- Lessons from a Trial Cohort**. Clin Endocrinol (Oxf). 2017 May ; 86(5): 698–707. doi:10.1111/cen.13311.

The Ajluni *et al* study concluded, in addition to known metabolic comorbidities; chronic pain (78.3%), hypertension (56.5%) and mood disorders (52.2%) were highly prevalent. Mean NAFLD Activity Score (NAS) score was 5±1 and 78.3% had fibrosis. Partial lipodystrophy is a complex multi-system disorder. Metabolic parameters correlate negatively with extremity fat and positively with liver fat.

Akinci B, *et al.* (2016). **Natural History of Congenital Generalized Lipodystrophy: A Nationwide Study From Turkey.** J Clin Endocrinol Metab. 2016 Jul;101(7):2759-67. doi: 10.1210/jc.2016-1005. Epub 2016 May 4.

The Akinci *et al.* study outlined the natural history and disease burden of the (untreated) congenital generalised lipodystrophy population in Turkey. Abnormalities developing during childhood or early adulthood included severe hypertriglyceridemia, hepatic steatosis. micro and macrovascular complications of diabetes, retinopathy and diabetic kidney disease. End-stage organ diseases included, cirrhosis, end-stage renal disease requiring hemodialysis or renal transplantation and fatal cardiovascular events.

Brown RJ, *et al.* (2016). **The Diagnosis and Management of Lipodystrophy Syndromes: A Multi Society Practice Guideline.** J Clin Endocrinol Metab. 2016 Dec; 101(12): 4500–4511

Brown *et al.* conclude that metreleptin therapy is effective for metabolic complications in hypoleptinemic patients with generalized lipodystrophy and selected patients with partial lipodystrophy.

Brown RJ, *et al.* (2017). **Effects of Metreleptin in Pediatric Patients With Lipodystrophy.** J Clin Endocrinol Metab. 2017 May 1;102(5):1511-1519. doi: 10.1210/jc.2016-3628.

In their 2017 pediatric study, Brown *et al.* concluded metreleptin lowered A1c and triglyceride levels, and improved biomarkers of NAFLD in pediatric patients with lipodystrophy. These improvements are likely to reduce the lifetime burden of disease. After 12 months, the A1c level decreased from 8.3% to 6.5%, and median triglyceride level decreased from 374 mg/dL to 189 mg/dL (despite decreased glucose- and lipid-lowering medications).

Brown RJ, *et al.* (2018). **Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy.** Endocrine. 2018 Jun;60(3):479-489. doi: 10.1007/s12020-018-1589-1. Epub 2018 Apr 12.

The Brown *et al.* study on metreleptin treatment in congenital generalised lipodystrophy states long-term treatment with metreleptin was well tolerated and resulted in sustained improvements in hypertriglyceridemia, glycemic control, and liver volume. At month ≥12, 80% of patients had a 1% decrease in HbA1c or ≥30% decrease in TGs, and 66% had a decrease of ≥2% in HbA1c or ≥40% decrease in TGs. Of those on medications, 41%, 22%, and 24% discontinued insulin, oral antidiabetic medications, or lipid-lowering medications, respectively. Mean decrease in liver volume at month 12 was 33.8%.

Chan JL, *et al.* (2011). **Clinical effects of long-term metreleptin treatment in patients with lipodystrophy.** Endocr Pract. 2011 Nov-Dec;17(6):922-32. doi: 10.4158/EP11229.OR.

Chan *et al.* in the NIH study detail "robust and sustained reductions" in HbA1c and triglycerides (−2.1% and −35.4%, respectively), concluding that metreleptin treatment substantially reduced glycemic variables, triglycerides, and liver enzymes (ALT and AST) and demonstrated durability of response throughout a 3-year treatment period. These results support metreleptin as a potential treatment for certain metabolic disorders (for example, diabetes mellitus and hypertriglyceridemia) associated with lipodystrophy

Gu *et al.* (2008) **Leptin therapy for partial LD linked to PPARg mutation**. Clin Endocrinol (Oxf). 2008 April ; 68(4): 547–554. doi:10.1111/j.1365-2265.2007.03095.x.

Gu *et al.* report, eighteen months of metreleptin therapy was associated with a marked improvement in glucose homeostasis as evidenced by normalization of the fasting blood glucose (baseline = 8·3 mmol/l; 18 months = 4·9 mmol/l), lowering of HbA1c (baseline = 9·9%; 18 months = 7·2%) and improved tolerance to an oral glucose load. In addition, a striking amelioration in the patient's refractory, severe hypertriglyceridaemia was observed (baseline = 21·15 mmol/l; 18 months = 5·96 mmol/l).

Park *et al.* (2007) **Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy**. Metabolism. 2007 April ; 56(4): 508–516. doi:10.1016/j.metabol.2006.11.010.

Park *et al.* report triglycerides were reduced by 65% at 4 months and significantly reduced at 12 months for 5 patients. Total cholesterol also decreased. Insulin sensitivity and fasting glucose levels improved … As shown in patients with GL, patients with FPLD have improvement in

triglycerides, fasting glucose, and insulin sensitivity with leptin replacement. Low-dose metreleptin for patients with FPLD has an important role in improving triglycerides, beyond that of available lipid-lowering agents. In improving glycemic control, normalization of glucose tolerance in hypoinsulinemic patients with FPLD requires insulin and leptin therapy.