National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Metreleptin for treating lipodystrophy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Aegerion	Metreleptin for the treatment of lipodystrophy (LD) has been proposed for an STA. Aegerion disagrees with this proposal and considers that if a referral is to be made to NICE, an HST appraisal provides the most appropriate framework for the evaluation of metreleptin for LD, an ultra-orphan, chronic condition often associated with severe metabolic complications. The STA evaluation framework is not conducive to an appropriate and complete evaluation of the value of metreleptin for the treatment of such a condition. In particular, the key issues are the high costs, limited data (small single arm trials) and, whilst expected high per patient QALY benefits, the cost/QALY is likely to be much above the conventional thresholds considered via STA process giving a very low prospect for a positive recommendation to be issued. Hence, the STA process can be considered inappropriate for the evaluation of metreleptin for a number of reasons, in particular: • There are very small patient numbers with LD in England, and who would be eligible for metreleptin. Whilst the per patient cost maybe high the total budget impact would be expected to be limited, and treatment	Thank you for your comment. This topic has been referred to the HST programme for evaluation.

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		concentrated in a few centres. An STA is typically reserved for therapies that have sufficient patient numbers for the indication and a sufficient evidence base to justify the use of a standard appraisal framework, and for which national guidance can be issued to reduce variation in use across health care localities in England. These do not apply to metreleptin for LD, which can be expected to be funded by national specialised commissioning, and contribute to specialised service delivery for LD patients. • The pricing of metreleptin will reflect the rarity and severity of the condition and the need to recoup high R and D costs associated with treatments such ultra-rare conditions. Hence it is likely that any cost per QALY gained estimates for metreleptin will be very high. Evaluating metreleptin under the STA process would therefore provide limited value to the NHS as it can be anticipated that NICE will be tied to issuing a not recommended guidance due to the high cost /QALY estimates, with no reasonable prospect of metreleptin achieving an ICER below £30,000/QALY gained. As metreleptin is not an end of life therapy there are no specific criteria that would enable a higher ICER threshold to be considered. • As the condition is severe and disabling and associated with numerous short and longer term adverse health complications and consequences, assessment of these outcomes would ideally include use of a cost –consequences analysis approach (which includes QALY assessment). As the condition affects children and young people there will be a potentially large caregiver and societal impact, and potential benefits beyond the NHS. These aspects are unlikely to be taken as completely into account though a standard STA process with its focus on cost-effectiveness from a NHS and PSS perspective, but could be considered fully within the value for money criteria adopted through HST appraisal. The case for Metreleptin to be considered via an HST process is similar to other therapies that NICE have been invited to evaluate via the HST process, for instance alipogene tiparvovec for treating familial lipoprotein lipase deficiency, or afamelanotide for treating erythropoietic protoporphyria. Both of	

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		these are rare conditions with potential impacts beyond patients and direct health outcomes, with an impact on the delivery of a specialised service and hence similar to metreleptin. Aegerion believe the framework used for an HST appraisal would be the most appropriate for metreleptin in order to provide a balanced assessment of the value to patients, caregivers and the NHS, and an assessment of value for money by consideration of the direct patient and wider health and non-health benefits of this new therapy against the total costs the NHS are expected to incur from its introduction to a national service. We have set out in a separate letter to the Associate Director Highly Specialised Technologies, Centre for Health Technology Evaluation the reasons why we believe metreleptin fits all the prioritisation criteria for an HST appraisal. In summary: • The target patient population is so small the treatment will be concentrated in a few centres in the NHS: The scope estimates 712 patients, a prevalence of 0.66 per 50,000 patients which means LD can be considered an ultra-orphan condition. Evidence set out in our letter to NICE indicates that the actual number in England is likely to be much lower and, when considering the proposed indication, it is expected that less than 200 patients will be eligible for metreleptin. Due to the small patient numbers, there are just a few treatment centres with Addenbrookes Hospital, Cambridge providing the national Insulin resistant service under an NHS England service specification. Metreleptin is currently being used within this service under a company access programme with currently only 21 patients on treatment and a further 6 awaiting access to metreleptin. • The target patient group is distinct for clinical reasons: The diagnosis of patients with generalised lipodystrophy (GL) or partial lipodystrophy (PL) is clinically relatively straightforward for clinical experts. GL patients present with a total loss of adipose tissue which induces very low leptin levels and consequently severe metabolic disorder. In PL patients who have partial loss of adipose tissue where there is some more heterogeneity in the condition,	

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		the proposed indication for metreleptin will restrict use to those with low leptin levels and uncontrolled metabolic disorders. • The technology is expected to be used in the context of a highly-specialised service: Currently, metreleptin is restricted under the established service specification for the National insulin resistant diabetes service A03/S9HSS)/ based at Addenbrookes Hospital, Cambridge. We would anticipate this specialist centre approach continuing. The only other specialist centre managing lipodystrophy identified to date is the Oxford Centre for Diabetes, Endocrinology and Metabolism. • The technology is likely to have a very high acquisition cost: The price of metreleptin is not yet established but is expected to be comparable with treatments for other ultra-rare, severe metabolic conditions. While the cost per patient can be expected to be high, the limited patient numbers can be expected to limit total drug budget impact. • The technology has the potential for life long use: Metreleptin is not curative of the underlying condition but can restore leptin levels in affected patients. Consequently, metreleptin must be given for life long use. There are no known cures for LD. • The need for national commissioning of the technology is significant: GL and PL patients within the indication are rare and at significant risk of progressing comorbidities. Such patients are optimally managed by specialists with experience of their condition as established in the National Insulin resistance service specification. Hence, there is a strong need for national commissioning. The HST evaluation framework that considers in more depth other criteria such as severity of the condition, value of the health benefits, cost and budget impact, and wider caregiver and societal benefits is more relevant for the evaluation of metreleptin in the context of the rarity of the condition. In view of the above points, we believe that an STA would be inappropriate and if the topic is to be considered by NICE, metreleptin should be considered via the	

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		framework for assessing rare severe diseases as adopted by the HST process.	
	Genetic Alliance UK	We are concerned that the decision appears to have been made to consider this treatment through an STA before resolving the question of the size of the population that would be considered for treatment. We suggest that it would be better to resolve questions about which subtypes would be considered for treatment and the likely population numbers involved during topic selection, in order that the most appropriate route for evaluation be selected at the outset. We understand that the manufacturer intends to seek a license for use of the treatment in patients with generalised forms of lipodystrophy and a subset (about a third) of patients with partial lipodystrophy (those with low leptin levels already experiencing metabolic consequences). This suggests that if the population calculations in the scope are correct, the population eligible for treatment is smaller than 300. However, as we state in a later answer, we believe the population calculations in the scope are based on an over-estimate of prevalence. This population size makes the treatment eligible for consideration through the HST programme. The treatment also meets the other criteria for consideration via the HST programme, as it would likely be commissioned through the single national specialist service and would require lifelong use. We believe the HST Evaluation process is more appropriate for this treatment than the Single Technology Appraisal process.	Thank you for your comment. This topic has been referred to the HST programme for evaluation.
	National Severe Insulin Resistance Service	"Would it be appropriate to refer this topic to NICE for appraisal?" - Yes.	Comment noted. No changes to the scope are needed.
Wording	Aegerion	The remit proposes to appraise metreleptin within its marketing authorisation. The proposed indication for metreleptin is as follows (not currently in the public domain and to be treated as confidential):	Comment noted. No changes to the scope are needed.

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		[redacted]	
	Genetic Alliance UK	The wording of the remit matches the standard format.	Comment noted. No changes to the scope are needed.
	National Severe Insulin Resistance Service	Yes, but Metreleptin does not have a Marketing Authorisation yet (30.11.16)	Comment noted. No changes to the scope are needed.
Timing Issues	Aegerion	Metreleptin will be submitted for a marketing authorisation under exceptional circumstances on 20th December 2016. [redacted].	Comment noted. No changes to the scope are needed.
	Genetic Alliance UK	There are currently no treatments licensed in the UK for generalised or partial lipodystrophy, conditions which can cause substantial metabolic difficulties as well as impact substantially on quality of life. We understand that metreleptin has been licensed in the US since 2014, however the transfer from the previous to the current manufacturer has caused delays seeking a license in the EU. It is important that there not be further delays to access for UK patients, should metreleptin be shown to be clinically and cost effective.	Comment noted. No changes to the scope are needed.
	National Severe Insulin	There are approximately 25 patients with lipodystrophy in the UK already taking metrepleptin on a compassionate use/expanded access programme. These patients are all under the care of our National Service at Addenbrooke's Hospital, Cambridge. It is therefore very important that the	Thank you for your comment. This topic has been referred to the HST programme for

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	Resistance Service	cost effectiveness/access decisions for Metreleptin are made as soon as possible once the drug has a Marketing Authorisation. Submission to the EMEA is expected Q4 2016 with accelerated review expected.	evaluation. NICE aims to publish draft guidance within 6 months of marketing authorisation.
Additional comments on the draft remit	National Severe Insulin Resistance Service	This is a very rare condition and there will be realtively few patients prescribed metreleptin. The cost of Metreleptin is likley to be high. Does NICE have an alternative process for assessing new treatments for rare diseases?	Thank you for your comment. This topic has been referred to the HST programme for evaluation.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Aegerion	The background information does not adequately reflect the severity of LD from a morbidity and mortality perspective. The condition is chronic and often associated with severe metabolic abnormalities: LD is either genetic and presents from birth or acquired usually subsequent to an autoimmune condition, and there is no cure. Patients with LD are at risk of life threatening pancreatitis, and /or accelerated atherosclerosis, among other potential severe metabolic complications. In addition, it leads to the build-up of ectopic fat deposition in non-adipose tissue which, if deposited in the muscle, can result in insulin resistance and diabetes while the fat accumulation in the liver can progress from hepatomegaly to steatohepatitis, cirrhosis and liver failure. Living with the condition can have a significant impact on patient HRQoL, with symptoms including: • extreme hunger and fatigue	Thank you for your comment. The scope has been amended for clarity. The intention of the background section is to introduce the disease and treatments that are available in established NHS clinical practice. Please include all relevant details as part of your submission.

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		• esthetical issues due to fat deposition around the neck and face in many PL patients and a swollen abdomen in GL, a muscular appearance in PL and GL • the effects of severe insulin resistance such as polycystic ovary syndrome, hirsutism and acanthosis nigricans • pancreatitis, uncontrolled diabetes and very raised triglycerides. The prevalence data used in the scope significantly overestimates the population size for whom metreleptin would be potentially indicated. This is addressed in the section on population. Through the National Insulin Resistance Service Specification and the Aegerion access scheme, standard of care in England within the proposed indication includes metreleptin and is not as described in the background information.	
	National Severe Insulin Resistance Service	Severe hypertriglyceridaemia can cause recurrent pancreatitis which can be life threatening. The National Severe Insulin Resistance Service was established in 2011 (not 2012). It is important to state that in patients with congenital generalised lipodystrophy the absence of fat tissue is from birth, so these metabolic problems start in early childhood. The absence of leptin causes dyregulation of appetite and extreme hyperphagia (hunger) so that the patients have food seeking behaviour which exacerbates the metabolic complications. Also due to severe insulin resistance, conventional therapies have limited efficacy and so high doses of drugs are required. Administration of high doses of insulin is problematic in this patient group due to the lack of subcutaeous fat in which to inject the insulin. Theoretically if children were to be treated optimally from a very young age then there is potential for diabetes and other metabolic complications to be delayed and thus premature	Thank you for your comment. The scope has been amended for clarity. The intention of the background section is to introduce the disease and treatments that are available in established NHS clinical practice. We encourage consultees to submit all relevant information in

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		morbidity/mortality reduced. The metabolic complications put these patients at risk of early microvascular (visual loss, nerve damage, foot ulcers, renal impairment and macrovascular complications (stroke, ishaemic heart disease) of diabetes. Patients are also at high risk of fatty liver disease, liver cirrhosis and increased risk of hepatocellular carcinoma.	submissions to inform the evaluation.
The technology/ intervention	Aegerion	The description of the technology is correct. Metreleptin has been developed as a lyophilised powder for reconstitution and self-administration through sub-cutaneous injection	Comment noted. No changes to the scope are needed.
Population	Aegerion	The population should be defined as patients within the proposed marketing authorisation given above. Although data are limited and varies significantly, the available data on prevalence for generalised lipodystrophy (combined congenital (CGL) and acquired (AGL)) is slightly under 0.1 to <1.5 in 100,000 and the prevalence for partial lipodystrophy (combined congenital (FPL) and acquired (APL)) is approximately 0.2 to <3.0 in 100,000. Aegerion considers the true prevalence to be at the low end of the range based on available literature and databases, which is also consistent with the low end of the range from the original Orphan Drug Designation application. A recent analysis of 5 electronic medical record databases including the UK GPRD gives a prevalence of 0.02 and 0.3 cases per 100,000 for GL and PL respectively. The proposed indication for metreleptin is for the treatment for patients with GL and for a subset of patients with PL who have low leptin levels and metabolic abnormalities. This leptin level would exclude the more prevalent familial partial lipodystrophy type 1 (FPLD1) patients who do not present with low leptin levels. Although the data are limited, an analysis of the lipodystrophy database of Dr. Abhimanyu Garg at UT Southwestern Medical Centre shows that, of 141 PL patients where data is available for leptin, HbA1c and triglyceride levels, approximately 30% would meet the proposed	Thank you for your comment. NICE can only make a recommendation within the marketing authorisation. The prevalence information in the background section of the scope has been updated based on feedback received during consultation.

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		indication. The prevalence of the proposed PL subgroup would likely be <0.03 in 10,000. This would give a prevalent PL population in England relevant to the indication of less than 159 patients. Information received last year from the National Insulin resistance service at Addenbrookes indicated that they had 195 patients within the service of whom 136 had lipodystrophy including 51 with FPLD1 who would not be appropriate for metreleptin as described above. Addenbrookes have to date requested access to metreleptin for 12 GL patients and 15 PL patients. While it would be appropriate for NICE to obtain more recent numbers from the service, this would again indicate that the prevalence from the scoping document for patients within the proposed marketing authorisation is considerably overstated.	
	Genetic Alliance UK	We understand that the single national specialist service at Cambridge has contact with approximately 140 patients with lipodystrophy. This is likely to be a large proportion of the patients diagnosed with lipodystrophy (unconnected to HIV) in the UK, which suggest that the prevalence figures quoted may be an overestimate. Data published so far suggest different response to treatment in patients with partial and generalised lipodystrophy, and as such it would be appropriate to consider these populations separately.	Thank you for your comment. The prevalence information in the background section of the scope has been updated based on feedback received during consultation.
	National Severe Insulin Resistance Service	Please replace 'people' with adults and children.	Comment noted. No changes to the scope are needed.

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Comparators	Aegerion	It is anticipated that metreleptin will be used on top of established clinical management. Current management does not address the underlying leptin deficiency in lipodystrophy patients within the indication.	Comment noted. No changes to the scope are needed.
	National Severe Insulin Resistance Service	Dietary intervention is also important (strict low fat diet) Low fat diet is important (with growth monitored carefully in children).	Comment noted. No changes to the scope are needed.
Outcomes	Aegerion	In addition to those described, outcomes should include the benefit of leptin replacement on the complications of the metabolic abnormalities in lipodystrophy such as reduction in liver volume, improvements in liver and renal function, reduction in pancreatitis, regression of diabetes, achievement of insulin independence and satiety improvement.	Thank you for your comment. The scope has been updated and outcomes include: o liver function (including cirrhosis) o glucose control and diabetes (including complications of diabetes and need for diabetes therapies) o satiety o pancreatitis o use of other drugs

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			○ organ damage including heart and kidneys ○ growth and development ○ reproductive dysfunction ○ infection ○ health-related quality of life (for patients and carers; including effects on appearance)
	Genetic Alliance UK	The outcomes listed are appropriate, however we would also suggest adding more specific information on the different metabolic abnormalities, as well as reproductive dysfunction, liver and kidney problems, heart disease, autoimmune disease, etc. In addition to these issues and the lipid/glucose control issues, key aspects of the condition that impact on the patient's quality of life relate to the effects of lipodystrophy on the individual's appearance (lack of fat, inappropriate fat deposits and skin hyperpgmentation), discomfort (for example due to a lack of fat pads on the buttocks or feet), and the requirement (in many cases) to maintain a strict diet. While of importance to affected individuals these are unlikely to be propoerly considered as part of QALY calculations.	Thank you for your comment. The scope has been updated, and outcomes include: ○ liver function (including cirrhosis) ○ glucose control and diabetes (including complications of diabetes and need for

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			diabetes therapies) ○ satiety ○ pancreatitis ○ use of other drugs ○ organ damage including heart and kidneys ○ growth and development ○ reproductive dysfunction ○ infection ○ health-related quality of life (for patients and carers; including effects on appearance)
	National Severe Insulin Resistance Service	Diabetes microvascular complications (retinopathy, nephropathy, neuropathy) Diabetes macrovascular complications (coronary artery disease, cerebrovascular disease) Liver function tests and percentage liver fat/liver fibrosis	Thank you for your comment. The scope has been updated, and outcomes include:

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		Reduction in use requirement of other drugs (eg insulin can sometimes be stopped when a patient startsmetreleptin therapy). Menstrual cycle/pubertal status Metreleptin has significant effects on reducing appetite in leptin deficient individuals so changes in food intake could be used as an outcome measure Quality of life	○ liver function (including cirrhosis) ○ glucose control and diabetes (including complications of diabetes and need for diabetes therapies) ○ satiety ○ pancreatitis ○ use of other drugs ○ organ damage including heart and kidneys ○ growth and development ○ reproductive dysfunction ○ infection ○ health-related quality of life (for patients and carers; including

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			effects on appearance)
Economic analysis	Aegerion	The appropriate time horizon is lifetime, and for this rare and severely disabling condition it would be appropriate to consider the economic analysis from both an NHS and personal social services, and societal perspective. The lifetime time horizon is appropriate as LD is a chronic condition with costs and consequences (complications – see outcomes above) incurred both in the short and long term. Cost-utility analysis could be performed modelling the risk of complications and mortality based on clinical data available and generating QALY outcomes, however a cost consequence approach could be most appropriate in order to capture the range of clinical and health outcomes related to LD and the impact of metreleptin on these.	Thank you for your comment. No changes to the scope are needed.
	National Severe Insulin Resistance Service	This can be lifelong in patients with congenital lipodystrophy and shorter in acquired lipodystrophy (although the latter sometimes has a childhood onset)	Comment noted. No changes to the scope are needed.
Equality and Diversity	Aegerion	From an equality perspective, the issues faced by these patients are similar to many suffering from very rare, chronic and incurable conditions. There are few patients suffering from lipodystrophy; they not only look different due to absence of adipose tissue and/or ectopic deposition of fat but they also suffer the consequences of their diabetes and hypertriglyceridemia that cannot be managed with currently available medications.	Comment noted. No changes to the scope are needed.
	Genetic Alliance UK	We understand that, as is the case in the US, the likely licensed indication for the medicine will specifically exclude patients whose lipodystrophy is connected to their treatment for HIV. Under the Equality Act 2010, patients are regarded as having the protected characteristic of disability from the point of diagnosis with HIV; many of these people may also have other protected characteristics. We understand that there has been less investigation of the	Comment noted. No changes to the scope are needed.

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		effects of treatment in HIV-associated lipodystrophy, however this still warrants consideration. Clearly the scope of NICE's work is set by the marketing authorisation, we raise this to ensure the issue is on the horizon for NICE.	
	National Severe Insulin Resistance Service	This treatment is for both adults and children. Some patients with lipodystrophy have learning difficulties.	Comment noted.
Other considerations	Aegerion	In the UK, metreleptin is already considered as standard of care within the National Insulin Resistance Service and has been included in international guidelines on the management of lipodystrophy. Currently there are 21 patients on metreleptin under the National Insulin Resistance service. Metreleptin was provided free of charge within this service by a previous owner of the molecule. Aegerion has continued to provide supplies to date pending marketing authorisation.	Comment noted. No changes to the scope are needed.
	National Severe Insulin Resistance Service	Metreleptin will be the only specific treatment available for this rare patient population.	Comment noted. No changes to the scope are needed.
Innovation	Aegerion	Aegerion consider metreleptin to be an innovative technology, providing a fresh approach to managing this rare and serious condition. Metreleptin as a synthetic analogue of leptin, acts as a leptin replacement therapy. Clinical studies in patients with LD suggest that metreleptin exerts its function through multiple proposed direct and downstream effects, including the following. • Correcting hyperphagia secondary to leptin deficiency with concomitant reduction in caloric and fat intake.	Comment noted. The committee will consider the innovative nature of the technology in its deliberations. No changes to the scope required.

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		• Stimulating fatty acid oxidation throughout the body and lowering plasma, hepatic, and myocellular lipid levels resulting in increased insulin sensitivity. • Improving insulin suppression of glucose production in the liver and increasing insulin-stimulated peripheral glucose uptake in the muscle 1. The classical anti-diabetes treatments and lipid lowering drugs do not achieve diabetes or triglyceride control. For LD patients, there is no alternative treatment to manage the underlying leptin deficiency. 2. Due to this mechanism of action, metreleptin corrects hyperphagia, induces significant reduction of HbA1C and triglycerides level, reduces liver volume with normalisation of transaminases and improves renal function. The license application for metreleptin has been filed for approval under "exceptional circumstances" based on the "inability to provide comprehensive efficacy and safety data due to rarity of the indication", under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence in the foreseeable future". There was no placebo control in the studies on metreleptin because it was deemed unethical to provide a placebo to patients who are affected by lipodystrophy based on the results from the proof of concept. Both the degree and duration of metabolic improvement with metreleptin treatment was so robust that the likelihood of these improvements having occurred solely as part of the natural history of the condition or by chance alone is highly improbable. Evidence for the efficacy of metreleptin is further strengthened by the published finding that metabolic parameters worsened following controlled withdrawal of metreleptin and improved upon resumption of metreleptin therapy in some of the patients enrolled in these studies.	

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		One pivotal efficacy and safety study has been conducted in patients with PL or GL. This was an open-label investigator sponsored study which included integrated analysis from 2 studies. Study NIH 991265 was the initial open-label pilot study of metreleptin administration in LD patients. Based on the positive findings from this pilot study, an open-label, long-term study of metreleptin administration (Study NIH 20010769) was initiated. This long-term study permitted the rollover of patients from the pilot study as well as the enrolment of new patients. Although conducted as separate studies, Studies 991265 and 20010769 can be considered as a single extended study since the 2 studies employed a similar protocol and most of the patients studied under the pilot study continued long-term treatment in the second study. Thus, results from these 2 studies have been presented in a single clinical study report. A total of 107 patients have been treated for up to 14 years. The co-primary efficacy endpoints in the study were: • Actual change from baseline in haemoglobin A1c (HbA1c) at Month 12. • Percent change from baseline in fasting serum triglycerides at Month 12 Clinical effectiveness data can be provided on both the GL and the indicated PL populations. No clinical outcomes or quality of life data has been collected in the above studies	
	National Severe Insulin Resistance Service	Yes metreleptin is likely to have a substantial impact and have significant health benefits, especially in patients with generalised lipodystrophy. There are no other specific treatments available for patients with lipodystrophy. We have seen marked benefits in patients attending our service who are taking metreleptin on the compassionate use programme. The health benefits are likely to be over a long time span (years).	Comment noted. The committee will consider the innovative nature of the technology in its deliberations. No

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		I am not familiar with the precise data used in the QALY calculation so I cannot comment on this. There is limited data available as this is a rare disease. This is a very rare condition and there will be relatively few UK patients prescribed metreleptin. The cost of Metreleptin is likely to be high. Does NICE have an alternative process for assessing new treatments for rare diseases?	changes to the scope required.
Questions for consultation	Aegerion	<u>Is the population defined appropriately?</u> Metreleptin will be submitted for regulatory approval for generalised lipodystrophy and a subset of partial lipodystrophy as described above. The indication for metreleptin will not include HIV associated lipodystrophy. <u>How many people would be expected to be considered for metreleptin treatment in clinical practice in England?</u> The anticipated population in England within the proposed indication based on prevalence and the experience from Addenbrookes is under 100- 200. (see section on population above) <u>Are the outcomes listed appropriate?</u> The outcomes that should be considered are listed above <u>Are the subgroups listed in other considerations appropriate?</u> Regarding subgroups, our economic analysis would be based on the whole licensed indications, but with the potential for GL and the PL sub-group analyses to be available separately (if appropriate based on the data available). No other sub-groups are expected. The data available may not	Comments noted.

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		enable a meaningful analysis of the congenital or acquired forms independently. Do you consider metreleptin to be innovative in its potential to make a significant and substantial impact on health-related benefits…? As described above, metreleptin is an innovative treatment developed to address the underlying cause of the metabolic consequences of lipodystrophy, the relative leptin deficiency resulting from partial or complete loss of adipose tissue. Metreleptin is the only means to replace the deficient leptin in indicated patients. In addition to significantly reducing HbA1c and triglyceride levels, metreleptin reduces liver volume, improves liver and renal function, improves insulin sensitivity and satiety. In an analysis of the GL patients, 41% were able to come off insulin, 22% off oral anti-diabetics and 24% off lipid lowering therapies. Please identify the nature of the data which you understand to be available..? (See section on Innovation) Comments on appropriateness of a single technology appraisal for this innovation? As described above in the section on appropriateness, Aegerion does not believe that metreleptin meets the prioritisation criteria for an STA and, if NICE is to appraise metreleptin, an HST appraisal is considered more appropriate as this technology meets all the criteria of this process.	
	National Severe Insulin Resistance Service	There are no other specific treatments for lipodystrophy (see above). The effect in patients with generalised lipodystrophy can be marked. It also appears very effective in patients with partial lipodytrophy and a low baseline leptin concentration.	Comment noted.

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		It is likely that the Marketing Authorisation will be for patients with generalised and 'severe partial' lipodystrophy- the precise definition of the latter is currently unclear but an upper limit of leptin concentration may be specified. It is unclear whether the Marketing Authorisation will specify any predetermined metabolic criteria (eg diabetes/ triglyceride control at baseline). It is unlikely that patients with HIV lipodystrophy will be included in the Marketing Authorisation There is a single national highly specialised service for patients with lipodystrophy based at Addenbrookes Hospital, Cambridge. This is the only UK centre currently authorised by Aegerion to provide metreleptin on a compassionate use programme. A small number of other patients with lipodystrophy are managed in paediatric and adult diabetes and endocrine units throughout the UK. Some patients, especially with partial lipodystrophy remain undiagnosed. The centre in Cambridge currently has approximately 25 patients treated with metreleptin and around 8 patients waiting to join the compassionate use programme if approved by Aegerion. We anticipate that 3-6 new patients per year may be eligible start metreleptin in the future depending on the Marketing Authorisation.	
Additional comments on the draft scope	Aegerion	The proposed trade name for metreleptin approved by EMA will be Myalepta	Comment noted. No changes to the scope are needed.
	National Severe Insulin Resistance Service	This is a very rare condition and there will be relatively few UK patients prescribed metreleptin. The cost of Metreleptin is likely to be high. Does NICE have an alternative process for assessing new potentially high cost treatments for rare diseases?	Thank you for your comment. This topic has been referred to the HST programme for evaluation. NICE aims to publish draft guidance within 6

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			months of marketing authorisation.

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

Department of Health