APPEAL AGAINST THE FINAL EVALUATION DETERMINATION FOR METRELEPTIN FOR THE TREATMENT OF LIPODYSTROPHY

EXECUTIVE SUMMARY

Aegerion's appeal against the Final Evaluation Document for metreleptin for the treatment of lipodystrophy is based on the following grounds:

Ground 1

- The Evaluation Committee has provided no adequate reasons to explain its conclusion that the clinical data for metreleptin are insufficient
- The Evaluation Committee has seemingly failed to understand the serious consequences of untreated lipodystrophy
- The advice provided to Aegerion by the NICE technical team and by the Evidence Review Group (ERG) in relation to the response to the ECD conflicted with the subsequent observations of the ERG in written and oral submissions to the Evaluation Committee and the fact and substance of the advice received by Aegerion was not recognised or considered by the Committee in preparing the FED.
- The Committee's conclusions in relation to the cost-effectiveness of metreleptin are inadequately explained
- The Committee has failed to take into account the benefits of metreleptin that are not reflected in the economic model
- The Committee has failed to consider the status of children with lipodystrophy in accordance with the provisions of the Human Rights Act 1998
- The Committee's overall conclusion in this evaluation exceeds its powers

Ground 2

- The Final Evaluation Document is subject to multiple factual errors which, taken together, cast doubt on the reasonableness of the Committee's conclusions

INTRODUCTION

Metreleptin (Myalepta) is indicated for the treatment of lipodystrophy. It is the only treatment for patients with this condition and has been shown in clinical studies to result in substantial and clinically important improvements in metabolic parameters including tyiglyceride levels and glycaemic control.

Metreleptin is a synthetic analogue of the human hormone, leptin, which is secreted by adipocytes. Metreleptin is an orphan medicinal product, granted a marketing authorisation by the European Commission under the centralised procedure on 29 July 2018 under exceptional

circumstances, following a, positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) issued on 31 May 2018.

It is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy 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; and
- with confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

PROCEDURAL HISTORY OF THE EVALUATION

Below is a summary of the history of the NICE HST evaluation for metreleptin.

21 April 2017	**Metreleptin referred for HST evaluation by NICE**
November 2017	Final Scope for HST evaluation of metreleptin
17 January 2018	Submission to NICE by Aegerion Pharmaceuticals Ltd in relation to metreleptin for the treatment of lipodystrophy
28 June 2018	**First meeting of the Evaluation Committee to consider metreleptin**
23 July - 13 August 2018	**Consultation on first Evaluation Consultation Document (ECD)**
29 July 2018	**Metreleptin granted marketing authorisation for the treatment of lipodystrophy by the European Commission under "exceptional circumstances"**
1 August 2018	**Aegerion meets with NICE technical team and ERG to consider response to ECD and approach to address concerns of Evaluation Committee**
16 August 2018	Advice from NICE technical team and ERG in relation to response to ECD confirmed by Aegerion in writing
5 November 2018	Aegerion submits response to ECD with additional evidence for consideration by the Evaluation Committee
10 December 2018	Aegerion provides a further submission in response to a request for clarification from the ERG

15 January 2019	ERG completes supplementary/addendum ERG report
12 February 2019	**Second meeting of the Evaluation Committee to consider metreleptin**
14 June 2019	**Final Evaluation Determination (FED) is issued to consultees:**

LIPODYSTROPHY: BACKGROUND INFORMATION

Lipodystrophy and its treatment are considered in detail in Aegerion's original submission to NICE for the purposes of this HST evaluation, dated 17 January 2018. In this Appeal Letter, we provide a brief summary, as background information to assist the Panel. This summary does not, however, replace the more detailed information submitted earlier in the HST evaluation process.

Lipodystrophy is an ultra-rare disease characterised by the complete or partial absence of adipose tissue (respectively generalised and partial lipodystrophy) and impaired leptin production. The disease affects multiple organ systems and results in early mortality. Life expectancy in patients with generalised lipodystrophy is reduced by an estimated 25 years. Patients with partial lipodystrophy typically follow a similar course to those with generalised lipodystrophy, once organ abnormalities become manifest.

The inability to store fat in adipose tissue and inability to secrete the hormone leptin result in numerous abnormalities in affected patients. Ectopic fat deposition occurs in multiple organs, including liver, kidney, pancreas and heart, resulting in progressive derangement in organ function. In addition, lipodystrophy adversely impacts quality of life by:

- Causing severe metabolic derangements (which in many patients cannot be controlled by diet or treatment with alternative medicines), including elevated triglycerides, insulin resistance (associated with acanthosis nigrans and hirsuitism), poorly controlled blood glucose with early onset type 2 diabetes mellitus and pancreatitis.

- Causing hyperphagia (extreme hunger, which is not satisfied, irrespective of the quantity of food ingested);

- Affecting the reproductive system in women and girls, with resulting delayed puberty and infertility;

- Causing distress as a consequence of the abnormal, disfigured appearance suffered by affected patients.

Most patients have genetic/familial disease and are affected from birth, with symptoms such as hyperphagia and organ dysfunction becoming manifest in childhood. In addition to the impact of the disease on affected patients, it also affects families and caregivers through

restrictions on ability to work, anxiety and the need to manage the consequences of the disease, such as pancreatitis, hyperphagia and organ dysfunction.

The life expectancy of affected patients depends on the severity of disease. A study from Brazil described patients with congenital generalized lipodystrophy or Berardinelli-Seip Congenital Lipodystrophy[1]. The authors reported that twenty patients (12 female and 8 male) who died between 1997 and 2017 in Rio Grande do Norte. The mean age at the time of death was 27.1±12.4 years (women 25.2±12.5 vs. men 29.9±12.6 years, p = 0.41). Life expectancy for the study population (i.e. the unaffected population) was 62.9±4.8 years. The potential number of years of life lost was 35.6±16.6 years.

Metreleptin is the only authorised treatment for lipodystrophy. In the absence of metreleptin, patients receive supportive care only, with symptomatic treatment for diabetes and hypertriglyceridemia . Metreleptin is administered by subcutaneous injection by the patient or carer at home. It is currently provided to patients under an early access programme (EAP) sponsored by Aegerion, through the NHS specialised service specification of the National Severe Insulin Resistance Service at Addenbrookes Hospital, Cambridge.

The prevalence of the disease is approximately 2.5 affected persons per million population, with an estimated 200 lipodystrophy patients in England. Only a small proportion of these patients require treatment with metreleptin, as demonstrated by the fact that, while the EAP has been in place for 11 years, only 20 patients are in receipt of treatment.

GROUNDS OF APPEAL

1. GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS

1.1. The Evaluation Committee has provided no adequate reasons to explain its conclusion that the clinical data for metreleptin are insufficient

At paragraphs 4.3 and 4.4 of the FED, the Evaluation Committee considered the clinical trial data including the systemic literature review conducted by Aegerion in response to the ECD, in order to provide data on the history of lipodystrophy in the absence of metreleptin treatment. The Evaluation Committee noted the ERG's concerns that there were no separate comparator arms in the metreleptin trials and no evidence from Aegerion's literature review of "patient experience in people who did not have metreleptin so any estimates of relative effectiveness would be highly uncertain". The Evaluation Committee then suggested that "the updated systematic review may have missed relevant studies", before expressing its overall conclusion:

> "However, it considered that the new literature review lacked structure and agreed that its concerns had not been sufficiently addressed. It therefore concluded that the evidence presented to support the relative effectiveness of metreleptin was insufficient".

[1] JG Lima et al. Causes of death in patients with Berardinelli-Seip congenital generalized lipodystrophy. PLoS ONE 13(6): e0199052. https://doi.org/10.1371/journal.pone.0199052

The reasons provided by Committee at paragraph 4.4 of the FED do not however support this conclusion:

- The ERG had commented (see page 22 of ERG addendum report) that, in circumstances where the aim of the systematic literature review was to provide comparative data i.e. natural history studies or studies of dietary modifications, the exclusion of studies with no intervention was not appropriate -

  However paragraph 4.4 of the FED notes that Aegerion had explained that the criterion of "no intervention" was used to specify studies in which the relationship between intervention and outcomes was not assessed.

- The ERG criticised the exclusion of studies on the basis of ineligible/ incorrect intervention (see page 22 of ERG addendum report) -

  However paragraph 4.4 of the FED notes that Aegerion had explained that the criterion of "incorrect intervention" was used where a relevant intervention was assessed but focussed on irrelevant outcomes (e,g, HIV).

- The ERG had observed that a GL/PL natural history study had been used as a comparator in the economic model but not in the clinical section -

  However paragraph 4.4 of the FED notes that Aegerion had explained that the GL/PL study could not be used for the purposes of the clinical assessment because it did not report any changes in HbA1c, triglycerides or hyperphagia.

- The ERG stated that several previously included studies were not identified in the new review.

  However the ERG themselves had noted (page 23 of their addendum report) that Aegerion had explained that seven studies had been excluded from the current search because they either did not contain outcome related search terms in the context of lipodystrophy or were abstracts dated prior to 2015. It is standard methodology to restrict searches of abstracts to those published in the last 3 years, as this period is generally sufficient for studies to move from conference presentations to published journal articles. Older abstracts will either be duplicative of studies also identified as journal articles or will reflect work that was presented only at congresses but did not proceed to a peer reviewed article. The original SLR conducted for this evaluation, was carried out some 18 months earlier than the second, latest version. Therefore a number of abstracts published in 2013-2014 were included in the original search but not in the second search. Neither the ERG nor the Committee criticized this particular design choice and the reason for objecting to exclusion of the earlier abstracts is therefore unclear.

In the above circumstances, the conclusions of the Evaluation Committee are inadequately explained and procedurally unfair.

a) Paragraph 4.4 of the FED does not state at any point that the Evaluation Committee rejected the explanations given by Aegerion or express any doubt about the validity of these reasons. Therefore the basis for the Committee's conclusions that "the

updated systematic review may have missed relevant studies", "the new literature review lacked structure" and "its concerns had not been sufficiently addressed" is unclear. This lack of transparency is procedurally unfair and prejudices Aegerion in its ability to understand the reasons for the Committee's negative finding and to respond to the Committee's concerns.

b) There is a particularly high requirement for transparency in this case, in circumstances where the Evaluation Committee's overall conclusion regarding the clinical trial data was that "the evidence presented to support the relative effectiveness of metreleptin was insufficient", which presents a stark contrast with that of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), which concluded:.

> "A clear effect on HbA1c and triglyceride levels have been demonstrated for metreleptin from the data submitted in patients with GL and PL. Therefore it was concluded that metreleptin is an effective treatment option for patients with congenital or acquired generalised lipodystrophy and familial or acquired partial lipodystrophy for whom standard treatments have failed to achieve adequate metabolic control".

The patients in the trials therefore demonstrated clear improvements in HbA1c and triglycerides as compared with a baseline position where standard treatments had failed to demonstrate metabolic control. The Evaluation Committee is not required to reach the same conclusion as the CHMP in relation to effectiveness, but where it reaches a different conclusion, it is incumbent upon the Committee to explain the reasons for that divergence.

c) Furthermore, if the Evaluation Committee concludes that, in the context of this ultra-rare disease and heterogeneous population an indirect comparison with historical data relating to a range of supportive or lifestyle measures is more reliable than a comparison where each trial participant provides its own comparative data before and after commencement of treatment (baseline data), as reflected in the metreleptin clinical trials, the Committee's reasons should be provided.

1.2. The Evaluation Committee has seemingly failed to understand the serious consequences of untreated lipodystrophy

The Evaluation Committee describes the condition of lipodystrophy at paragraph 2.1 of the FED, stating that it exerts important negative effects on quality of life but failing to mention the impact on triglyceride levels and glycaemic control. Similarly, the Committee's conclusions at paragraph 4.25 focus on the effects of hyperphagia on quality of life and seem to disregard the important metabolic consequences of lipodystrophy. These descriptions of the effect of lipodystrophy on the lives of affected persons do not take into account the impact of the condition on mortality or the fact that patients with generalised lipodystrophy may expect to die 20-30 years earlier than unaffected persons. These omissions are fundamental and reflect a misunderstanding of the disease which impacts the entirety of this evaluation.

1.3. **The advice provided to Aegerion by the NICE technical team and by the Evidence Review Group (ERG) in relation to the response to the ECD conflicted with the subsequent observations of the ERG in written and oral submissions to the Evaluation Committee and the fact and substance of the advice received by Aegerion was not recognised or considered by the Committee in preparing the FED.**

As explained above, in view of the rarity of lipodystrophy and the heterogeneous nature of the patient population with the associated challenges in meeting NICE criteria in the HST process, Aegerion has sought to co-operate closely with NICE throughout this evaluation in order to ensure that most relevant and appropriate data were provided to the Evaluation Committee. In particular, Aegerion was conscious that the HST procedure had undergone recent revision and that there was limited experience with application of the new procedures and thresholds.

In that context and in circumstances where the NICE technical team and the ERG, who are generally present during the closed session of the Evaluation Committee meetings and would therefore be expected to have greater insights into the Committee's thinking and concerns, Aegerion arranged a meeting with the NICE technical team and with a number of members from the ERG in order to obtain advice on the appropriate response to the ECD. That meeting took place on 1 August 2018; in advance of the meeting, Aegerion communicated its proposals by email dated 24 July 2018. After the meeting, Aegerion documented the results and corresponded by email with NICE in relation to the proposed approach to collection of utilities data, in order to ensure that the advice received during the meeting had been correctly understood and that the resulting approach proposed by Aegerion was viewed as appropriate by the NICE technical team and the ERG (in view of their greater knowledge of the HST processes and the views of the Evaluation Committee). Aegerion received no communication indicating that it had misunderstood the advice or expressing any objection to its proposals.

Following the meeting on 1 August 2018 and relying on the advice received from the NICE technical team and the ERG, Aegerion invested in extensive work to provide a comprehensive response to the ECD and to address the Evaluation Committee's concerns. That work resulted in detailed submissions provided to NICE on 5 November and 10 December 2018.

However, at the second meeting of the Evaluation Committee on 12 February 2019, the work conducted by Aegerion in response to the ECD, in reliance on advice from the NICE technical team and the ERG, was largely disregarded, Aegerion received substantial criticism and, so far as we are aware, the Evaluation Committee was not informed that Aegerion's approach had been determined by the advice received on 1 August 2018. There was limited time for discussion (this was the first occasion on which the Committee had considered three technologies rather than two, during one meeting) and there was no opportunity for the company to make submissions. Furthermore, not only did the NICE technical team and the ERG fail to explain to the Evaluation Committee why Aegerion had adopted the approaches reflected in its ECD response, the ERG criticised the substance of Aegerion's response and the approach followed - in direct conflict with the advice the ERG had itself previously provided to Aegerion.

Further detail in relation to the specific issues discussed at the 1 August meeting are provided below.

The systematic literature review

During the first Evaluation Committee meeting, the Committee had asked Aegerion to conduct a further systemic literature review. Aegerion's proposed search strategy following the ECD was set out in an email to the NICE technical team on 24 July which stated:

> "We intend to complete a systematic literature review to identify comparator studies using the following approach:
>
> - Include lipodystrophy related search terms to identify studies in patients with lipodystrophy patients
> - Exclude HIV related studies using a combination of HIV and AIDS related search terms
> - Further limit to studies that include burden of illness or outcome related terms
> - Exclude editorials, case reports, etc
> - Exclude conference abstracts prior to 2015
>
> An example of this approach implemented in EMBASE yields a manageable set of results to screen (see attached). The search strategy would be implemented in MEDLINE and Cochrane databases, in addition to EMBASE.
>
> This approach differs from the approach include in the ERG report, which focused on epidemiology and natural history terms [sic]. As the request from the committee was specific to identifying comparator studies, the additional inclusion of epidemiology terms does not seem necessary".

The above proposals were discussed at the meeting on 1 August 2018. The ERG were keen that Aegerion did not exclude HIV from the search criteria, as the company had proposed and this advice was reflected in the work subsequently carried out by Aegerion. The ERG however agreed that the focus of the Evaluation Committee's interest was comparator studies rather than epidemiology studies, consistent with Aegerion's understanding and this again influenced Aegerion's approach to the searches carried out for the purposes of the ECD response.

However at the second Evaluation Committee meeting, Aegerion was criticised by both the ERG and the Committee for the structure of its review (even though this had been discussed with and approved by the ERG) as well as for its approach to identification of studies of interest and for the exclusion of abstracts prior to 2015. (We explain under appeal point 1.1 why this strategy was adopted.)

The collection of utilities

The Evaluation Committee also criticised Aegerion's approach to utilities and encouraged the company to investigate the impact of hyperphagia and impact on carers. The appropriate approach was discussed during the meeting with the NICE technical team and the ERG on 1 August 2018.

During the meeting Aegerion proposed a method constructed to gain utilities data from patients currently on treatment and to also ask them to recall their experience before treatment commenced. A member of the ERG however suggested that this method was associated with

bias and suggested that gathering the data from clinicians would be a preferred methodology, They also suggested that vignettes should be used to obtain data from clinicians.

Following the meeting, Aegerion contacted NICE on 16 August by email to confirm the advice received from the NICE technical team and the ERG:

> "It was mainly the utility data that I wanted to update you on. You will recall from our phone calls that originally we came to the meeting with the ERG with the proposal of doing a utility assessment using EQ5D with a small number of patients currently on treatment, assessing their current QoL and asking them to recall there quality of life before they were put on treatment [sic]. The ERG expressed concern about the risk of bias asking the patients to recall what their quality of life was like due to a natural assumption that there treatment has improved there QoL [sic]. The ERG suggested that we could gain the utility data from the treating experts, and it was clear from the meeting that this was seen as being a more credible approach.
>
> We left the meeting feeling we would carry out both approaches but as we have explored them in greater detail we have realised that going directly to patients even through the patient group would require us to go through ethics and the time that this would take would be unpredictable and potentially lengthy and could put our time lines at risk. Given that the ERG clearly preferred the method of gathering data from the expert clinicians we have opted just to go for this approach, and do this in the most robust manner we can within the time lines available.
>
> I was really keen to check in with you to confirm that this approach remains in line with the conversations we have had. If this is easier for you to discuss on the phone please feel free to call me on [number provided]".

Aegerion received no further communication from NICE in relation to this issue and understood that its proposals were therefore in-line with what had been approved at the meeting on 1 August 2018 and reflected an approach which was likely to be acceptable to the Committee.

However, during the second meeting of the Evaluation Committee the ERG stated that "the ERG had concerns about using utility values elicited from clinicians based on treatment rather than health state descriptions. It explained that values from patients would have been preferable" This criticism is particularly surprising in view of the fact that Aegerion followed the clear advice provided by the ERG at the meeting on 1 August and confirmed in the subsequent email to NICE; while the two groups were called "treated" and "untreated", the vignettes suggested by the ERG and used by Aegerion were, in fact, based on health states.

<u>The economic model</u>

During the first Evaluation Committee meeting, the Committee criticised Aegerion's economic model and indicated that it would prefer one that modelled the progression of metabolic disease. However by that stage, additional data had become available to Aegerion and the company was concerned to discuss with the NICE technical team and the ERG how these data could be incorporated into the assessment.

In preparation for the advice meeting on 1 August, on 24 July 2018, Aegerion sent an email to NICE stating the following:

"Alternate cost-effectiveness analysis approach…

We understand that the committee would appreciate a cost-effectiveness analysis of metreleptin that is tractable and draws on well-established models. In the context of validating the original cost-effectiveness model, we developed a simple "area under the curve" CE model that leverages the results of a refined survival analysis (presented at the American Diabetes Associated meeting in June 2018). We would like to share this model with the committee and also use this model to explore refined utility values…..

This model makes the following assumptions:

- Generalised lipodystrophy and partial lipodystrophy are modelled separately
- There are four health states: Alive and treated with standard of care, Alive and treated with metreleptin, Alive and discontinued metreleptin, and dead
- The proportion of the metreleptin cohort (either currently treated or discontinued) that are still alive in each period is assumed to be the same as observed in the NIH follow-up study for the first 16 periods of the model and to follow an exponential extrapolation of that curve for periods 16-90.
- The proportion of the metreleptin cohort that discontinues is assumed to be 8% after the first period and 2 percent thereafter (matching observed discontinuation in the NIH follow up study)
- The proportion of the standard of care cohort still alive in each period matches the Kaplan Meier curve for the matched natural history cohort in the first 16 periods of the model and to follow an exponential extrapolation of that curve for periods 16-90. Alternate extrapolations can be explored
- A range of utility values for the standard of care and discontinued metreleptin patients are included as sensitivity analyses, and will include values supported by interviews with patients and caregivers and reflecting our response to request 3
- A range of utility gains associated with metreleptin treated are applied to the proportion of the metreleptin cohort who is still receiving treatment in each period. The values considered are based on values from the discrete choice experiment using in the original CE model, additional analysis and calibration of the DCE data, literature based values, and our response to [the request in relation to utilities]

While this model is not a model of metabolic disease progression, the refined approach used to match metreleptin treated patients with untreated patients (with underlies the survival assumptions of the simplified model) supplements organ abnormality indicators with an indicator of elevated HbA1c levels to better account for metabolic markers of lipodystrophy severity [sic]. "

During the meeting on 1 August, Aegerion discussed the proposed model methodology referring to the details already sent via e mail. This was seen as a sensible approach by members of the ERG and the NICE technical team.

However, at the second meeting of the Evaluation Committee, the Committee rejected the new modelling (paragraph 4.10 of the FED) indicating that the directions given at the first meeting should have been followed. Neither NICE's technical team nor the ERG expressed any opinions in support of Aegerion's modelling despite (i) the advice they had provided earlier to Aegerion and (ii) the fact that no objections to the model were expressed by the ERG in its

report on the response to the ECD. (The fact that the Committee seems wholly to have rejected the views of the ERG in relation to the model at this stage and provide no positive perspective to balance its criticisms, is stark.)

Procedural unfairness

Aegerion accepts that the Evaluation Committee is not bound by any position (or advice) of the NICE technical team or the ERG, however the experience of Aegerion in this evaluation is conspicuously unfair in circumstances where:

(a) If NICE and/or the ERG had no insights into the concerns of the Evaluation Committee that fact should have been made clear to Aegerion at the outset. However, in this case, Aegerion received the strong impression from the NICE technical team and the ERG, that they were aware of the thinking of the Evaluation Committee and that the proposed response to the ECD would be an acceptable method to address the Committee's concerns

(b) In view of the rarity of lypodystrophy and the difficulties with the clinical data, Aegerion had been concerned to co-operate fully with NICE and with the ERG in order to understand what it needed to do in order to address the Committee's concerns. That co-operative approach was seemingly disregarded by the Committee, even though it was specifically stated in Part B of Aegerion's ECD response:

> "We discussed these requests with NICE highly specialised technology (HST) technical staff and members of the ERG following the release of the ECD and aligned on specific analyses, including a systematic literature review (SLR) search strategy, approach for elicitation of further utility values and reanalysis of existing data, and an alternate cost-effectiveness model structure that would address the uncertainties around the economic model that prevented the committee from issuing a preliminary decision. These additional data and analyses are detailed in this document and present a more complete set of evidence describing the value of metreleptin in NHS clinical practice. An alternative model structure based on partitioned survival analysis has been adopted to address the ERG's concerns, detailed in section 2.4. This new approach is largely structured around the survival of lipodystrophy patients and requires minimal assumptions on the relative importance of lipodystrophy disease attributes, how these disease attributes progress, or how they are related to each other. A new range of plausible cost-effectiveness results are presented in section 2.6 showing that adoption of metreleptin for the treatment of lipodystrophy represents an appropriate use of NHS resources."

(c) The Evaluation Committee should been reminded that Aegerion had sought and followed the advice of NICE's technical team and the ERG in its response to the ECD. Had the Committee been aware of this situation, the Committee might have given Aegerion's ECD response greater consideration and been less critical of the company in the FED.

(d) The inconsistent views and opinions of the ERG represent on any view an area of substantial unfairness in this evaluation. It is patently unacceptable for the ERG to advise Aegerion to follow a specific approach (e.g. in relation to collection of utilities)

and then to criticise that approach in submissions to the Committee. The unfairness in relation to the actions of the ERG are particularly marked in this case, in circumstances where the Evaluation Committee accepted and relied upon the ERG's advice for the purposes of its conclusions in the FED.

1.4. The Committee's conclusions in relation to the cost-effectiveness of metreleptin are inadequately explained

At paragraph 4.22 of the FED, the Evaluation Committee states:

> "It noted that, even when the patient access scheme was incorporated, the ICERs for the base case and all scenarios explored were above the range considered an effective use of NHS resources for highly specialised technologies".

However, the basis for the Committee's conclusion is unexplained and appears inconsistent with other statements in the FED:

a) There is no explanation of the scenarios which were seemingly explored by the Evaluation Committee, so Aegerion and other stakeholders have no visibility of this assertion or way to know whether it is correct or test its reliability or otherwise to respond to the conclusion in paragraph 4.22.

b) Aegerion's response to the ECD (table 2 of Part A of Aegerion's response to the ECD) included estimated ICERs for an alternative base case, which were within the range considered an effective use of NHS resources for highly specialised technologies (assuming a QALY weighting was accepted). The FED includes no explicit reference to these analyses and paragraph 4.22 suggests that they were wholly disregarded even on an exploratory basis.

c) Paragraph 4.22 of the FED states that "all scenarios explored" were above the cost-effectiveness threshold, whereas paragraphs 1 and 4..25 indicates instead that the Committee's concerns related to uncertainty and that "the committee concluded that it had not been presented with the evidence or any framework on which to base an opinion on metreleptin's clinical effectiveness and the plausibility of its value for money. These two conclusions are contradictory: either all scenarios were above the cost-effectiveness threshold or it was not possible to reach an opinion on such matters.

d) Paragraph 4.10 suggests that Aegerion submitted only one economic model for metreleptin. However the company submitted two different economic models, adopting different approaches in order to demonstrate the cost-effectiveness of the product and both of these produced similar results. This fact has seemingly been disregarded by the Committee or, if it has been considered, there is no explanation of how the fact of two different models reaching similar conclusions has been taken into account.

Transparency is a fundamental aspect of procedural fairness. However the Committee's conclusions in relation cost-effectiveness are opaque - beyond a conclusion that the approach to modelling was not that preferred by Committee and that the Committee considered the clinical data to be uncertain (as they inevitably will be in the context of an ultra-rare heterogeneous condition, such as lipodystrophy). In these circumstances, the conclusion that "the base case and all scenarios explored" were not viewed as cost-effective

is unexplained. There is in fact no indication that any "scenarios" were explored by the Committee or what the outcome of such assessments was in any case. This is patently unfair.

1.5. The Committee has failed to take into account the benefits of metreleptin that are not reflected in the economic model

While the Committee recognises at paragraphs 1 and 4.25 of the FED that important benefits of metreleptin therapy were not adequately reflected in the economic model, they did not consider whether and/or how these elements could impact the overall cost-effectiveness of metreleptin. In particular, in circumstances where these factors would inevitably improve the cost-effectiveness of metreleptin treatment, the Committee should have assessed whether the impact of what are accepted to be important elements could have balanced any uncertainty and reassured the Committee that usage of metreleptin was likely to be cost-effective. The Committee's failure to take into account these aspects of treatment was unfair.

1.6. The Committee has failed to consider the status of children with lipodystrophy in accordance with the provisions of the Human Rights Act 1998

The Appeal Panel who considered the appeal against the Final Appraisal Determination for dinutuximab for treating high-risk neuroblastoma considered whether the failure to recommend that technology as a treatment option was contrary to human rights legislation, in view of the particular status of patients eligible for treatment in accordance with its marketing authorisation, as children. The Panel agreed that articles 2, 8 and 14 of the European Convention on Human Rights were engaged by the decision and expressed the view that the status of patients as children was also a factor to be taken into account in accordance with English public law principles. While recognising that NICE was not obliged to give the status of children "paramount weight", the Panel found that the Appraisal Committee was required to consider such status as a relevant issue and, in circumstances where the appraisal documents did not record such consideration, was not satisfied that the Committee's treatment of the issue met that requirement.

Similar issues were raised in the appeal against the FED for sebelipase alfa for treating lysosomal acid lipase deficiency. The Appeal Panel who heard that case again upheld the appeal on that basis.

Similar considerations are applicable to the current HST evaluation of metreleptin and, in particular, to the Evaluation Committee's assessment of use of the product in children, despite recognising that there is a compelling clinical need for treatment of such patients. That clinical need was reflected in the grant of a marketing authorisation based on exceptional circumstances, in view of the fact that there is no alternative treatment available for patients with lipodystrophy. Without treatment, children with congenital/ familial lipodystrophy will suffer substantial impairment to their quality of life and irreparable organ damage leading to premature mortality. In addition to the suffering experienced by affected patients, in circumstances where an effective licensed treatment is available, but the authorities refuse to make this available, their parents will also experience mental suffering. Finally, in circumstances where the situation of children is different to that of adults and an extension of life and prevention of ill health and suffering may be valued more greatly in this group and their parents, refusal to recommend use of a technology in children may constitute discrimination based on age.

On this basis, Aegerion submits that Articles 2,3, 8 and 14 of the European Convention on Human Rights are engaged by this evaluation and that the Committee is required to take into account the particular status of children who may receive treatment with metreleptin. As stated by the Appeal Panel in the dinutuximab appeal:

> "Provided the Committee asks itself whether its approach should change to reflect the fact that the population targeted for this technology are children, and gives a reasoned answer, it will have corrected the error identified by the Panel. What it should then do will be a matter for its judgement and will depend on whether or not it considers a different approach is needed and the evidence available to it"

Such consideration is not documented in the evaluation documents for metreleptin and must therefore be assumed to have been absent from the Committee's review of the technology to date.

1.7. The Committee's overall conclusion in this evaluation exceeds its powers

At paragraph 1 of the FED, the Evaluation Committee criticises the economic model submitted by Aegerion and states:

> "Also, even with an appropriate model, any benefits to metreleptin would be highly uncertain, because of the substantial uncertainties in the clinical evidence. Therefore 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".

Metreleptin was granted a marketing authorisation by the European Commission for the treatment of lipodystrophy under "exceptional circumstances". The extreme rarity of lipodystrophy was recognised by the CHMP during its assessment, together with the fact that the heterogeneous nature of the condition, made active or placebo controlled clinical trials not feasible. However, despite the fact that the data were not comprehensive, the CHMP recommended that a marketing authorisation under "exceptional circumstances" should be granted, subject to conditions namely a disease registry in order to evaluate the long-term effectiveness of metreleptin under conditions of routine clinical care and an open label study to characterise further the effects of metreleptin on metaboilic control.

The role of NICE is different from that of the regulatory authority (in this case the European Medicines Agency (EMA) advised by the CHMP). In these circumstances, its conclusion that, irrespective of clinical need and any economic modelling, price or assumptions, the clinical evidence is so uncertain that metreleptin should not be recommended for use within the NHS, extends beyond the role of NICE and conflicts with the decision of the regulatory authority and the grant of the marketing authorisation for metreleptin. For the avoidance of doubt, the situation in this evaluation is different from that where the Committee is required to conduct an evaluation of relative effectiveness against a standard UK treatment different from that considered by the regulators. Here the assessment by both CHMP and by NICE related to the benefits of metreleptin over and above supportive/ lifestyle measures (i.e. no treatment directed specifically at lipodystrophy pathology).

By saying that, irrespective of the economic model, the product could not be recommended, the conclusion of the Evaluation Committee at paragraph 1 is (despite the reference to value for money) is based not on cost-effectiveness but on the strength of the clinical evidence.

The determination by the Evaluation Committee is not only wholly contrary to that of the CHMP, referenced at appeal point 1.1(b) above, it assumes a regulatory role and undermines the decision to grant a marketing authorisation under exceptional circumstances in the context of high clinical need. In summary, while NICE is entitled to find (subject to procedural fairness and reasonableness) that the cost effectiveness or value for money of a particular technology has not been demonstrated, it is not permitted to conclude, that the clinical evidence of benefit associated with a licensed medicine and accepted by the regulators, is so weak or uncertain that it can never be recommended for use.

2. GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE

2.1. The Final Evaluation Document is subject to multiple factual errors which, taken together cast doubt on the reasonableness of the Committee's conclusions

The factual errors are listed in Schedule I to this appeal letter.

THE DETERMINATION OF THIS APPEAL

Aegerion requests an oral hearing for the determination of this appeal.

REMEDY FOLLOWING APPEAL

Aegerion respectfully requests the Appeal Panel to direct

- That the Evaluation Committee should provide adequate reasons to explain its conclusions in relation to the sufficiency of the clinical data for metreleptin
- That the Evaluation Committee should reconsider this evaluation in the context of the serious consequences of untreated lipodystrophy in terms of metabolic consequences and premature mortality as well as poor quality of life
- That, in view of the inconsistent and confused advice provided to Aegerion and the Evaluation Committee by NICE's technical team and the ERG, the Evaluation Committee should reconsider its conclusions on the SLR, the utilities data and the economic model in the context of a further submission from Aegerion.
- That the Committee should provide clear and detailed reasons for its conclusions in relation to the cost-effectiveness of metreleptin
- That the Committee should consider the benefits of metreleptin that are not reflected in the economic model when reaching its conclusions
- That the Committee should consider the particular status of children with lipodystrophy in accordance with the provisions of the Human Rights Act 1998 when issuing guidance for metreleptin
- That the Committee should not exceed its powers by suggesting that the clinical data for metreleptin are inadequate to allow it to be recommended for use in NHS patients irrespective of the economic case

- That the Evaluation Committee should reconsider this evaluation in the context of the multiple factual errors present in the FED and correct those matters before reaching any conclusion in relation to metreleptin.

SCHEDULE

This schedule lists the factual errors, not otherwise mentioned in this appeal, for the purposes of appeal point 2.1

Paragraph in Final Evaluation Document	**Factual error**	**Corrected text**
1.1	Incomplete description in first bullet	"2 years and over, and have congenital or acquired generalised lipodystrophy or"
3.4	Price of metreleptin lists only 10mg presentation (and omits 2.5mg and 5mg presentations) even though 5mg presentation is that most frequently prescribed[2].	"The price of metreleptin per 3mg vial (2.5mg dose) is £583.80, per 5.8mg vial (5mg dose) is £1,167.50 and per 11.3mg vial (10mg dose) is £2,335……"
4.3	Text reports that Aegerion made "no attempt" to do indirect comparisons to study the effects of established clinical management even though such indirect comparisons were presented in the economic evidence (Appendix 6, page 225, of Aegerion's submission dated 17 January 2018).	"It stated that the submission did not include any search term for comparators and that ~~there was no attempt to do~~ indirect comparisons to study the effects of established clinical management were not presented in the clinical evidence."
4.7	No mention of improvements in metabolic parameters associated with metreleptin treatment, shown in NIH follow up study	"Results from the NIH follow-up study showed that 99% of people who had metreleptin reported improvements in hyperphagia (as well as improvements in many of the severe metabolic consequences of lipodystrophy, including: effects on the pancreas, heart, liver, kidneys and reproductive system; ability to work/ function at school; and diabetic and triglyceride control)."

[2] Prices for 2.5mg and 5mg presentations provided to NICE in Aegerion's response to ECD dated 2 November 2018 and confirmed in correspondence with the NICE technical team