Aegerion Pharmaceuticals Limited
Royal Albert House, first floor
Sheet Street, Windsor, SL4 1BE, UK
Tel: +44 (0) 1753 842 674 Fax: +44 (0) 208 622 3592
www.novelion.com

Mr Tim Irish
Appeals Committee Vice Chair
National Institute for Health & Care Excellence
10 Spring Gardens
LONDON
SW1A 2BU

27th July 2019

Dear Mr Irish

Appeal against the final evaluation determination for metreleptin for lipodystrophy

Thank you for your letter dated 16 July 2019 in which you provided your initial view of Aegerion's appeal dated 5 July 2019 in relation to the FED for metreleptin for lipodystrophy.

In your letter you agreed that three of the points raised by Aegerion were valid points of appeal and should be passed to an appeal panel for consideration. In relation to points you were not minded to refer we have provided further clarification below using the same numbering as that in our letter of appeal.

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

We have considered the preliminary conclusion expressed in your letter, that paragraph 4.4 provides the Committee's reasons and there is no requirement for the Committee to provide more detail than it has already done and believe there may have been some misunderstanding of this point of appeal.

Aegerion's appeal point referred to the fact that the criticisms of the clinical data made by the Evaluation Committee in the FED had all previously been addressed by Aegerion, but the Committee had wholly failed to provide any reason for disregarding these explanations in reaching the conclusions set out in the FED. Furthermore, some of the reasons given in the FED were in places internally inconsistent. This is not therefore a situation where Aegerion disagrees with the reasons given by the Committee, but rather a case where the Committee has provided no explanation for its position in the context of the matters raised by Aegerion.

It is well understood that the role of NICE is different from the role of the EMA. Importantly however, the regulatory framework and the grant of a marketing authorisation is not limited to determining whether a medicinal product may be "promoted". The role of the EMA is intended to ensure that medicines supplied to patients in the EU meet appropriate standards of safety, quality and efficacy. The dossier of clinical evidence submitted in support of an application for a marketing authorisation is central to that assessment. In this case, a marketing authorisation was granted under exceptional circumstances in the context of high levels of clinical need and the positive results shown from the available clinical evidence. NICE's role in contrast is to determine whether particular medicines are cost-effective, i.e. whether the

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magnitude of benefit is sufficient to justify the associated costs, in the context of limited NHS resources. The conclusions of the Evaluation Committee appear however to be that the evidence of benefit is so uncertain that, irrespective of cost, metreleptin could never be recommended (see paragraph 1 as well as paragraph 4). This is not therefore a conclusion based on cost-effectiveness, but one seemingly based on evidence of efficacy which contradicts the regulatory assessment by EMA/CHMP. As indicated in our appeal letter, the Evaluation Committee is entitled to reach a different conclusion from that of the EMA; however if it does so, there is a high requirement for the provision of adequate reasons to explain a divergent approach.

The result is that Aegerion does not understand the basis for the Committee's conclusions regarding the clinical data for metreleptin, in the context of the explanations given by the Company (which have not been addressed), the inconsistent statements in the FED and the conflict with the assessment of EMA/CHMP. While these issues do not seem to have been considered in your letter, they represent a patent breach of the Committee's obligation of transparency and are fundamentally unfair.

Appeal point 1.2: The Evaluation Committee has seemingly failed to understand the serious consequences of untreated lipodystrophy

In your letter you indicate that you see no evidence that the Committee failed to understand the serious consequences of lipodystrophy in conducting this evaluation. You refer, in particular to paragraphs 4.1,4.6, 4.10, 4.13 and 4.14.

However:

- Paragraph 4.1 represents a description of disease burden provided by the patient experts. The committee's conclusions are expressed at the end of the paragraph, namely that lipodystrophy is "debilitating" and hyperphagia is associated with a "very poor quality of life".
- Paragraph 4.6 simply constitutes the Committee's consideration of the clinical evidence and the outcomes measured in the clinical studies, but includes no consideration of burden of disease.
- Paragraph 4.10 describes the structure of the economic model presented by Aegerion (and criticised by the Committee); it includes no evidence that the Committee understood the extent of the serious consequences of untreated lipodystrophy. In fact, the Committee refers on two occasions in this paragraph to "outcomes important to patients" or "important features of lipodystrophy", but on both occasions mentions only "hyperphagia" and fails to recognise important consequences in terms of mortality.
- Paragraphs 4.13 and 4.14 address the modelling conducted for the purposes of the economic model submitted by Aegerion, which focussed on survival. The Committee was critical of the approach followed by Aegerion and, in particular, the model structure.

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Overall, therefore, we disagree with the preliminary conclusion expressed in your letter, that the Committee had understood the serious consequences of the disease. The paragraphs to which you refer either merely describe Aegerion's approach or the views of patient experts and the references to the Committee's views are consistent with paragraph 2 where the Committee states that lipodystrophy is a disease affecting quality of life and disregards the impact on mortality. We believe the misunderstanding of the Committee in this respect has unfairly prejudiced its approach to this evaluation and the economic modelling conducted by Aegerion.

Appeal point 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

Noted

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

Noted

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

You say, in your letter, that "given the Committee says in the FED that it was unable to arrive at a most plausible scenario based on the evidence base, it would have been impossible for the Committee to go on to carry out the exercise [Aegerion] suggests", to consider whether the benefits which were not taken into account could impact the overall cost-effectiveness of metreleptin.

However, despite the statements quoted above, at paragraph 4.21 of the FED, the Committee states 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". The Committee therefore has calculated ICERs and a range of scenarios and it is unclear whether the conclusions expressed in paragraph 4.21 would have been any different had the Committee taken into account the additional benefits of metreleptin therapy.

Appeal point 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

Noted

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Appeal point 1.7: The Committee's overall conclusion in this evaluation exceeds its powers

In your letter you say that you do not believe it is arguable "to suggest that by finding the evidence of relative effectiveness to be insufficient to support a recommendation for public funding, NICE stepped into the shoes of the EMA, which carries out the very different function of determining whether the treatment can be promoted as a medicine for use in humans".

As stated under appeal point 1.1 above, contrary to your letter, the regulatory framework and the grant of a marketing authorisation is not limited to determining whether a medicinal product may be "promoted" and the role of the EMA is intended to ensure that medicines supplied to patients in the EU meet appropriate standards of safety, quality and efficacy. In contrast, as you say in your letter, NICE's role is limited to making recommendations on the cost effectiveness of medicines and whether they constitute an appropriate use of NHS resources. Assessment of clinical effectiveness is an element of this assessment; this may involve consideration of effectiveness relative to standard treatment - which in the case of metreleptin means "best supportive care", precisely the assessment conducted by EMA/CHMP.

While you suggest that the Committee's conclusion was simply that "the evidence available to the Committee was so uncertain that it could not be recommended as providing good value for money in the national health system", this is contradicted by the Committee's explicit statement that, irrespective of the economic modelling, metreleptin could not be recommended for use in NHS patients. In other words they say, in terms, that the decision is not about value for money it is due to the clinical evidence. It is this conclusion in paragraph 1, that substantially exceeds the remit of NICE to issue guidance based on cost-effectiveness and infringes the territory of the regulators, whose function is to decide which medicines may be made available to patients based on standards of safety, quality and (clinical) efficacy.

Appeal point 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

Your comments are noted. Aegerion is content for the matters raised under this point of appeal to be corrected by NICE as factual inaccuracies, rather than bringing them before the Appeal Panel.

Should you require any further information or clarification, please let us know and we will provide this. Alternatively, we look forward to receiving your final determination on the admissibility of our appeal.

Yours sincerely,

Paul Greenland