CLINUVEL

Dr R. Benneyworth (Vice Chair)
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Sent by email to: appeals@nice.org.uk
CC: Marie Manley, Sidley Austin LLP [redacted]

*** PLEASE NOTE THAT PART OF THIS SUBMISSION IS CONFIDENTIAL ***

6 June 2018

Re: Final Evaluation Determination - Afamelanotide for treatment of protoporphyria (erythropoietic) [927]

Dear Dr Benneyworth,

Introduction

1. We refer to the Final Evaluation Document dated 15 May 2018 (the "**FED**") provided by the National Institute for Health and Care Excellence ("**NICE**") to CLINUVEL (UK) LTD (the "**Company**") in relation to the Company's product, SCENESSE® (afamelanotide 16mg) (the "**Product**"). A copy of the FED was published on the NICE website on 22 May 2018. The FED records the evaluation of the Product conducted by NICE's Highly Specialised Technology Evaluations Committee (the "**HST Committee**") and states that the Product is not recommended by NICE and, in consequence, will not be nationally commissioned by NHS England.

2. For the reasons more fully described below, the Company hereby appeals the FED and the failure by NICE to recommend the Product on the basis that: (i) NICE failed to act fairly; and (ii) the conclusions in the FED are unreasonable and/or irrational in light of the evidence submitted to NICE. We respectfully request an oral hearing in this case. As some of the information referred to in this submission is commercially confidential in nature, we request that, when discussion about the terms of the Company's Proposed MAA takes place (see Ground Five and definition at paragraph 29 of this submission), that part of the oral hearing of this appeal be conducted in private.

3. For background purposes, at Appendix 1 to this submission is a chronology of key events relevant to the Company's dealings with NICE and the issues in appeal. Unless otherwise stated, reference in this submission to the "**NICE Guidelines**" means the NICE Interim Process and Methods of the Highly Specialised Technologies Programme (updated to reflect 2017 changes).

Summary of EPP condition and the Product

4. Erythropoietic protoporphyria ("**EPP**") is a very rare metabolic disorder which causes phototoxicity when patients are exposed to particular wavelengths of visible light, including sunlight: exposure to light can lead to anaphylactoid reactions and incapacitating phototoxicity, which may involve redness and swelling of the skin.

5. EPP reactions can last days to weeks. EPP patients are unable to lead normal lives owing to their inability to spent time outdoors and/or be exposed to artificial light sources. EPP patients develop lifelong conditioned behaviour leading to isolation and a lack of social interaction.

6. The Product is the only product authorised for the prevention of phototoxicity in EPP anywhere in the world. The European Medicines Agency ("**EMA**") granted an EU centralised marketing authorisation in 2014 under 'exceptional circumstances'. The EMA recognised the complexity of the disorder and that the specificity of the condition made it impossible for the Company to provide the usual comprehensive clinical trial data required to demonstrate the extent of efficacy of the Product and, instead, the EMA relied both on the statistical evidence of photoprotection and on additional evidence including the testimony of patients and expert clinicians.

7. To date, EPP patients only have access to the Product through expert academic centres (funded through national or regional healthcare systems or through insurance company arrangements) in [redacted].

8. The Product can only be made available to EPP patients under a controlled distribution program in line with the approved risk management plan as agreed with the EMA. [redacted] The Company was and is willing to enter into commercial discussions and negotiation with NHS England with a view to concluding a managed access agreement ("**MAA**") to minimise the financial risk associated with the Product.

Grounds of Appeal

Ground One: NICE acted unfairly in that: (i) one influential panel member of the HST Committee was not impartial; and (ii) NICE failed to take any action in respect of his partiality upon notification by the Company *(NICE Appeal Guidelines: Ground 1(a))*

9. works as a health economics consultant operating through a private consultancy firm, Bresmed in Sheffield. The Company approached in early 2015 with a view to engaging him to advise in relation to health-economics and market access issues relating to the Product.

10. entered into a confidentiality agreement with the Company on 27 February 2015 pursuant to which he was provided with confidential information including pricing information relevant to the Product in Europe, clinical study results, evidence from ongoing clinical assessments in Europe and the Company's commercial strategy as regards the Product generally and the required and/or likely required action for obtaining country-specific regulatory approvals and recommendations, including by NICE in England.

11. During the course of February and March 2015, representatives of the Company met with in London. During these meetings, the Company shared background information relating to the Product, discussed the confidential information that had been provided and invited to submit a formal financial proposal for his services to the Company, which was provided on 27 March 2015. The Company rejected financial proposal by telephone.

12. The Company was informed that the HST Committee panel for evaluation of the Product would be chaired by but was given no further indication as to the other HST Committee panel members. At both the first and second HST Committee meetings (on 23 November 2017 and 20 February 2018, respectively), NICE confirmed on record that no conflict of interest had been declared.

13. However, at the second HST Committee meeting, a senior representative of the Company present at that meeting, recognised and realised that he was the person the Company had sought to engage in 2015.

14. Following the second HST Committee meeting on 20 February 2018, the Company considered the matter further internally and sought legal advice. By letter dated 6 April 2018, the Company notified NICE of the historic relationship between the Company and in the capacity of consultant and expressed its concerns about the failure by NICE (and/or by directly) to disclose any conflict of interest (within the applicable NICE policies or as a matter of law) and the failure by NICE to properly address the impartiality of in his capacity as a HST Committee member.

15. By email on 12 April 2018 and by telephone on 13 April 2018, NICE confirmed to the Company that it had investigated whether or not a conflict of interest existed for the purposes of the evaluation and concluded that it had "*found no evidence of a direct interest - where there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit either financial (a financial interest) or non-financial (a non-financial personal or professional interest)*". NICE also state that it "*confirmed this with the Centre Director*" and concluded that was "*not conflicted for this topic*". Neither the 12 April 2018 email nor the statements made by NICE by telephone on 13 April 2018 addressed the Company's concerns regarding the impartiality of in his capacity as a HST Committee panel member.

16. It is submitted that should not have sat on the HST Committee panel in the first place and, when objection was raised, he should have recused himself for two reasons:

    16.1 First, prior to the HST Committee's assessment of the Product, had received confidential information from the Company including relevant information as to pricing in England and strategy relating to the Company's future dealings with NICE. Having received such information under terms of confidence, there is a real risk of unfairness if contributed to the discussions of the HST Committee.

    16.2 Second, a fair-minded and informed observer, having considered the relevant facts, would conclude that there was a real possibility that was biased against the Company and his views and judgment in the context of his role in the HST Committee were not impartial, given the Company's rejection of his financial proposal to provide consultancy services in relation to the Product (see, by analogy, *Howell v Lees Millais* [2007] EWCA Civ 720 in which the Court of Appeal held that a judge should have recused himself from hearing a case in which one of the parties had previously rejected his application for appointment).

17. In these respects, NICE acted unfairly.

Ground Two: NICE acted unreasonably and/or irrationally in the light of the evidence in treating the ICER, expressed as a cost per QALY, as effectively determinative of its decision not to recommend the Product *(NICE Appeal Guidelines: Ground 2)*

18. Section 46 of the NICE Guidelines provides that, as part of its consideration of value for money, the HST Committee "*must give consideration to the balance of the costs associated with the technology relative to the benefits it provides*". Section 46 further states that, to do so, the HST Committee will consider the incremental cost-effectiveness ratio (the "**ICER**"), expressed as an incremental cost per quality-adjusted life year ("**QALY**") gained. But nothing in the NICE Guidelines suggests that technologies for which the ICER falls outside the normal range cannot, in principle, be recommended. Indeed, HSTs have, in the recent past, been recommended in circumstances where it is not possible to identify a "*plausible*" ICER within the normal range (see NICE's recommendation in respect of Strimvelis for treating adenosine deaminase deficiency-severe combined immunodeficiency).

19. The HST Committee's overall conclusion (at paragraph 4.24 of the FED) was that "*in both the Company's base case and the ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources*". Although some consideration was given to the impact of the technology beyond direct health benefits (see paragraph 4.21), these benefits too were, in the HST Committee's view, "*highly unlikely*" to be "*sufficient to overcome the HST Committee's concerns about value for money ... and also unlikely to bring the most plausible ICERs to a level considered to be an acceptable use of NHS resources*". Likewise, although the Company was willing to enter into discussions with NHS England to cap the financial risk to the NHS by means of a MAA, the HST Committee declined even to permit such discussions again because the ICERs were "*very much above what could be considered an acceptable use of NHS resources*". These passages, and the FED read as a whole, demonstrate that the HST Committee treated the ICER as effectively determinative of its decision.

20. In Standard Technology Appraisals (which are distinct from HST appraisals), it may be appropriate to treat the ICERs in this way but, in the case of this Product, it was not. The ICER was based on clinical trial data based on a quality of life measure called the Dermatology Life Quality Index (the "**DLQI**"). Yet, despite this, the HST Committee itself acknowledged that "*the ERG's exploratory results*" were "*highly uncertain*" because the benefits of the Product "*may not have been fully captured by the DLQI measured in the clinical trials*" (see paragraph 4.23 of the FED). The HST Committee – by its own admission – recognised therefore correctly the inadequacy of the standard quality of life metrics for EPP.

21. In short, the DLQI was not designed to, and does not, capture the impact on quality of life experienced by patients with EPP. The DLQI was designed and validated for dermatological disorders, such as psoriasis and eczema. EPP, by contrast, is a genetic metabolic disorder for which there is no fully validated, disease-specific quality of life specific tool. The same point was made by the EMA at section 2.5.3 of the Assessment Report (see paragraph 26.1 below).

22. The lack of data on the treatment's efficacy has been a continued issue throughout NICE's evaluation of the Product. As the Company has continuously explained, there is, in fact, no health economic evaluation model that is entirely suitable to reflect the complexities in EPP: neither the QALYs tool (as preferred by NICE) nor the DALYs tool is appropriate in this case. This position was accepted by representatives of NICE at the second HST Committee Meeting.

23. Indeed, prior to the publication of the NICE Guidelines, during the course of March 2016 to March 2017, the Company engaged in protracted discussions with NICE regarding the status of the Product as a Standard Technology or a Highly Specialised Technology (or HST). In the event and following significant delay and admitted error on the part of NICE during evaluation of the Company's submitted documentation and evidence, NICE confirmed (in line with the Company's submissions) that the Product should indeed be assessed as a HST and referred back for a second time to the HST pathway. Significantly, a key focus of the Company's review of the relevant guidelines was the suitability (or lack thereof) of the various methodologies and criteria available to and to be applied by NICE for evaluation of an innovative therapy in a most complex disorder.

24. Section 44 of the NICE Guidelines states that the HST Committee's judgment on clinical effectiveness will be informed by certain factors and, the extent to which these factors are taken into account when making such judgments is a matter for the HST Committee's discretion; such discretion is to be exercised in the light of the "*particular features of the condition and the technology*". Sections 36 and 41 of the NICE Guidelines further afford NICE a discretion to take into account the factors it thinks "*most appropriate*" to the particular evaluation in issue and the "*full range of clinical studies*" that have been carried out in respect of that evaluation and is "*not expected to restrict itself to considering only certain categories of evidence*". In this case, however, it is submitted that NICE unreasonably treated the ICER as effectively determinative despite the fact that it had itself accepted that the quality of life instrument and outcomes on which it was based were inadequate for evaluation of the therapeutic modality in EPP.

Ground Three: NICE unreasonably and/or irrationally departed from the conclusions of the EMA in its assessment of the Product without proper justification and without transparency *(NICE Appeal Guidelines: Ground 2)*

25. As noted above, the EMA, via its Committee for Medicinal Products for Human Use ("**CHMP**") granted marketing authorisation in respect of the Product valid from 22 December 2014; such marketing authorisation was granted under "*exceptional circumstances*". On granting marketing authorisation, in its Assessment Report dated 23 October 2014 (the "**Assessment Report**") the EMA concluded that, on the basis of quality, safety and efficacy data submitted to it (via the CHMP) by the Company, the benefits of the Product are greater than its risks and such "*risk-benefit balance*" is favourable to recommend the granting of the marketing authorisation under exceptional circumstances. It is well established (and accepted by the Company) that the function of the EMA is to evaluate the quality, safety and efficacy of drugs and medicinal products and in the light thereof to grant a marketing authorisation. The EMA evaluates efficacy, a component of effectiveness, but not cost or cost-effectiveness.

26. Despite the differing function of the EMA, certain of the conclusions made by it in the Assessment Report are of the utmost relevance in this appeal against the conclusions made by NICE. Although NICE is not bound by the conclusions made by the EMA in respect of the Product, it must explain adequately why it has differed: *Servier Laboratories Limited v NICE* [2010] EWCA Civ 346, at paragraph 52. In this case, NICE unreasonably and/or irrationally failed to do so. In particular:

26.1 The EMA concluded that, owing to the conditioned behaviour and disease characteristic, EPP patients were "*reluctant to expose themselves to light sources during clinical trials*" and, accordingly, there is a "*lack of available scientific instruments to capture and measure the impact and efficacy*" of the Product and "*comprehensive data on the efficacy and safety under normal conditions of use could not be generated*". Further, at section 2.5.3 of the Assessment Report, it is noted that in view of the "*uniquely painful*" and "*debilitating*" nature of EPP, it would, in fact, be contrary to medical ethics to collect evidence of clinical efficacy in a controlled clinical study in EPP patients. One is reminded that the Product is currently being prescribed in Europe and Switzerland *under normal conditions of use*.

26.2 The EMA further accepted in its assessment of the Product that there is no tool appropriate for the effectiveness assessment of EPP so it was necessary to base its conclusions on matters including, but not limited to, expert and patient testimony. The HST Committee similarly accept that there is "*substantial uncertainty*" about how tools could be interpreted in the context of EPP and whether a tool would "*reliably capture all treatment benefits*" (see paragraph 4.10 of the FED). Nonetheless, the HST Committee based its conclusions on the effectiveness of the Product on the ICERs (see above and paragraph 4.23 of the FED), which themselves were calculated using the very tool which the HST Committee had previously recognised was uncertain and

unreliable. In considering other available aspects for the purpose of its conclusions, without justification, the HST Committee rejected evidence of the treatment compliance rate as a "*quantifiable marker of effectiveness*" even though the HST Committee "*appreciated the compliance rate was high*" and "*believed that [the Product] did offer a clinical benefit*". It is submitted that NICE unreasonably and/or irrationally failed to give reasons for departing from the approach adopted by the EMA in its assessment of the Product of utilising and placing reliance on alternative methods available to it (having been presented to it by the Company).

27. The unreasonable and/or irrational failure by NICE to properly consider alternative or exceptional arrangements in respect of the Product is further demonstrated by the examples followed by other European jurisdictions such as [redacted] through various regional and insurance based funding arrangements.

Ground Four: NICE acted unfairly by failing to give the Company an opportunity to discuss and negotiate its proposed MAA to NHS England before presenting it *(NICE Appeal Guidelines: Ground 1(a))*

28. Managed access agreements (or MAAs) are used to enable NICE to recommend technologies which would otherwise not be considered cost-effective and therefore not be recommended. In this case, the Company requested to engage in negotiation with NHS England with a view to reaching a mutually acceptable MAA.

29. There was extensive discussion at the second HST Committee Meeting between the Company and members of the HST Committee and NICE about the possibility of a MAA; this included statements from the representative of NHS England present at that meeting that NHS England would want to negotiate terms of a MAA directly with the Company. There was further such discussion between the Company and representatives of NICE after the second HST Committee Meeting about a possible MAA. As a result of those discussions, the Company understood that it would be given the opportunity to discuss its proposed MAA with NHS England before submitting its final proposal. The Company submitted its proposed Managed Access Agreement on 23 April 2018 (the "**Proposed MAA**").

30. However, in fact: (i) NICE declined to facilitate any discussion between the Company and NHS England on a proposed MAA prior to its submission; (ii) the Company therefore had to submit its proposal without the expected discussion / negotiation with NHS England; (iii) NICE and the Chair of the HST Committee privately consulted with NHS England on the Company's Proposed MAA without disclosing to the Company the substance of any views expressed on behalf of NHS England; and (iv) in the FED, the HST Committee then ruled out the suitability of a MAA on (inter alia) cost-effectiveness (ICER) grounds.

31. This was: (i) procedurally unfair in that it denied the Company the opportunity to formulate a MAA acceptable to NHS England; and (ii) unreasonable and/or irrational in that it foreclosed discussion on the MAA on cost-effectiveness grounds when the point of the MAA was precisely to address (inter alia) cost considerations. Had that discussion been permitted, an MAA acceptable to NHS England might have been proposed; and that fact would itself have been highly relevant to NICE's analysis of cost-effectiveness. As a matter of fact, during the 20 February Committee meeting the honourable senior representative expressed publicly that he wished to see the commercial negotiations to take place between NHS England and the Company without NICE pre-empting outcome or "taking away any further leeway to negotiate a best economic outcome".

32. In the event, a call was facilitated between NICE, the Company and NHS England on 30 May 2018 (after publication of the FED) [redacted]

Ground Five: NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities

33. Patients with EPP are disabled within the meaning of the Equality Act 2010 (the "**Equality Act**"). NICE is a public authority within the meaning of section 29 of the Equality Act. The approach adopted by NICE in the FED, in which ICERs were treated as effectively determinative, amounts to a provision, criterion or practice which puts disabled people with EPP – a condition for which there is acknowledgment by EMA of the lack of adequate scientific instruments, and by NICE of not having a validated, disease-specific quality of life tool – at a substantial disadvantage in comparison with persons who do not have that disability. Indeed, the effect of NICE's approach is to deny treatment to patients with EPP (and other conditions for which no fully validated, disease-specific quality of life measure exists).

34. This being so, NICE was obliged by sections 20(3) and 29(6) of the Equality Act to make reasonable adjustments to its practice. It could have done and could have reasonably been expected to do so by accepting other evidence of the effectiveness of the Product, as the EMA had done, and by recommending the Product subject to an MAA limiting the financial risk to the NHS. However, at no time did NICE make any attempt to make any such adjustments, nor to consider them.

35. Further, NICE has failed to comply with its duty to have regard to the need to eliminate discrimination and advance equal opportunities (such duty as set out in section 149 of the Equality Act); there is no indication in the FED, or elsewhere, that any such regard was given by NICE in its assessment of the Product.

Conclusion

36. For all the reasons set out above, the Company appeals the decision of the FED. We respectfully request a re-evaluation of the Product on the basis of the approach and methods as outlined in this submission. All of our rights remain strictly reserved.

Yours sincerely,

Lachlan Hay
General Manager
CLINUVEL (UK) LTD

Attachment: Appendix 1

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