CLINUVEL

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

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

28 June 2018

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

Dear Dr Benneyworth,

It is apparent during lengthy interaction with NICE that the interests of serving a rare disease patient population are not shared. I take this opportunity to express my astonishment at NICE's unwillingness to find a solution for a small number of patients treated in two expert centres in England whereby budget impact tests have not been exceeded. I am equally taken aback by your correspondence of 28 June 2018 and your emphasis on now needing to adhere to timelines after NICE wasted between 16 and 22 months following an opaque decision and, by NICE's own admission, an error to correctly identify patient data although they had been provided by the Company in candour.

Background

1. We refer to your letter dated 14 June 2018 (the "**Initial Scrutiny**") written in response to the appeal submission dated 6 June 2018 (the "**Appeal**") by CLINUVEL (UK) LTD (the "**Company**") against the Final Evaluation Document dated 15 May 2018 (the "**FED**") published by the National Institute for Health and Care Excellence ("**NICE**"). Unless otherwise stated, capitalised terms in this letter have the meaning ascribed to them in the Appeal and FED.

2. The Initial Scrutiny makes clear that NICE has not properly understood key aspects of the Appeal. This letter is intended to provide clarification and responds to the specific requests in the Initial Scrutiny for further submission. The Company intends, if possible, to further address the statements made by NICE in the Initial Scrutiny and the decision of the FED by way of oral submission at the hearing on 30 July 2018.

3. By letter dated 18 and 22 June 2018, the Company took issue with the scheduling of the hearing during the British summer/school holidays and informed NICE that, owing to the holiday period, key representatives of the Company would not be able to attend the hearing. Accordingly, the Company requested that the hearing date be postponed. By letter dated 20 and 28 June 2018 (and as at the date of this letter), NICE has rejected the Company's request for a postponement. The Company contends that it should seek to include the most knowledgeable individuals on our dossier to represent us, with our legal team central to this. Key members of our team are unable to attend due to summer/school holidays. If you deem it reasonable and fair that the hearing should take place on 30 July 2018, the Company will be required to attend the hearing with professionals who are less familiar with this case and may not be appropriately represented. The Company intends to make further submissions on this issue.

   For ease of review, in this letter, the Company will respond to the points made by NICE in respect of its Grounds of Appeal in the order set out in the Initial Scrutiny; namely: Grounds One and Four (*unfairness*); then Grounds Two and Three (*unreasonableness and/or irrationality*). Ground Five (*exceeded powers*) has been accepted by NICE for consideration at the oral hearing, will be addressed further at that hearing, and has not been addressed in this letter.

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

4. In its Initial Scrutiny, NICE summarise the established test for apparent bias. NICE accept (correctly) that "*it is enough*" that there is a "*possibility*" of bias and that there is no need to show that any possible bias "*in fact made a difference to the decision*" of NICE or the HST Committee. However, NICE go on to ask how the information received by in his dealings with the Company in relation to a potential instruction in or around March 2015 differs from that which was received in his capacity as HST Committee member and to request further submissions from the Company.

5. As described at paragraph 10 of the Appeal, the confidential information provided to in or around March 2015 comprised "*current pricing information relevant to the Product, clinical study results, evidence from ongoing clinical assessments in Europe*" and the Company's "*commercial strategy*" as regards the Product's various regulatory approvals. This included confidential material (particularly as regards pricing and commercial strategy) which no participant in a NICE appraisal would expect to place before the HST Committee or NICE, particularly in circumstances where commercial discussions with NHS England with a view to a MAA could readily be envisaged. For the avoidance of doubt, the confidential information relevant to pricing and commercial strategy was **not** among the information submitted by the Company to the HST Committee. It would plainly be inappropriate for the Company now to provide further details, beyond those set out in paragraph 10 of the Appeal, of the material to which was privy in 2015: the Company was and is entitled to maintain the confidentiality of that material.

6. Insofar as it is necessary to explain why apparent bias arises in these circumstances, an analogy can be drawn with the position of a judge. Suppose a professional person becomes privy, in the course of his profession, to confidential information about a party's commercial strategy; suppose further that the information relates in part to its strategy in contemplated legal proceedings. Could such a person then properly act as a judge or arbitrator in those legal proceedings? We suggest the answer is obvious: he could not. A fair-minded objective observer would conclude that there was a real risk of his taking the confidential information into account in reaching his decision. Nor would the position be any different if the person in question were sitting as one member of a panel of judges or arbitrators.

7. NICE suggests that the Company's complaint of apparent bias rests on two assumptions: firstly, that would recall the information to which he was privy; secondly, that he would "*not honour the undertaking of confidentiality*" given by him to and by way of signing a Confidentiality Agreement with the Company in or around March 2015. As to the first, received the confidential information just under one year before the start of the HST workshop and appraisal in which he participated. There is plainly, at the very least, a real risk that he would recall some or all of the confidential information he had received. As to the second premise, the Company's complaint of apparent bias does not depend on any breach by of his duty of confidentiality. It is obvious that the Company has no way of knowing what was or was not said in private to other members of the HST Committee. But, in any event, it is enough that himself, a member of the Committee, might have been influenced by the confidential information he had seen. As the Court of Appeal's judgment in *Howell v Lees Millais* shows, the Company's rejection of his financial proposal to provide consultancy services, and the possibility that that rejection might have affected his judgment, is a further factor in this case.

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

8. In the Initial Scrutiny of this Ground of Appeal, NICE contends that there was no duty on NICE to facilitate discussions between the Company and NHS England. It is obvious that a MAA, as a commercial negotiation offering, must be drawn up and submitted by the entity seeking that commercial negotiation. The Company has never suggested to the contrary. In this case, however, representatives of the Company actively sought to engage with NHS England and NICE following the second HST Committee meeting on 20 February 2018 with a view to preparing and submitting a MAA, on the understanding that NICE and the HST Committee would welcome one. This understanding was based on public comments made by NICE representatives and HST Committee members at the second HST Committee meeting, as well as discussions with NICE representatives immediately following it.

9. Further to the request in the Initial Scrutiny, the Company has outlined key events and conversations relevant to this Ground of Appeal. Immediately following the second HST Committee meeting, and in a subsequent telephone conversation on 23 February 2018, representatives of NICE confirmed that the Company must await an invitation by NICE for any such commercial discussion with NHS England to take place, and for a MAA proposal to be submitted. NICE also confirmed that an invitation would only follow after NICE had concluded its review and assessed the parameters of any discussion with NHS England.

10. In the event, the Company was not invited to make a MAA proposal by NICE, and instead the draft FED was provided to the Company, without explanation as to why an invitation was not made on either point, on 29 March 2018. Following this, the Company requested an explanation as to why the invitation to submit a MAA proposal was not made and had to request again an opportunity to engage with NHS England. This request was acknowledged by representatives of NICE on a teleconference of 13 April 2018, when an invitation to submit a MAA proposal was also made. Representatives of NICE set a deadline for submitting a proposed MAA of 20 April 2018, which was later extended by mutual agreement to 23 April 2018. During the teleconference of 13 April, NICE made clear that it would facilitate discussions between the Company and representatives of NHS England prior to submission of a MAA proposal. NICE failed to facilitate these discussions, and the Company submitted the Proposed MAA on 23 April 2018. NICE advised the Company that it would consider the Proposed MAA and respond by 6 May 2018.

11. On 10 May 2018, NICE advised the Company by email that NICE needed more time to seek "*advice from NHS England to gain their opinion on the Clinuvel (sic) proposed Managed Access Agreement (MAA) and commercial offer*". In telephone conversations of 10 May 2018 between the Company and representatives of NICE, the Company was advised that NICE were seeking to determine the *"transactability"* of the proposal with NHS England. On 11 May 2018, NICE informed the Company that the Proposed MAA would not be presented to the HST Committee. On 30 May 2018, at the request of the Company, NICE facilitated a teleconference between NICE, the Company and NHS England to discuss the rejection of the Proposed MAA by NICE.

12. The Company was unable to submit its Proposed MAA without prior discussion with NHS England. Had an invitation to discuss matters with NHS England been extended to the Company at the time initially requested, or at any time prior to the main deliberations of representatives of NICE and the HST Committee on the MAA, the Company may have been in a position to come to an acceptable commercial agreement with NHS England (indeed, a MAA may have been accepted). The Company intends to make further oral submissions on this Ground of Appeal at the hearing.

13. Given NICE's clear statement that the Company must await an invitation to submit a MAA, it is unfair and wholly unreasonable and illogical to criticise the Company for submitting its MAA at a late stage in the process, whereby the Company had been precluded from seeking alternative avenues to market the drug during prior interactions with the NICE representative.

14. It is also unclear why, in the Initial Scrutiny, NICE state that the "*Company seems to have seen major difficulties with any MAA*" and that the Company's desire to submit a MAA "*was apparently rather less than enthusiastic*". In various conversations during the course of interactions with NICE the Project Manager representing NICE had emphasised that the Company was not yet in the position to request or submit an MAA. On the contrary to the statements of the Initial Scrutiny, as the above facts show, the Company was at all times willing to engage with all stakeholders relevant to a MAA to facilitate its implementation in the short timeframes eventually provided by NICE and after its invitation to submit a MAA. The Company notes, including in correspondence about the Proposed MAA, that the Product has been made available in other European countries under near-identical terms to those outlined in the Proposed MAA. The Company further notes that a major difficulty with the MAA process as a whole was the unwillingness of NICE to facilitate a discussion with NHS England.

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

15. In the Initial Scrutiny, in response to the Company's contention that the ICER has been effectively determinative of NICE's decision not to recommend the Product, NICE state that there is no evidence in the FED such that the HST Committee was "*unaware that a technology that falls outside the usual ICER range cannot be recommended*". The question, however, is not whether the reasoning in the FED demonstrates a defect in the HST Committee's understanding in the abstract. The question is whether the reasoning in the FED demonstrates a defect in its approach **in this case.**

16. The passages set out at paragraph 19 of the FED do indeed demonstrate such a defect in this case: namely that the ICERs were treated as effectively determinative, even though (as expressly recognised at paragraph 4.23 of the FED) they were based on standard quality of life metrics which were inappropriate for EPP. This is an orthodox irrationality challenge. In the words of Sedley J in *R v Parliamentary Commissioner for Administration ex p. Balchin* (No. 1) [1998] 1 PLR 1, at [27], the reasoning in the FED **in this case** "*did not add up*"; it contained an "*error of reasoning which robs the decision of logic*". Indeed, in the context of the Company's Proposed MAA, by email dated 11 May 2018, NICE use the ICERs to support its contention that the Company's proposal [redacted] is not an "*implementable commercial proposal*". [redacted] The Company intends to make further oral submissions on this Ground of Appeal at the hearing.

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

17. In the Initial Scrutiny, NICE request that the Company clarify "*specifically what conclusion of the EMA NICE has departed from*" and state that, "*if explanation [as to any departure] is needed is it not provided in the FED and in the [NICE] process guides?*". NICE allude to the differing approaches of the EMA and NICE in relation to EPP as being representative of a "*difference of opinion*" and make reference to the fact that the patient and expert testimony, although considered by NICE, was not "*given decisive weight*" in the FED. Again, it is apparent from these statements that the Company's Ground of Appeal as regards the approach taken by NICE in contrast to the EMA has not been properly understood.

18. The Company's position is straightforward, as set out at paragraphs 25 to 27 of the Company's Appeal: the EMA, in recognition of the unique nature of EPP and the lack of available data and appropriate scientific measurement tools, actively departed from its normal, strict guidelines and granted marketing authorisation under "*exceptional circumstances*". In contrast, NICE and the HST Committee based its conclusions on the effectiveness of the Product on the ICERs (see paragraph 4.23 of the FED), in accordance with the normal NICE Guidelines, and failed to give reasons for departing from the approach of the EMA (which, as set out at paragraph 26.2 of the Appeal, was to rely on alternative, effectiveness-based tools and patient and expert testimony). The Company intends to make further oral submissions on this Ground of Appeal at the hearing.

Conclusion

19. For all the reasons set out above, the Company restates its Appeal submission and appeals the FED. The Company will make further submissions at the oral hearing. All of the Company's rights remain strictly reserved.

Yours sincerely,

Lachlan Hay
General Manager
CLINUVEL (UK) LTD