28 June 2018

Dr Rosie Benneyworth

Vice Chair

National Institute for Health and Care Excellence

10 Spring Gardens

London SW1A 2BU

Dear Dr Benneyworth

Re: Final Evaluation Determination – Afamelanotide for treating erythropoietic protoporphyria (ID927) / Initial scrutiny

Thank you for your letter of 14 June / initial scrutiny regarding IPPN's appeal against the above Final Evaluation Determination.

IPPN would like to use the opportunity to comment on the initial scrutiny letter in order to elaborate on or clarify our points raised and hope to convince you to reconsider your decision to not refer in our opinion crucial appeal points to the Appeal Panel.

Ground 1: In making the assessment that preceded the recommendation, NICE has: (a) failed to act fairly

1a.1 The Committee failed to act fairly by not acknowledging the evidence provided in patient testimonies and by expert physicians on the overwhelming clinical benefit [of treatment]

By not acknowledging, not actively using and, effectively, simply ignoring crucial evidence provided by stakeholders with the greatest knowledge and experience on the treatment effectiveness of afamelanotide, we maintain our position that NICE not only provided an unreasonable recommendation (reason 2), but also acted unfairly. Patient testimonies and inputs all independently point to a transformative treatment effectiveness, most prominently to the dramatic increase in light exposure times that patients are able to experience. IPPN has also provided the scientific explanation on why a standardised trial outcome on minutes per day is not a realistic and fair measure (it is an average value calculated including all rainy days and days spent entirely indoors – A standardisation on minutes per day when assessing a treatment against headache would rightfully be considered as nonsensical). In addition, IPPN pointed out that the standardised trial results have to be compared to the average time a "normal" person spends outdoors, which we showed as falling in the same range as patients treated with afamelanotide. In spite of all this and although the committee pointed out that the real benefit is not accurately quantifiable but likely to be underestimated from the standardised clinical trial data, the committee in its final evaluation maintains its previous opinion that the effectiveness is only a "few minutes" additional sunlight exposure.

If the arguments put forward by the two groups of stakeholders with the greatest treatment experience and the explanation on why the trial outcome might appear small but in fact is substantial are only mentioned *pro forma* in the Final Evaluation Determination document (FED) but not reflected in the recommendation, which maintains that the "Clinical trial results suggest small benefits", then the obvious conclusion is that the arguments have been ignored, even if the committee state otherwise. By accepting all three appeal points on the unreasonable recommendation in the light of the provided evidence (2.1; 2.1 and 2.3), the Vice-Chair agrees that the provided evidence is not adequately reflected in the FED, which in our opinion equates to an act of unfairness toward EPP patients, and we therefore maintain our position, asking to refer our arguments to the appeal panel under appeal ground 1a (unfair action of the committee, and even 1b, abuse of power).

1a.2 The committee failed to act fairly by omitting to discuss the evidence and the arguments provided by the consultees in a scientific and transparent way

We agree with the Vice-Chair that our complaint under this point was too general and does not need to be referred to the appeal panel. We however maintain our position on

the more specific observations made in point 1a.1 and 1a.3, which we ask to be referred to the appeal panel (under appeal ground 1 and not 2).

1a.3 The committee failed to act fairly by choosing an approach for its assessment which knowingly underestimates the benefit of the treatment and therefore actively discriminates against EPP patients

As detailed under 1a.1, as the committee did not consider nor use the evidence provided, it is not possible that they acted in the way described by the Vice-Chair, i.e., that "The intent is to ensure that while the model may underestimate benefits, the committee will not" (letter of initial scrutiny, p. 3). We therefore maintain that by choosing an ERG model which knowingly "may have underestimated the real-life benefits of the afamelanotide treatment" (FED p.16) and at the same time ignoring the real-world evidence provided during the consultation period, the committee unfairly discriminates EPP sufferers compared to other, more appropriately evaluated applications for reimbursement. We maintain our position and ask this point to be referred to the appeal panel.

1a.4 The committee failed to act fairly by denying a managed access agreement based on the same arguments put forward on why it had already rejected a recommendation [to use]

We maintain that by denying the possibility for a managed access agreement (MAA) the committee acted unfairly. The committee concludes that "data collection in the context of a MAA was unlikely to resolve the existing uncertainties in the evidence base because it was likely to face challenges similar to those faced in the trials" (FED p. 21). The committee's conclusion is in stark contrast to what is effectively already occurring in European countries, where patients have access to afamelanotide and the marketing authorisation holder needs to comply with a Post-Authorization Safety Study (PASS), mandated by the European Medicines Agency (EMA) and which in the case of afamelanotide also includes data collection related to treatment effectiveness. As a matter of fact, the data of the first year PASS regime was already submitted to EMA for evaluation and led to a positive recommendation by EMA for continuation of marketing authorisation. We therefore regard the argument that the uncertainties in demonstrating the treatment effects in the post-marketing phase make an MAA impossible as not valid and maintain that the committee is acting unfairly by not giving this opportunity to EPP sufferers in England, denying them strictly controlled and controllable access to the only treatment for their severe condition. In fact, we are highly concerned by what we consider a systematic refusal to give patients any option to access afamelanotide and by the implacable maintenance of the committee's initial conclusions, which have not budged by a millimeter after all the input provided by expert stakeholders. Frankly, as patient community we feel that we are only being invited to provide our input in order for

NICE to check the box of patient inclusion and we request that this point be referred to the appeal panel.

1a.5 The committee failed to act fairly by not ensuring full representation of the patients voice at the committee meetings

As IPPN was unfairly denied participation in the entire evaluation process and prevented form providing unique insights (appeal point 1a.6, which was accepted as a valid appeal point by the Vice-Chair), we conclude that full representation of the patient voice was unfairly denied by the committee. As detailed under appeal point 1a.6 NICE did make procedural mistakes, like not inviting IPPN to meetings after initially accepting the organization as stakeholders in the scoping workshop, therefore negative consequences like the one detailed in point 1a.5 are directly caused by this procedural omission by NICE. While we are not alleging an intentional omission, it is important to mention that we had to engage in an intense exchange with NICE officials in order to be re-admitted to the discussions. These exchanges bordered to deliberate chicaneries. We had expected immediate recognition of the procedural mistake and were surprised by the response, which albeit politely still denied our participation. Without our persistence, we would not have even been able to provide our written comments and, despite our insistence, we were still denied participation as stakeholder at the February 2018 committee meeting. This is not acceptable and is unfair: A patient group, or any other stakeholder for that matter, should not have to be subjected to such chicaneries after NICE's own procedural mistake. We should have been admitted as fully participating stakeholder, with the ability to both submit written comments and to actively participate at committee meetings in order to orally elaborate on our comments and provide needed clarifications. We therefore request this point to be referred to the appeal panel.

1a.7 The Committee failed to act fairly by not declaring a conflict of interest of a lead committee member

We are not alleging that has a conflict of interest (see original Appeal document: "1a.7 The committee failed to act fairly by not declaring a potential conflict of interest of a lead committee member") but are asking to give him the opportunity to declare that he has none since we consider a potential conflict of interest to subsist. In fact, employer, Biogen Idec, is active in disease areas different from EPP that could also benefit from afamelanotide's biological properties and therapeutic efficacy, as we detailed in our appeal. Should there be a potential conflict of interest, this may bias assessment of afamelanotide. A statement by that such a conflict of interest does not subsist would suffice to warrant the committee's integrity, and by reflection NICE's own integrity, and we therefore request that this point be referred to the appeal panel.

Ground 1: In making the assessment that preceded the recommendation, NICE has: (b) exceeded its powers

1b.1 The Committee exceeded its powers by basing its decision on opinion rather than on evidence

We strongly disagree to refer to patient and physician experience as "opinion" (letter of initial scrutiny, p. 4), and insist that a) real-world evidence provided by patients and physicians has to be taken into account and b) that the evidence provided contains quantifiable outcomes collected by partly validated tools like the disease specific quality of life questionnaire "EPP-QoL". As the Vice-Chair accepted our appeal points under ground 2, i.e., that the recommendation is unreasonable in the light of the evidence submitted to NICE, it is inconsequent to not also accept that the committee exceeded its powers in not providing a scientific coherent explanation for their decisions. If patient and expert physician input is considered as "opinion" which can arbitrarily be overruled by the committee, then the entire consultation efforts are reduced to a pointless exercise.

We maintain that the committee should have based their decisions on evidence and that by not doing so they exceeded their powers. We therefore ask that this point be referred to the appeal panel.

1b.2 The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward

Our point about the arbitrary conclusions of the committee relates to their succinct statement that "No potential equalities issues have been identified". We maintain that EPP patients have not been given equal opportunities as compared to other patient communities because the committee is ignoring evidence which adds value to the assessment of the therapeutic intervention in EPP. As opposed to other disease areas with more established and clearer assessment measures, EPP is at a disadvantage because of its rarity and related lack of knowledge and experience with it. Therapeutic interventions in EPP are not easily measured, both for the lack of any measurable pharmacodynamic read-outs and because of the multiparametric nature of the factors which can precipitate a phototoxic reaction. By not considering these factors and ignoring the existing quantitative evidence on afamelanotide's effectiveness, we believe that the committee is discriminating against EPP patients compared to other patient communities affected by diseases with a stronger knowledge foundation and measurable intervention outcomes. We as EPP patients feel doubly affected: Unlike these other patient communities, not only do we suffer from a complex, poorly understood and difficult to measure ultra-rare condition, but we are also confronted by the inexorable firmness of NICE of not including evidence of value to assess the

effectiveness of afamelanotide. We therefore find this point to be valid for further referral to an appeal panel.

1b.3 The committee exceeded its powers by reassessing the regulatory conclusions of the [EMA]

We believe that the committee should have built on EMA's regulatory decision rather than trying to duplicate EMA's assessment of the clinical effectiveness of afamelanotide without giving any plausible explanation for their conclusions. Therefore, we disagree with the Vice-Chair's statement that "The EMA has no remit at all (still less "overriding authority") in decisions as to what products should be reimbursed in a national health system, indeed, that decision rests with member states and not at the EU level". To underscore our disagreement, we refer to the case *R (Servier Laboratories Limited) v National Institute for Health and Clinical Excellence & Anr* [2010] EWCA Civ 346 [1].

In this case, "The court noted in particular that these issues would very likely have been considered and dismissed by the EMA and so, if NICE considered any of these issues material, it should have explained its reasoning for deciding differently to the EMA." [2]

"This decision is particularly interesting as the Court of Appeal was clearly willing to exert a high level of scrutiny over the decision of a specialist body and was unwilling to accept a generic explanation for NICE's decision. The decision emphasises the importance for public bodies of providing sufficiently cogent reasons for their decisions, in particular where those decisions adopt a different approach to that taken by other expert bodies in the same field." [2]

EMA in its approval under exceptional circumstances argued that the treatment effects are not accurately quantifiable, but that it would be unethical to not grant access to the afamelanotide treatment because EPP is a debilitating and severely painful condition and patients and expert physicians consistently report transformative effects on quality of life.

Similar to the court case mentioned above, NICE is assessing afamelanotide differently from EMA, without however providing a plausible explanation for why they decided to do so. By unreasonably assessing the treatment effects as small (instead of "not quantifiable", ground 2), the committee make the afamelanotide treatment for EPP appear less effective/beneficial and, based on this conclusion, unfairly assess the treatment as not providing sufficient value for money.

We therefore maintain that NICE abuses its powers by not building on EMA's assessment and so discriminates against EPP sufferers, and we ask that this point be referred to the appeal panel.

References:

[1] Case *R (Servier Laboratories Limited) v National Institute for Health and Clinical Excellence & Anr* [2010] EWCA Civ 346:

http://www.bailii.org/ew/cases/EWCA/Civ/2010/346.html

Last accessed: 28 June 2018

[2] NICE, but unreasonable: the Court of Appeal quashes a decision of NICE on the grounds that it is inadequately reasoned. By: Herbert Smith Freehills LLP

https://www.lexology.com/library/detail.aspx?g=5a54d4b6-74d5-4d53-9c8a-015966f4f0f3.

Last accessed: 28 June 2018

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1; 2.2.; 2.3.

We thank the Vice-Chair for assessing our three points under ground 2 ("The recommendation is unreasonable in the light of the evidence submitted to NICE") as valid and for referring them to the appeal panel.

Yours sincerely

Dr. Jasmin Barman-Aksözen

Co-founder and Vice-Chair of the International Porphyria Patient Network

Co-founder and Scientific Advisor of the Swiss Society for Porphyria

Dr. Rocco Falchetto

Co-founder and Chairman of the International Porphyria Patient Network

Co-founder and Chairman and of the Swiss Society for Porphyria