

**British Association of Dermatologists**  
**Response to NICE Highly Specialised Technology Appraisal**  
**Final evaluation determination:**  
**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

On behalf of the British Association of Dermatologists (the BAD), thank you for the opportunity to comment on this Final Evaluation Determination. We wish to request an appeal on Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

1. Recommendation

Page 1: *“Clinical trial results suggest “small benefits” with afamelanotide.”*

- (i) The NICE committee makes an incorrect assumption that the extra number of minutes in sunlight gained by EPP patients on afamelanotide is a “small benefit”. The average number of minutes experienced without pain increased markedly in the trials; this is clinically as well as statistically significant. Moreover, data on time gained should be considered in the context of several factors including number of days the patients underwent sun-exposure, and the number of minutes an average person (healthy, indoor worker) spends in sunlight. However, the NICE committee misinterpret that this benefit is small, and do not take the relevant scientific literature or photobiology clinical expert opinion into account.
- (ii) The NICE committee have made the assumption that the dermatology life quality index (DLQI) is appropriate for use in clinical trials of treatment of EPP, and that it is reproducible over time in this disorder. They repeatedly refer to the Holme et al. paper as justification that the DLQI is an appropriate tool for assessing quality of life (QoL) in EPP in clinical trials. However, Holme examined DLQI on one occasion only in each patient. The misgivings of patient and clinical experts regarding appropriateness of this tool were disregarded, and the complexity of the situation not taken into account in NICE’s quantitative assessment of impact of treatment on QoL in EPP. Patients with this unique disorder have to unlearn their long-lived fear and anxiety related to sunlight exposure, thus QoL can show a lag in its full improvement.
- (iii) The patient testimony suggests large and significant benefits with afamelanotide. Trials in this unique and complex condition face several photobiological confounders, together with the small number of patients available in whom to refine assessment tools. Despite all these challenges, the trials show improvements in outcome measures that are clinically significant to patients as well as statistically significant. It is unreasonable to regard these as “small benefits”.

There is a new factor which has come to light regarding the issue of QoL tools suited to picking up therapeutic effects in EPP. We have just come across a piece of research which has studied different QoL measures in EPP (Naik H et al., International Congress on porphyrins and porphyrias 2017 <https://icpp2017.org/plenary-lectures/>, abstract attached) which indicates that the PROMIS-57 validated QoL scale is a promising and potentially more sensitive QoL tool than those previously used in EPP. We await the publication of a full paper by the authors but see this as a potentially important new piece of information which may influence NICE’s decision.

Page 2: *“This is despite [NICE] taking into account the impact the condition and technology have on QoL, disability, etc.”*

The unique phototoxicity disorder that is EPP, and the multidisciplinary science (photobiology) regarding sunlight exposure and impact of non-ionising radiation on humans, are very complex areas. The BAD would argue that perhaps the NICE committee does not have the requisite expertise and understanding to fully take into account the impact of the condition and technology. This has unfortunately led to several incorrect assumptions being made to the disadvantage of the case for approving the treatment, including the NICE committee opinion that a clinically significant increase in exposure time is a “small benefit”. This has contributed to the committee making an unreasonable decision.

The new information detailed above about new QoL tools in EPP is also significant.

Page 2: *“cannot be recommended for routine funding in the NHS”*

The BAD previously suggested that if the routine funding route was not able to be recommended by NICE, then a Managed Access Agreement (MAA) should be considered. A potential MAA was then positively discussed towards the end of the February meeting. It was noted that the MAA would be discussed further at a meeting to include NHS England, the Company and the BAD clinical experts; however, the BAD clinical experts have not been invited to any meeting to discuss this further. The assistance and insight our clinical and photobiological expertise can give has been overlooked. In addition, the new information about new QoL tools in EPP detailed above means that NICE should re-evaluate their decision.

## 2. Consideration of the Evidence

- (i) Page 3: *“the committee took into account the full range of factors”*. Also addressed under 1. Recommendation. Page 1: *“Clinical trial results suggest “small benefits” with afamelanotide”* and Page 2: *“This is despite taking into account the impact the condition and technology have on QoL, disability, etc.”*

The NICE committee have not taken into account the full range of factors.

Being unfamiliar with considering human sun-exposure time data, the NICE committee makes an incorrect assumption that the extra number of minutes in sunlight gained by EPP patients on afamelanotide is a “small benefit”. However, the average number of minutes experienced without pain increased markedly in the trials; this is clinically as well as statistically significant. Moreover, data on time gained should be considered in the context of several factors including number of days the patients underwent sun-exposure, and the number of minutes an average person (healthy, indoor worker) spends in sunlight. However, the NICE committee rely on their opinion that this benefit is small, and do not take the relevant scientific literature or photobiology opinion into account.

We re-iterate that the unique phototoxicity disorder that is EPP, and the multidisciplinary science (photobiology) regarding sunlight-exposure and impact of non-ionising radiation on humans, are very complex territories, and that the new information which has just come to our attention, subsequent to the last NICE meeting, suggests that better tools for QoL measurement in EPP may now exist.

The patient testimony suggests large and significant benefits with afamelanotide and this is strong evidence that not all factors have been taken into account.

- (ii) 4.7, page 8-9. *“The committee concluded that the trials had shown relatively small benefits”*

We re-iterate that the NICE committee has made an incorrect assumption that benefits are small. Data quoted here by NICE show >7 fold and 1.7 fold increases in time outdoors (CUV029 and CUV039, respectively) and a reduction by approximately half of phototoxic reactions. These are clinically significant and should not be dismissed as a small benefit. This is confirmed by patients, who found the gain in time without pain, and the reduction of phototoxic episodes, highly clinically important to them.

The patient testimony suggests large and significant benefits with afamelanotide during the trials.

Please see extended comments above under 1. Recommendation. Page 1: *“Clinical trial results suggest “small benefits” with afamelanotide”* and Page 2: *“This is despite taking into account the impact the condition and technology have on QoL, disability, etc.”*

- (iii) Page 12-13, 4.11: *“It [DLQI] has been shown to be sensitive to the impact of EPP on people with the condition”, “The committee concluded that results based on DLQI were relevant to its decision making”.*

We re-iterate that the NICE committee have made the assumption that the DLQI is appropriate for use in clinical trials of treatment of EPP, and that it is reproducible over time in this disorder. They repeatedly refer to the Holme paper as justification that the DLQI is an appropriate tool for assessing QoL in EPP in clinical trials. However, Holme examined DLQI on one occasion only in each patient. The misgivings of patient and clinical experts regarding appropriateness of this tool were disregarded, and the complexity of the situation not taken into account in NICE’s quantitative assessment of impact of treatment on QoL in EPP. Patients with this unique disorder have to unlearn their long-lived fear and anxiety related to sunlight exposure, thus QoL can show a lag in its full improvement.

Please note the potentially important new issue regarding new tools to measure QoL in EPP which has been identified by us subsequent to the NICE meetings and reports.

- (iv) 4.22 – 4.24, page 21-23. Managed Access Agreement  
*“The committee considered that an MAA would not have the plausible potential to reduce the uncertainties identified during the evaluation or to reduce the financial risk to the NHS”*

We re-iterate that the BAD previously suggested (after the first negative evaluation by NICE) that if the routine funding route was not ultimately recommended by NICE, then a Managed Access Agreement (MAA) should be considered. A potential MAA was then briefly though positively discussed towards the end of the February meeting. It was noted that the MAA would be discussed further at a meeting including NHS England, the Company and the BAD clinical experts; however the BAD clinical experts have not so far been invited to any meetings to discuss this further. This would have assisted discussions, including exploration of the nature of the data collection during the MAA. The insight and assistance our clinical and photobiological expertise can give in developing a MAA proposal is overlooked.

The research (details above) regarding new tools to measure QoL in EPP was not included in the previous discussions and negotiation about an MAA. Clearly, this new research may be relevant to those discussions and considerations.

- (v) *“It (the Company) was willing to enter into discussions with NHS England to cap financial risk to the NHS. The committee considered this in the context of the cost-effectiveness estimates discussed in section 4.20...”*

From the several issues discussed above, including committee opinions on “small benefits”, and confounding behavioural and photobiological factors, the cost-effectiveness estimates are unsound and should not be relied upon here. There is an acknowledged unmet need for treatment of EPP, and there is a small number of patients in England. Realistically, a number of only up to ~200-250 patients are likely to start treatment during a 5-year period. The company was willing to enter into discussion with NHS England to cap financial risk and there appears no credible reason why this does not go ahead.

In summary, we consider that the evidence given to NICE overwhelmingly means that the drug should be authorised for funding and provision by the NHS without the need for further trials or MAA. However, if an MAA were to be pursued, new research about new tools to measure QoL in EPP, not included in the previous MAA discussions and only becoming known to us, further strengthens the case for an MAA.

Overall, we feel that NICE has been unreasonable in its assessment of the benefits, clearly exhibited by the patients and accepted by EU regulators; the use of an unreliable cost-effectiveness assessment; unwillingness to accept a capped expenditure, and further in not allowing a discussion between the clinical experts, NHS England and the company to develop a MAA.

**Dr Pamela McHenry, Dr Robert Sarkany and Prof Lesley Rhodes**  
On behalf of the BAD’s Therapy & Guidelines sub-committee