British Association of Dermatologists
Response to NICE Highly Specialised Technology Appraisal
Afamelanotide for treating erythropoietic protoporphyria [ID927]

On behalf of the British Association of Dermatologists, thank you for inviting us to the NICE meeting in order to address the upheld appeal points in the case of afamelanotide.

1) **Upheld Appeal Ground 1a.1: The committee failed to act fairly by demonstrating consistent discrimination against IPPN as a stakeholder group**

   We look forward to IPPN taking a full part in this NICE meeting. We strongly agree with the Appeal Panel that, given the extensive use, and much greater experience, of afamelanotide in treating EPP patients in other countries outside England (including Italy, Switzerland and several other countries), their long-term experience of treatment with afamelanotide in a real-world setting, their experience and their testimony is crucial to this process. With IPPN represented, NICE will have the opportunity to be provided with additional information about patients' experience from long-term treatment with afamelanotide.

2) **Upheld Appeal Ground 1b.1. (IPPN)**

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

   And upheld Appeal Ground 1b.1 (CLINUVEL (UK) Ltd): NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities

   Although these upheld appeal points were presented by IPPN and Clinuvel, the BAD strongly agrees with the Appeal Panel's decision and we have specific criticisms of NICE's qualitative evidence analysis methodology. It is critical that NICE has not followed its own procedure in terms of how it considers evidence in cases, like this, where the disease is rare and where the existing quality of life issues measures do not fully capture the quality of life issues in the disease. Specifically, NICE has been found by the Appeal Panel to have ignored its own 'Interim Process and Methods of the HST Programme' guidance, paragraph 41:

   "The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology being evaluated or are familiar with the relevant condition. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions."

   This is a critical point in this case where the ICER has been used alone in determining the NICE Panel's decision, in a situation where ICER was clearly inadequate and where NICE's own guidance required them to take the qualitative evidence into account in making their decision. In this case, the qualitative evidence from patient (and also physician) testimony was of a striking and dramatically effective therapeutic effect. It is critical that NICE's re-evaluation of afamelanotide, in light of the Appeal Panel's decision, must take a proper account of the qualitative evidence. Formal Qualitative analysis, by methodology including Framework Analysis, is a well-established core set of methodologies in the Social Sciences and in Health Psychology. NICE has previously made no attempt to formally analyse the extensive qualitative interview evidence with which they were presented. NICE has never

indicated that they have sought out any Qualitative Analysis expertise at all, from a Health Psychologist or other relevant expert. NICE was unable to answer the question posed during the Appeal Hearing by Dr Sarkany as to what methodology they had used to objectively assess the qualitative evidence. NICE was also unable to answer the question as to how the analysis of this evidence was incorporated into the NICE Panel's decision. In fact, senior members of the NICE panel and NICE organisation, during the previous meetings, made it clear on several occasions that their decision was made entirely on the basis of the ICER calculation. In the light of the Appeal Panel's decision against NICE on this point, the BAD requests that 1) NICE agree to use a recognised Qualitative Analysis methodology with the expertise of Qualitative Analysis Experts to formally analyse the qualitative evidence presented to them by patients and physicians in the previous hearings, and that these Experts can request further qualitative evidence as required 2) NICE specify, create and use in this case a transparent methodology which enables formally analysed qualitative submitted evidence to be formally incorporated into the process by which the decision is made. This will enable NICE to comply with paragraph 41 of their own guidance.

3) **Upheld Appeal point Ground 2.2: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide (This appeal point was named BAD 2.1 in initial correspondence and during the hearing)**
And Appeal point Ground 2.3: NICE is unreasonable to conclude that clinical trial results suggest "small benefits" with afamelanotide (This appeal point was named BAD 2.5 in initial correspondence and during the hearing)
And upheld Appeal point Ground 2.2: The evidence provided shows that the benefit is significant and not small, as assessed by the committee (This appeal point was named IPPN 2.1 in initial correspondence and during the hearing)

The BAD notes that the Appeal Panel upheld our Appeal on this crucial issue. Specifically, the BAD disputes the committee's view that the clinical trial results suggest "small" benefits with afamelanotide. The average absolute benefit of afamelanotide compared with placebo was approximately 10 minutes per day of additional time in the sun (15 minutes for placebo, 25 minutes for afamelanotide). This is meaningful as it increases the average time spent by patients with EPP who are on treatment to the expected level for this measure. Data presented by Professor Rhodes has shown that healthy indoor workers spend an average of only 22 minutes outdoors between 10 am and 3 pm on summer weekdays.[1] Several publications also show that time spent outdoors throughout the day (6 am to 8 pm) by the average person is of the order of minutes, not hours, i.e. minutes are of consequence: minutes matter. Moreover, it should be noted that time spent in direct sun may be less that time spent outdoors. The figure of approximately 10 minutes extra per day of sun exposure represents an average daily figure across all days in the trial (including for example rainy days), so patients must have spent a longer time in the sun on more days than this figure would suggest. We note the testimony of James Rawnsley, for IPPN, at the Appeal Hearing, who explained that for a patient with EPP, a small absolute change in the number of minutes in the sun could be life-changing. He commented that when he took part in the trial he was able to spend a whole day outside in the sun without any reaction, but that sometimes the feedback in his trial diary about how much time he had actually spent in the sun appeared less positive because of poor weather or his own work commitments. Other patients have made similar observations to us, and to the NICE Committee in the previous meetings. The observational study by Biolcati *et al*. (2015) may have been uncontrolled, but it still found

[1] Webb AR et al. The role of sunlight exposure in determining the vitamin D status of the UK white adult population. Br J Dermatol 2010; 163: 1050-5.

improvements in quality of life measured by the EPP-QOL from 32% to 74% in the first 6 months of treatment.

We will let the Appeal Panel's highly critical judgement of NICE on this point speak for itself, when the Appeal Panel judged this issue of NICE describing the benefits of afamelanotide in EPP patients as 'small'. The Appeal Panel said:

"Whilst the panel noted Dr Jackson's comment that the term "small benefits" was intended to refer to the randomised trial results rather than the overall benefit of treatment, it also noted that this term was used repeatedly both in the FED and during the hearing. The panel was persuaded by Professor Rhodes' argument that whether an increase of 10 minutes represents a small or a large change can only be interpreted with regard to the normal range for this measure. The panel noted that FED paragraph 4.7 cites differences in the amount of time spent in daylight and decreases in phototoxic reactions that would not necessarily sound small to someone reading the document. The panel judged that describing these differences as small lacks face validity….. Overall, the panel concluded that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide."

The BAD notes that evaluation of points (2) the qualitative evidence and (3) the size of the benefit would be assisted by participation in the forthcoming NICE meeting of a clinical expert with broad and long-term experience of prescribing afamelanotide for EPP patients, i.e. in a real-world setting, particularly Professor Elisabeth Minder, Zurich, senior author of Biolcati *et al.* (2015) (Elisabeth.Minder@triemli.zurich.ch). Professor Minder would be willing to attend the meeting. This is important and entirely consistent with participation of the international patient group (IPPN) in point (1) above.

Prof Nick Levell, Dr Robert Sarkany and Prof Lesley Rhodes
On behalf of the BAD's Therapy & Guidelines sub-committee