

**British Association of Dermatologists**  
**Response to NICE Highly Specialised Technology Appraisal**  
**Evaluation Consultation Document:**  
**Afamelanotide for treating erythropoietic protoporphyria [ID927]**

On behalf of the British Association of Dermatologists (BAD), thank you for the opportunity to comment on this Evaluation Consultation Document.

**Has all of the relevant evidence been taken into account?**

The expert and patient testimony has a prominent role in the evaluation of this treatment. That testimony has been taken into account in terms of the panel's response as human beings to the physicians and patients, but not for the evaluation of cost effectiveness. We acknowledge that this is difficult, and realise it may be challenging to do technically. However, we feel that if one did/could quantify "testimony" or "non-clinical trial data" (since the testimony shows such a dramatically greater efficacy than the trial data), it would result in a cost/QALY that would be fundable by NICE.

We also think that part of the problem is that the trials picked up *some* of the efficacy but not all of it, which has led to the high cost/QALY. We note that patient and physician testimony played a significant role in being considered along with the trial data, in decisions concerning the licensing of this drug. We are aware that the situation with considerations of funding may be different from those faced by a licensing body but wonder if the expert team at NICE can think of a way of factoring this in.

It is perhaps not surprising that the clinical trials have picked up a therapeutic effect, but not the full dramatic therapeutic effect, which was reported by patients and their physicians, to the NICE committee. The obstacles in conducting these trials were huge, both because of the challenges of dealing with a rare disease, and the difficulties regarding the measures and metrics used as endpoints.

A further major challenge, that was not discussed at the NICE meeting, is the influence that seasonality of EPP has on its impact on quality of life and clinical scoring within clinical trials. As trials plan a springtime start (before patients face their major sunlight challenges, and so that patients are treated across the summer months) patients enter the trials with a low baseline clinical score and low impact on QoL as their condition is less severe at that time, with a seasonal worsening of scores during the trial as they go into the summer. Although the trials are randomised and controlled, this seasonal variation in severity is likely to undermine the full assessment of efficacy.

There is also further evidence relevant to the DLQI to take into account. At the meeting there was much discussion, and questioning of a clinical expert, as to the potential reasons for the difference between the DLQI findings in the Holme *et al. Br J Dermatol* 2006 study (high DLQI score) and the EPP clinical trial in the *New Engl J Med* 2015 (lower baseline score). The clinical expert has examined the Holme paper subsequently and found an important aspect of the methodology was missing from the paper; she has personally contacted the paper's senior author who had also noted the omission, and provided the information that the DLQI was collected (by the junior researcher on personally visiting the patients) over the spring and summer months, i.e. predominantly when the patients would be most affected. This contrasts with the EPP clinical trials, where the treatment was aimed to start before the patients developed seasonal worsening.

**Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?**

Please see the response above.

**Are the provisional recommendations sound and a suitable basis for guidance to NHS England?**

We think the provisional recommendation is the wrong decision for patients with EPP. It is a deeply frustrating one and a deeply frustrating situation, for the patients, and physicians. If NICE could find a way of including/quantifying testimony from patients and physicians in the cost effectiveness calculation in some way, and potentially of quantifying the impact of the many unique confounding factors affecting assessment of this disorder, this would be invaluable.

If the funding cannot be made available in the 'classical' way, we request that consideration should be given to creating a 'managed access scheme' or similar. People with EPP could be treated during an agreed assessment period (e.g. at least 2 consecutive years) for further data collection. This could potentially be done in specialised centres in Manchester (Salford Royal) and London (Guy's & St Thomas') which would also aim to help people with EPP alter their behaviour – "unlearning" a lifetime of avoiding the outdoors due to the severe pain endured), one of the factors that has probably contributed to the mismatch between the trial data and the patient testimony.

The further data collection would focus on the lessons learned from the trials in order to collect information that more fully captures therapeutic effects by taking into account the following considerations:

- additional seasonality consideration makes it challenging to capture the full benefit of treatment using generic assessment tools, especially combined with the significant others that were discussed at the meeting, including the need for a specific assessment tool for this complex skin/metabolic/apprehension-avoidance condition that appropriately encompasses the pivotal impact of sunlight
- small differences in ability to tolerate sunlight exposure making major differences to patients
- understandable hesitancy in sunlight exposure during limited duration trials due to learned behaviour following experience of earlier severe pain attacks, and time taken to adapt.

**Additional comments:**

There are issues around the assessment of orphan/rare diseases by standard scoring and costing models and perhaps these have contributed to the problem. Is there more scope to factor in a multi-dimensional assessment of such conditions, where it was understood that they may not always fit standard models? We are aware that the measure used is cost effectiveness per patient. Nevertheless, we would like to make the obvious point that EPP is a rare condition, so that the total cost of treating all the EPP patients in the UK with afamelanotide would be relatively low.

**Dr Pamela McHenry, Dr Robert Sarkany and Professor Lesley Rhodes**

On behalf of the BAD's Therapy & Guidelines sub-committee