British Porphyria Association

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Dr Rosie Benneyworth
Vice Chair
National Institute for Health and Care Excellence
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7 June 2018

Dear Dr Benneyworth

RE: Final Evaluation Determination – Afamelanotide for treating erythropoietic protoporphyria, issue date: May 2018

The British Porphyria Association (BPA) is dismayed at NICE's final decision to not approve Afamelanotide on the grounds of the treatment not offering sufficient value for money.

The BPA is not looking for NICE to approve Afamelanotide 'at any cost'. However, we do believe there are sufficient grounds to appeal the current recommendation and ensure that EPP patients in the UK are not denied access to what many European patients report as a life changing treatment.

We appeal the decision on Ground 2.

Ground 2: Point 1

In initial submissions and, more significantly, throughout the consultation process, it has become clear that there is a huge gulf between the results of clinical trials that are communicated by NICE as "*small*" (FED p1; 4.7), and the benefits that patients in receipt of Afamelanotide repeatedly report as life changing. This is iterated in (4.9) as reported by a UK patient, but perhaps more significantly by numerous European patients.

Indeed, NICE themselves recognise (FED p.1) that "*The true benefit of afamelanotide has, however, not been quantified.*" Despite this recognition, the FED recommendation has been made primarily on the grounds of the ERG economic analysis that was published before this information came to light, which we consider to be unreasonable.

Ground 2: Point 2

The economic decision has been made using a flawed model that means the decision is unreasonable in light of the evidence submitted to NICE.

Conclusions reached by the committee largely ignored valid submissions from patient and clinical experts, who maintained that improved measures of patient benefit are required (as reported throughout the FED). The FED (throughout) also indicates that the strength and validity of the argument for improved measures increased as the consultation proceeded. Despite this, the ERG model remains NICE's preferred basis for assessing value for money; a model that has not been updated in light of the evidence submitted during the consultation process; a model that the committee itself recognises as highly uncertain (FED 4.23) *"[the committee] concluded that the ERG's exploratory results were also highly uncertain because the benefits of Afamelanotide may not have been fully captured by the DLQI measured in the clinical trials."*

Whilst we acknowledge that the committee made some attempt to extrapolate data, the BPA contends that an economic decision made on the basis of a highly flawed model is at best unreasonable, definitely inaccurate, and can even be considered as unscientific in light of the evidence submitted during the consultation process. It is therefore not logical to conclude that the recommendation is objective.

Ground 2: Point 3

Not only has the final economic decision been based primarily on a model that NICE acknowledged (FED 4.23) as *"highly uncertain"*, we are aware of no attempt by the ERG to engage patients in the development and/or refinement of the model.

Throughout the FED it is clear that the committee has gone to great lengths to develop a high level of understanding of EPP as an ultra-orphan condition. A condition for which the committee (FED 4.4) notes *"awareness and knowledge of the condition is very low, both among the public and in general medical practice (outside of specialist porphyria centres)".* Despite this, the same committee has **based its final decision on an economic model that is accepted to be flawed for use in relation to EPP, without further input from EPP patients.**

We also bring to your attention the additional points, which seem not to have been factored into the decision:

- The evident gulf between trial data and the many patient testimonies received from European patients fortunate enough to be able to access the treatment. This point was highlighted by the patient expert at the February committee meeting, yet this highly relevant and important point regarding the difference in experience between UK patients and their European peers is omitted from the FED.
- The patient expert also highlighted that testimony provided by European patients not receiving Afamelanotide, or prior to receiving Afamelanotide, is extremely consistent to that of UK patients in relation to how severely EPP impacts upon their life and the quality of life of those around them. Again, this highly valid point appears not to be reflected in the FED.
- Understanding of EPP is still developing - the now-accepted impact of fatigue (FED 4.1) is not fully reflected in either the EPP-QoL or the model adopted by the ERG. The committee also considered that the DLQI upon which the ERG model was based may not be fully applicable to EPP patients (FED 4.11).

Under such circumstances, the voice of true EPP patients becomes exceptionally relevant. Throughout the FED, reference is made to the gulf between the benefit conveyed in research papers and that communicated by clinical experts and patients alike. The BPA is therefore grateful that the committee recognised the need to consider wider factors (FED 4.6), *"The committee concluded that it was appropriate to consider the clinical effectiveness of afamelanotide, and the uncertainties in the evidence base, in its decision-making."* (FED 4.6).

The BPA fully accepts attempts to incorporate wider factors into the economic model via extrapolation, including extrapolation of the ERG model. However, important evidence (in the form of valid patient testimony) that became apparent during the consultation process was not correctly integrated into decision making. Whilst the FED makes frequent reference to the gulf between study and testimonies, the weight placed on the economic argument means that NICE has acted unreasonably in light of the evidence presented by EPP patients - by not taking adequate steps to ensure their testimonies were given appropriate weight, or translated into numerical data that should be incorporated into the economic decision.

Without fully considering the true benefit of Afamelanotide (FED 4.23 & P1) *"The true benefit of Afamelanotide has, however, not been quantified."*, the BPA feels that NICE has failed to act fairly on behalf of EPP patients in the UK by electing to speculate on potential value for money outcomes via extrapolation.

Ground 2, Point 4

The FED (4.22) noted that NICE had not been presented with an MAA proposal, however the BPA is aware that subsequent to the committee meeting of Feb 20th 2018, there was a round of discussions with Clinuvel and it is likely that these discussions may have included discussion around a possible MAA. However, no reference to these discussions is made in the FED, and this failure to disclose potentially relevant information is unreasonable.

The BPA suggests that in the interests of fairness and public interest, particularly that of EPP patients, the nature and content of these discussions be disclosed such that the content of the FED can be evaluated in the full light of day.

An MAA would, in our opinion, provide the opportunity to gather enhanced clinical data on relevant outcomes. We believe that in the case of this ultra-orphan condition, the small population size means that an MAA would substantially increase the understanding of Afamelanotide's effects on patients.

Given that even the EMA approval of Afamelanotide was based on data that rejected the two studies in which UK patients participated, surely our small, but highly impacted population of patients in the UK should be allowed the opportunity to define the true benefit of Afamelanotide. This could prove (or disprove) that the economic argument for the approval of Afamelanotide is much stronger than the highly flawed ERG model would

suggest, and is actually an economically justifiable use of funds when the impact on EPP patients is fully and correctly considered.

Further information

During the last committee meeting, the patient experts were asked whether or not they would be willing to receive Afamelanotide and participate in further studies to evaluate its efficacy. The patient experts responded positively, but given the impromptu nature of the question, did not feel entirely empowered to respond on behalf of all UK EPP patients. Although we are fully aware that new data cannot be introduced at this stage, to reinforce those individual patient expert answers, and demonstrate the gravity of the impact that a decision not to approve Afamelanotide (or consider an MAA) is likely to have on our members, we include some results of a recent survey (Appendix): 93% of the 100 people surveyed would want to try Scenesse and 6% would consider using Scenesse. Responses were limited to one per IP address to help prevent duplication and distortion of data. Responses are still being received.

Conclusion

The BPA contend there are grounds for appeal against NICE's recommendation, on:

- Ground Two: The recommendations are unreasonable in the light of evidence submitted to NICE

The BPA therefore contends that NICE's final recommendation denies EPP patients in the UK all funded access routes to demonstrate that the benefits of Afamelanotide are much greater than suggested by data from clinical trials, which were conducted at a time when the data models did not fully encapsulate the full impact of EPP. Only when assessed fairly, and in light of all evidence that has emerged during the consultation process, can the true benefit of Afamelanotide be quantified, and acceptable economic models applied to assess whether or not ICERs are within the range "*normally considered an acceptable use of NHS funds*".

The BPA would be happy to take part in an oral or written hearing.

Yours sincerely

John Chamberlayne

BPA Chairman

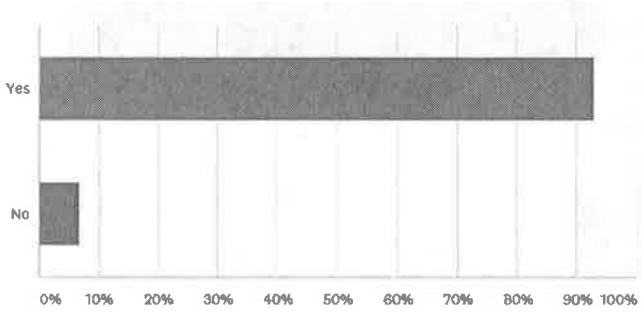
Appendix: BPA Patient Survey May 2018

Q1

Customize Export

Do you have a confirmed diagnosis of Erythropoietic Protoporphyria (EPP or XLEPP)?

Answered: 100 Skipped: 0



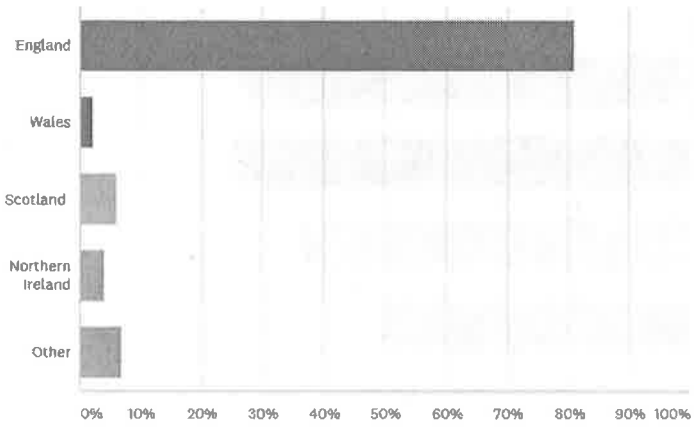
ANSWER CHOICES	RESPONSES	
Yes	93.00%	93
No	7.00%	7
TOTAL		100

Q2

Customize Export

Where do you live?

Answered: 100 Skipped: 0



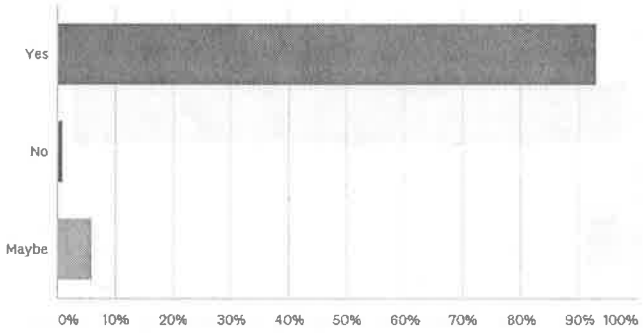
ANSWER CHOICES	RESPONSES	
England	81.00%	81
Wales	2.00%	2
Scotland	6.00%	6
Northern Ireland	4.00%	4
Other	7.00%	7
TOTAL		100

Q3

Customize Export

If Scenesse were to be approved for use on the NHS in the UK, would you try it to see if it worked for you?

Answered: 100 Skipped: 0



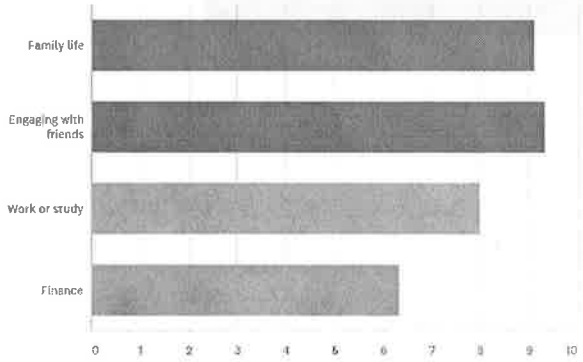
ANSWER CHOICES	RESPONSES	
Yes	93.00%	93
No	1.00%	1
Maybe	6.00%	6
TOTAL		100

Q4

Customize Export

On a scale of 0 to 10 (where 0 is not affected at all and 10 is extremely affected), how does EPP affect your life in the following categories?

Answered: 99 Skipped: 1



	0	1	2	3	4	5	6	7	8	9	10	TOTAL	WEIGHTED AVERAGE
Family life	2.02% 2	0.00% 0	3.03% 3	1.01% 1	5.05% 5	4.04% 4	2.02% 2	8.08% 8	22.22% 22	8.08% 8	44.44% 44	99	9.13
Engaging with friends	2.02% 2	0.00% 0	0.00% 0	2.02% 2	1.01% 1	4.04% 4	7.07% 7	7.07% 7	23.23% 23	10.10% 10	43.43% 43	99	9.33
Work or study	6.06% 6	1.01% 1	3.03% 3	2.02% 2	4.04% 4	6.06% 6	10.10% 10	13.13% 13	26.26% 26	6.06% 6	22.22% 22	99	7.99
Finance	16.16% 16	4.04% 4	5.05% 5	5.05% 5	6.06% 6	13.13% 13	10.10% 10	7.07% 7	12.12% 12	5.05% 5	16.16% 16	99	6.33