

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Evaluation consultation document

**Afamelanotide for treating erythropoietic
protoporphyrria**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using afamelanotide in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the [committee papers](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using afamelanotide in the context of national commissioning by NHS England.

For further details, see the [interim process and methods of the highly specialised technologies programme](#).

The key dates for this evaluation are:

Closing date for comments: 17th January 2018

Second evaluation committee meeting: 20th February 2018

Details of membership of the evaluation committee are given in section 6.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Recommendations

- 1.1 Afamelanotide is not recommended, within its marketing authorisation, for preventing phototoxicity in adults with erythropoietic protoporphyria (EPP).
- 1.2 This recommendation is not intended to affect treatment with afamelanotide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

EPP is a condition in which exposure to light causes painful and debilitating reactions in the body. Because there's no treatment, people try to avoid light. This limits their ability to do normal daily activities, and leads to feelings of social isolation, anxiety and poor quality of life.

Afamelanotide works by increasing melanin in the skin, which makes the skin tan, giving some protection against light damage.

Clinical trial results suggest that afamelanotide may be effective. But it's unclear how effective it is, whether the effectiveness varies from person to person and how it affects quality of life.

The cost-effectiveness estimates for afamelanotide are all much higher than the range normally considered acceptable for highly specialised technologies. This is despite taking account of the impact on quality of life, 'disability', and likely non-health-related benefits such as improving employment and study options, and that afamelanotide is an innovative treatment.

Therefore, afamelanotide does not appear to provide value for money within the context of a highly specialised service, so cannot be recommended for use in the NHS.

2 The condition

- 2.1 Erythropoietic protoporphyria (EPP) is a genetic storage disorder. It is usually caused by impaired activity of the enzyme, ferrochelatase. The condition results in excessive amounts of protoporphyrin IX in the skin, bone marrow, blood plasma and red blood cells. However, EPP is a cutaneous porphyria, and the major symptom is hypersensitivity of the skin to sunlight and some types of artificial light. This causes phototoxicity (a chemical reaction in the skin), and the skin may become painful, swollen, itchy and red. A phototoxic reaction typically lasts between 2 days and 3 days. However, it can last 10 or more days, with severe pain and loss of sleep. The pain is unresponsive to analgesics. These symptoms, along with anxiety and social isolation because of sunlight avoidance, can have a profound impact on quality of life. Over time, light exposure can cause thickening of the skin on the knuckles and scarring on the face. Some people with EPP may have complications related to liver and gallbladder function.

3 The technology

- 3.1 Afamelanotide (Scenesse, Clinuvel) activates the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin contributes to photoprotection by: strongly absorbing UV and visible light (acting as a filter); antioxidant activity; and inactivating the superoxide anion and increasing the availability of superoxide dismutase to reduce oxidative stress. Afamelanotide has a UK marketing authorisation under 'exceptional circumstances' for 'the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)'. It is administered as a subcutaneous dissolving implant. One implant is administered every 2 months before expected and during increased sunlight exposure, for

example, from spring to early autumn. Three implants are recommended annually, depending on the length of protection needed, and the maximum recommended dose is 4 per year. Treatment with afamelanotide would be life-long. The marketing authorisation stipulates that afamelanotide should only be prescribed by specialist clinicians in recognised porphyria centres, and that it should only be given by a clinician trained and accredited by the marketing authorisation holder to insert the implants.

3.2 The most common side effects with afamelanotide seen in clinical trials were nausea and headache, and discolouration, pain and redness at the implant site. These were generally mild and affected about 1 in 5 of people. Afamelanotide is contraindicated for people with reduced liver or kidney function. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Afamelanotide has not been launched in the UK, but the company has stated that the cost of an implant will be £12,020 (excluding VAT).

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Symptoms of erythropoietic protoporphyria (EPP)

- 4.1 The committee heard from patient experts that phototoxic reactions can be triggered by even a few minutes of exposure to light, particularly when light is at its most intense on sunny days in the summer, and the reaction itself can last for days. The patient experts described the pain during a reaction as intense, intolerable and not relieved by pain medication. Furthermore, the pain is neuropathic, meaning that even a light touch to the skin during a reaction exacerbates the pain. Patient experts also reported an all-encompassing tiredness associated with a phototoxic reaction. Sometimes, the phototoxic reactions are accompanied by redness and swelling but often there are no external signs. The committee concluded that phototoxic reactions can be associated with intense pain and extreme tiredness that lasts for days.

Current treatments

- 4.2 The committee heard that there is no effective treatment for the underlying cause of EPP, to protect against phototoxicity or to relieve pain caused by it. Clinical experts stated that beta carotene and narrow band UVB therapy have been tried as treatments to prevent phototoxicity but these are decreasingly used because of lack of clinical effectiveness. Light avoidance and covering the skin are the only options available to people with EPP. A clinical expert noted that light blocking creams like Dundee cream do not provide complete blocking of light and are also not ideal because they are conspicuous. The committee concluded that there is no effective treatment for preventing phototoxicity caused by EPP, so there is an unmet need for an effective treatment.

Light avoidance

- 4.3 People with EPP report the symptoms of phototoxic reactions as being debilitating, preventing them from being able to do day-to-day activities. They also say that, without anything to treat the pain or the phototoxicity,

their only option is to wait for the phototoxic reaction to stop and their bodies to heal. The patient experts explained that, because phototoxic reactions are unbearable, they will do anything it takes to prevent them. In the absence of any treatment that prevents phototoxicity, this involves avoiding light. The patient experts reported that they constantly assess the light conditions and measures they need to minimise the risk of a phototoxic reaction. This, and the fear of a phototoxic reaction, are major and constant causes of anxiety. People with EPP report that they often turn down invitations to activities or events, which leads to feelings of social isolation and compromises family life because they cannot take part in outdoor activities or go on holidays. A patient expert explained that his children cannot understand why he cannot join in, which leads to guilt and depression. The patient experts stated that they have had to adapt their careers to manage the measures they need to take to avoid light. The British Porphyria Association stated that its members reported choosing jobs that are indoors with minimal travel and even night jobs to minimise light exposure. Education choices are similarly affected. The British Porphyria Association stated that, for some families, the children may take on caring for a parent with EPP or other responsibilities that the parent cannot do because of their EPP. It also noted that EPP can place a financial burden on families because of loss of earnings and the expense of measures to protect against sun exposure. The committee heard from a clinical expert that EPP either causes debilitating pain if people with the condition try to live a normal life, or anxiety and isolation if they try to avoid the pain by staying indoors. The committee concluded that EPP can have a far reaching impact on the lives of patients and their families, resulting in anxiety, social isolation and very poor quality of life.

Diagnosis

- 4.4 The committee noted that, like many rare conditions, people with EPP have experienced delays in getting a diagnosis. The British Porphyria Association stated that the median age of diagnosis is 22 years, although

for most people the age of onset of EPP is at birth or soon after; 1 reason is that awareness and knowledge of the condition is very low, both among the public and in general medical practice (outside of specialist porphyria centres). People with EPP have reported that other people not understanding their experience, when it is not accompanied by external signs of phototoxicity, has led them to feeling isolated and means they have often had the condition without support for years. The committee concluded that delay in the diagnosis of EPP is a problem, and could result in people with the condition developing automatic behaviour over time to avoid light and so phototoxic reactions.

Variation in symptoms

- 4.5 The committee discussed the variation in symptom severity in people with EPP. A clinical expert stated that most people (around 70) under his care have 'classical' EPP. These people could have between 2 minutes and 40 minutes of sun exposure before experiencing a phototoxic reaction. However, the pain severity and duration of a phototoxic reaction are similar among these people. The clinical expert noted that he had treated around 16 people with mild EPP, who could be in very strong sunshine for several hours without a phototoxic reaction. Both clinical experts stated that people with mild EPP may not need or choose to have afamelanotide. The company stated that it is not possible to measure the severity of EPP. The committee concluded that there is some variation in how long people with EPP can be exposed to sunlight without a reaction, but the range across people diagnosed with EPP in England, and any variation in patient experience of the condition, was unclear because of a lack of data.

Impact of the new technology

Clinical benefits and uncertainties

- 4.6 The committee discussed the evidence available for afamelanotide, noting that there were 4 randomised placebo-controlled trials (CUV017, CUV029, CUV030, CUV039). The committee noted that, although the trials were

designed so that the patients would not know what they were having, some patients may have known they were having afamelanotide because it caused their skin to tan. The committee understood that CUV039 was the pivotal trial and this was carried out in the US. The committee noted that the other trials had included people from the UK and other European countries. It also noted the view of the clinical experts that the trials were generalisable to clinical practice in England. The committee was disappointed and concerned to note that the company submission did not include complete trial details, such as full baseline data. It meant that the ERG was unable to independently assess the methods and reliability of the clinical-effectiveness assessment of afamelanotide in the clinical trials. The committee understood that the ERG had, where possible, extracted data from publications available to supplement the information available in the company submission. The committee noted that the Good Clinical Practice inspection conducted by the European Medicines Agency (EMA) highlighted concerns with CUV029 and CUV030, including unsatisfactory collection and analyses of data. The company highlighted that it had been through a long and complex regulatory process and, based on input from patient and clinical experts, afamelanotide had been granted a marketing authorisation under exceptional circumstances. The company stated that the evaluation committee should not reopen the conclusions made by the EMA's Committee for Medicinal Products for Human Use about the efficacy of afamelanotide. The committee noted that its remit included an independent assessment of the benefits and costs of afamelanotide. It also noted that the EMA considers the potential efficacy of a technology in relation to its safety, The committee, on the other hand, considers the potential benefits ('effectiveness'), costs and uncertainties around recommending mandatory funding of a technology (in this case afamelanotide) within the overall objectives of the NHS to maximise health gain from limited resources. 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.

4.7 The committee considered the clinical trial data for afamelanotide. It noted that the trials had suggested a relatively small but statistically significant increase with afamelanotide in the amount of time a person could spend in daylight without pain, and a decrease in the number and severity of phototoxic reactions. It heard from patient experts and the British Porphyria Association that even small benefits such as being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large impact on people's lives. For example, a few minutes may allow a person with EPP to get into a shop or travel to work. A patient expert also explained that a few minutes in full daylight would typically equate to many more minutes, and even hours, in dappled light (shade). This would mean people with EPP would be in a much stronger position to manage their lives without being debilitated by the disease. Additionally, the committee understood that the company considered conditioned light avoidance behaviour was a likely reason the trial outcomes showed relatively small benefits with afamelanotide. The committee was aware that, in the trials, patients were asked to voluntarily expose themselves to light and the duration of light exposure was measured. It agreed that conditioned light avoidance could have impacted on the trial results, but it was unclear to what extent. The committee heard from a patient expert who had had afamelanotide that it had taken time to unlearn this behaviour and increase the amount of time spent in light. It understood that, with time, it was possible that conditioned light behaviour could be unlearned, but it was unclear how long this would take and whether it would vary from person to person. A clinical expert stated that the length of the clinical trials may have been too short for patients to have changed this ingrained behaviour. However, the committee also heard that, in the long-term observational study (Biolcati et al. 2015), there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials. The committee asked if there was any evidence about how the severity of EPP affected outcomes with afamelanotide, and heard there were no specific

data on this. However, the clinical experts suggested that, anecdotally, afamelanotide had been effective across the whole trial population. The committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen in the trials.

- 4.8 The committee noted that patient testimony about afamelanotide reported much better outcomes than the clinical trials. For example, a patient expert at the meeting stated that afamelanotide had allowed him to increase the time he spent in light by hours rather than by minutes (as had been seen in the trials) and described this as life changing. One clinical expert stated that the response of the patient expert to afamelanotide was similar to the anecdotal evidence he had heard from other people who had had afamelanotide. There was strong feedback from the experts that afamelanotide is a highly effective treatment option for a poorly characterised and debilitating condition. The committee considered the possibility that these testimonials were not reflective of all patients' experience on afamelanotide because it had not been presented with any data indicating that these were a representative sample of everyone who had had afamelanotide. The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear.

Quality of life

- 4.9 The committee discussed how quality of life had been assessed in the clinical trials. It noted that the generic short-form 36 (SF-36) and generic skin condition Dermatology Life Quality Index (DLQI) had been used in some of the clinical trials. However, the company stated that it had received advice that these measures were not appropriate for capturing the quality of life of people with EPP. The committee further noted that the company had developed a condition-specific quality-of-life questionnaire

called the EPP-QoL, but that this had not been validated. Furthermore, the EPP-QoL had been modified while the trials were ongoing and data were being collected, and some questions were removed. The company stated that it had consulted with EPP experts to develop the EPP-QoL, but was unable to provide the committee with a response to whether it had used standard methods for developing and validating this tool. The committee was particularly concerned that a question relating to capacity to go to work or school was removed from the EPP-QoL, and that there were no questions relating to the impact of pain, because these aspects were stated by people with EPP to be of great importance to them. The company stated that it had not included a question on how pain affected patient's quality of life because it was not considered to be comprehensive in describing symptoms during a reaction. The committee considered that any quality-of-life measure should capture the aspects of the condition that affect a person's quality of life and, for EPP, this should capture quality of life during and between phototoxic reactions. The committee concluded that the EPP-QoL did not appear to capture aspects of EPP that people with the condition and their clinicians report as important. It also concluded that, without appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture any treatment benefits with afamelanotide.

- 4.10 The committee discussed the DLQI. It was aware that this is a validated quality-of-life questionnaire, but validated for conditions only affecting the skin, rather than for EPP. The committee noted that the ERG considered that, although not perfect, the DLQI addresses some factors that impact on the quality of life of a person with EPP, such as pain and ability to work or study. The committee heard from the patient experts that the DLQI includes questions that are not relevant to EPP, such as feelings of embarrassment or self-consciousness relating to skin conditions, and that it does not capture non-skin components of EPP such as fatigue. The committee further heard from the clinical experts that the DLQI does not

ask anything about exposure to light, unlike the EPP-QoL. Furthermore, the company stated that the DLQI does not ask about feelings of anxiety. The committee was also disappointed that available SF-36 data had not been presented by the company because this measure includes questions on fatigue and anxiety that are not captured by the DLQI. The committee noted that DLQI data from the trials had shown a modest improvement in quality of life with afamelanotide and, in a large observational study, it had been shown to be sensitive to the impact of EPP on people with the condition. The committee concluded that the DLQI may not be fully applicable to EPP, but could capture some of the key aspects of EPP that people with the condition report affect their quality of life.

Cost to the NHS and value for money

Company's model

4.11 The committee discussed the company's model and noted that a large amount of information relating to the model structure and assumptions was considered confidential by the company. The committee was disappointed that this meant that its discussions and decisions on the model could not be fully described publicly. The committee noted that the modelled benefits were based on pooled trial data on EPP-QoL collected at 4 months. It noted that data were collected at 6 months, although from a smaller proportion of the trial population, but these data had not been presented by the company. The committee considered that the longer follow-up data could be useful to see, particularly because it heard from a clinical expert that the benefits of afamelanotide may take time to become apparent if people adapt their conditioned behaviour gradually. The committee noted that the company had stratified the data to represent mild, moderate and severe disease by splitting the EPP-QoL scores into 3 equal ranges. It heard that, in the absence of validated cut-offs for EPP severity using the EPP-QoL, the company considered the arbitrary division of the EPP-QoL into thirds to be the fairest approach. The

committee considered the validity of the EPP-QoL to be highly uncertain (see section 4.9) and concluded that the company's arbitrary approach to stratifying disease severity added to this uncertainty.

- 4.12 The committee noted that the company's analyses estimated disability-adjusted life years (DALYs) averted, and the incremental cost-effectiveness ratios (ICERs) were presented as cost per DALY averted. The company stated that it was more appropriate to consider the impact of EPP and afamelanotide on people's quality of life in terms of disability rather than utility because of a lack of available robust data from which to derive utility values. The committee noted that the [NICE interim process and methods guide of the Highly Specialised Technologies Programme](#) states that benefits of a technology should be expressed as utility values to determine the impact of a technology on quality and quantity of life that is, quality-adjusted life years (QALYs) gained. The committee stated that using QALYs was in the NICE reference case (that is, the preferred methods to be applied consistently across evaluations), and that this was important to allow consistent evaluation across therapy areas. The committee was aware of the importance of the consistent approach used by NICE and the NHS to ensure fair allocation of finite budgets because funding of a treatment may mean other treatments or services are displaced. The committee noted, however, that it could consider non-reference case methods alongside those in the reference case if there is a strong case for it. However, it was not persuaded by the theoretical argument for preferring an analysis based on the DALY to one based on the QALY. In addition, the committee considered that it had not been provided with evidence that the data on which disability was assessed were more robust than the data on utility. The committee questioned why the company preferred to map from other diseases that may not be fully representative of EPP rather than directly use patient-level quality-of-life data collected in EPP trials. The committee understood from the company that it needed a proxy condition to derive disability weights because these

were not available for EPP (see section 4.13). However, it did not consider that the company had made a strong case for using disability weights to justify the added uncertainty of using a proxy condition rather than direct trial data. The committee was aware that the ERG had provided a simple adaptation of the company's model, which showed that the differences between the DALY and the QALY did not matter in this instance because both approaches produced similar results and so would not affect the committee's conclusions. The committee concluded that, although it would take a DALY-based model into account in its decision-making, its preferred approach was one aligned with the NICE reference case.

- 4.13 The committee noted that, in its DALY-based framework, the company had used disability weights from the World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) to model the disability associated with mild, moderate or severe EPP. However, because the GBD survey had not asked about EPP, the company had used weights for a proxy condition it considered similar to EPP in its modelling. The committee noted that the company considered the proxy condition to be confidential. It appreciated similarities between some important aspects of the conditions but was aware of other important aspects that were not similar. The committee stated that it was unclear about the extent to which the proxy condition reflected the disability associated with EPP and whether it was valid to assume that the disability associated with mild, moderate or severe disease in the proxy condition would correspond with mild, moderate or severe EPP. Furthermore, it reiterated its concerns about the uncertainties surrounding the stratification of people with mild, moderate and severe EPP based on EPP-QoL data collected in the trials (see section 4.11). The committee concluded that the proxy condition used by the company may not fully capture the experience of people with EPP, and the assumption that it is

similar to EPP in general and at different levels of severity was not sufficiently robust.

ERG's exploratory analyses

4.14 The committee discussed the alternative approach taken by the ERG in its exploratory base case to model the benefits of afamelanotide. That is, using DLQI data from one of the clinical trials and mapping this to EQ-5D to derive utility values using a published algorithm. The committee considered that this approach provided a more direct link between quality of life measured in patients in the clinical trials and the modelled benefits, and with fewer assumptions than the company's proxy-condition base-case approach. However, the committee reiterated questions about whether the DLQI measured in the trials adequately captured the quality of life associated with EPP and the benefits of afamelanotide (see section 4.10). The committee therefore considered that the ERG's approach may have underestimated the real-life benefits of afamelanotide because these may potentially have been underestimated in the trials, but that it was not possible to quantify by how much. It concluded that the ERG's exploratory modelling approach was its preferred approach.

Treatment duration

4.15 The committee noted that the company assumed in its modelling that the benefits of afamelanotide would be immediate and would remain constant for the whole year, including after the last implant. It also noted that the ERG had tested a number of assumptions around this in sensitivity analyses. These included analyses around how long it would take for a person to experience the benefits of afamelanotide and how long the treatment effects of afamelanotide would persist after the last implant of the year. The committee considered that it was likely that it would take some time before patients would experience the benefits of afamelanotide, not least because time would be needed to unlearn conditioned behaviour associated with light avoidance. The clinical

experts described how the protective antioxidant effect of afamelanotide needed time to build up after the first implant but would persist for a period of time after the last implant. The committee noted the lack of data to support these assumptions. However, on balance, it concluded that the ERG's analyses assuming that the effect of afamelanotide would build up over the first 2 months (as the ERG had modelled in its base case), and that the treatment effect would slowly decrease over 6 months after the last implant, used plausible assumptions.

Dosage of afamelanotide

4.16 The committee discussed the likely use of afamelanotide in clinical practice. It was aware that the marketing authorisation recommended administering an implant every 2 months before expected, and during increased, sunlight exposure from spring to early autumn, and recommended a maximum of 4 implants per year. The clinical experts stated that they expected the implants to be used from around March to October in England, meaning that 4 implants would be used, but that some people may not need the maximum number. The committee noted that the company had provided an estimate of the average number of implants people with EPP may have, but had provided no detail on how this average was determined and whether it was generalisable to people using afamelanotide in clinical practice in England. The committee concluded that it should take into account that people may have up to 4 implants in its decision-making.

Cost-effectiveness results

4.17 The committee understood that the [interim process and methods of the highly specialised technologies programme](#) (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resource. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as

an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained. The committee discussed the QALY gains associated with afamelanotide, noting that EPP is not associated with a reduced life expectancy and, as such, afamelanotide does not extend life. The QALY gains were therefore driven by improvements in quality of life, which were relatively modest in both the company's base case and ERG's exploratory analyses. The undiscounted incremental DALYs in the company's base case and the ERG's estimated incremental QALYs based on the company's use of a proxy disease cannot be reported because the company has stated that these are commercial in confidence. Over the life-time of a patient the undiscounted QALYs gained with afamelanotide in the ERG's exploratory base case were 0.56, and did not exceed 0.8 in the ERG's sensitivity analyses. The committee concluded that, although there was uncertainty around the utility estimates (and disability estimates in the company's model), there was no evidence provided to suggest that afamelanotide would meet the criteria for applying a QALY weight (that is, a lifetime undiscounted incremental QALY gain of at least 10).

4.18 The committee noted that the following key ICERs were all over £100,000 per QALY gained:

- the company's base case: £278,471 per DALY averted (£278,386 per QALY gained when converted to a QALY-based ICER using the ERG's simple QALY adaptation)
- the ERG's exploratory base case: £1,605,478 per QALY gained
- the ERG's exploratory base case with the committee's preferred assumptions on gradual onset and 6-month attenuation of treatment effect: £1,343,359 per QALY gained
- the ERG's exploratory base case assuming 2 implants per year: £1,337,494 per QALY gained

- the ERG's exploratory base case assuming a maximum of 4 implants per year: £1,785,957 per QALY gained.

The committee concluded that the ICERs based on its preferred methods and assumptions were likely to be between £1,343,359 and £1,785,957 per QALY gained and that, even if the company's preferred analysis was considered, the ICER was substantially higher than £100,000 per QALY gained.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.19 The committee discussed the impact of afamelanotide beyond its direct health benefits and the testimony of the patient experts. It noted that people with EPP might alter their career plans to accommodate the effects of their disease and might be unable to take up enhanced career opportunities. The committee considered that people who had already taken a certain career path because there had historically been no treatment options would not necessarily change career if they had afamelanotide, but appreciated that it would allow them the freedom to pursue more opportunities. Additionally, people diagnosed with EPP starting out in their careers may not need to alter their preferred career plans to accommodate managing their EPP. However, the committee was unclear about the financial implications of these career choices. The committee acknowledged that afamelanotide reduced phototoxic reactions in the clinical trials and that this could affect a person's ability to work and study. However, it noted that it had not been provided with any data showing how the reduction in phototoxic reactions seen with afamelanotide affected peoples' ability to work or study. The committee was aware that the company had provided exploratory analyses on loss of earnings associated with EPP, but it was unclear what the data underpinning the company's assumptions were. The committee concluded

that afamelanotide would have an impact beyond direct health benefits but that the extent of this impact was unclear.

Conclusion

4.20 The committee acknowledged that EPP, although not life threatening, can cause extreme pain, be very debilitating and have far reaching consequences on living a normal life. It was aware that even small increases in time spent under light could significantly improve people's lives. It noted that afamelanotide is the only treatment for preventing phototoxicity in EPP for which efficacy has been shown. However, it maintained that the extent of the clinical effectiveness of afamelanotide is unclear. The committee noted the possibility that deeply ingrained light avoidance behaviour may have influenced the trial results. However, it was aware that this alone may not explain the huge gap between expert testimonies, anecdotal evidence of those present at the meeting and the trial results. The committee considered that the economic analyses were associated with substantial uncertainty. On balance, it concluded that the ERG's modelling approach was more plausible than the company's because it used trial data in a more direct way. The committee also concluded that it was unclear on how to interpret the non-validated EPP-QoL data and proxy-condition weights, which the company had used to model the benefits of afamelanotide. However, it 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. The committee considered that, in both the company's base case and the ERG's exploratory analyses, the ICERs were above the range normally considered a cost-effective use of NHS resources, and that afamelanotide did not meet the criteria for QALY weighting to be applied. It agreed that afamelanotide is innovative and has non-health-related benefits, and that these should be taken into account in its decision-making alongside the uncertainty surrounding the cost-effectiveness estimates. The committee considered that it did not have

adequate quantitative or qualitative data, but considered that, even taking such factors into account, it was unlikely that afamelanotide would be considered a cost-effective use of NHS resources. The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

5 Proposed date for review of guidance

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

December 2017

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

[Committee members](#) are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Mary Hughes

Technical Lead

Raisa Sidhu

Technical Adviser

Joanne Ekeledo

Project Manager

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