

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final evaluation document

**Afamelanotide for treating erythropoietic
protoporphyrria**

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 is 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.

Clinical trial results suggest small benefits with afamelanotide. Testimonies from patients and clinical experts suggest that the benefits may be greater than those seen in trials, and that even small improvements would be of great importance to them. The true benefit of afamelanotide has, however, not been quantified.

The cost-effectiveness estimates for afamelanotide are all very much higher than the range normally considered acceptable for highly

specialised technologies. This is despite taking into account the impact the condition and technology have on quality of life, 'disability', and likely non-health-related benefits such as improving employment and study options, and the fact that afamelanotide is an innovative treatment.

Overall, afamelanotide does not appear to provide value for money within the context of a highly specialised service, and cannot be recommended for routine funding in the NHS.

2 The condition

2.1 Erythropoietic protoporphyria (EPP) is a genetic disorder. It is 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. EPP is a cutaneous porphyria, and the major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and some types of artificial light. The skin may become painful, swollen, itchy and red, and skin erosions can also occur. 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. 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. A small proportion of people with EPP may have important 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

Burden of disease

- 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 acknowledged that phototoxic reactions can be associated with intense pain and extreme tiredness that lasts for days.
- 4.2 People with erythropoietic protoporphyria (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 take 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. A study from Holme et al. (2006) reported that most people with EPP were in employment or education but that 47% (n=66/127) of those in work felt their choice of profession had been influenced by their condition. 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. Testimonies received during consultation emphasised the extent of the burden of the condition, including the physical pain from light exposure, and the severe anxiety and social isolation from having to avoid light. The committee was clear that EPP can have a far reaching impact on the lives of patients and their families, resulting in poor quality of life.

Current treatments

- 4.3 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 and associated adverse effects (such as an increased risk of death from lung cancer and cardiovascular disease with beta carotene, and an increased risk of developing skin cancer with narrow band UVB). 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

noticeable on the skin. 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.

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 it 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 acknowledged that there is some variation in how long people with EPP can be exposed to sunlight without

a reaction. It concluded that 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: 100 patients and 12-month duration; CUV029: 76 patients and 9-month duration; CUV030: 77 patients and 6-month duration; CUV039: 94 patients and 6-month duration). 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. It 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 ERG pointed out 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. This was because the EMA recognised that the comprehensive data on the efficacy and safety required for a regular marketing authorisation could

not be generated but that the benefit-risk balance based on the evidence available was favourable. 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 population health gains 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 noted that the clinical trial results indicated a relatively small but statistically significant increase with afamelanotide compared with placebo in the median amount of time a person could spend in daylight (between 10:00 and 15:00) without pain (CUV029: 5.63 hours with afamelanotide and 0.75 hours with placebo, $p=0.006$; CUV039: 69.4 hours and 40.8 hours respectively, $p=0.044$), and a decrease in the median number and severity of phototoxic reactions (CUV029: 77 reactions with afamelanotide and 146 with placebo, $p=0.04$). The data on severity are not reported because the company has deemed them to be commercial in confidence. 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. The comments received following consultation strongly echoed these statements. 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. 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, and that clinical and patient experts believed the effects would be greater than those seen in the trials.

- 4.8 The committee heard that, in the long-term observational study (Biolcati et al., 2015), quality-of-life scores measured by the EPP-QoL (a condition-specific quality-of-life questionnaire) increased from 32% to 74% of the maximum in the first 6 months of treatment with afamelanotide, with little change over the next 6 years of observation. This indicated that there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials. A clinical expert stated that the increase in the first 6 months was important, and speculated that the climate in Switzerland and Italy may have contributed towards the

stabilisation in scores beyond 6 months. The committee was aware that, in the trial, there was also an improvement in quality-of-life scores in the placebo arm; the company explained that this was likely because EPP is a neglected disorder and the opportunity to enrol in a trial would have provided patients hope for the first time. The committee considered that these results were in contrast to the discussions around the impact of conditioned light avoidance. The committee concluded that afamelanotide was likely to improve quality of life but the true size of any improvement was uncertain.

- 4.9 The committee took into consideration patient reports that afamelanotide resulted in much better outcomes than it had in 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 received afamelanotide. There was strong feedback from the experts that afamelanotide is a highly effective treatment option for a poorly characterised and debilitating condition. The comments from individual patients received during consultation reiterated these testimonies. The committee was convinced that patients valued the benefits of afamelanotide but remained concerned that no data were available to quantify this impact. It heard from the company that the issue was of a lack of scientific tools to capture the true impact of the disease and so the benefit of afamelanotide, rather than a lack of data. The company and experts stated that an indicator of the effectiveness of afamelanotide was the compliance rate of about 94% despite the cost and time associated with travel for treatment. The committee appreciated the compliance rate was high but noted that it was not a quantifiable marker of effectiveness. It concluded that, although there was a substantial difference between patient and clinical expert testimonies and trial

outcomes and although it believed afamelanotide did offer a clinical benefit, the size of the benefit remained uncertain.

Quality of life

4.10 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 from clinical experts 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 fully validated. The committee noted that, to be appropriately validated, it should be suitable to support labelling claims granted by the EMA and the US Food and Drug Administration. 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. Following consultation, the company also stated that, because patients avoid light, it is rare for them to experience pain and so it would not yield useful results. The committee appreciated the nuances of capturing the burden of the condition because of light avoidance but, based on extensive patient testimonies, it maintained that pain was an important outcome. A clinical expert added

that, because of small numbers of patients, there was a limit to how much the tool could be optimised, and that additionally seasonal variations were important in interpreting the results. They explained that, ideally, a quality-of-life assessment should be done during each of the 4 seasons to capture these variations. 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. It also considered that the EPP-QoL did not appear to capture some aspects of EPP that people with the condition and their clinicians report as important. However, the committee was aware of the substantial feedback from stakeholders that EPP-QoL is a relevant tool. The committee concluded that it would take the EPP-QoL into account in its decision-making but that, without full and appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide.

- 4.11 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. Following consultation, clinical experts stated that the DLQI had not been validated

specifically for EPP, whereas the EPP-QoL was developed by experts in EPP and queried the committee's preference for DLQI. The committee noted that DLQI data from the trials had shown a modest but not statistically significant 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 noted that the same issue seen with EPP-QoL on seasonal variations (see section 4.10) applied to the interpretation of DLQI scores. Importantly, the committee explained that the DLQI could be mapped, using a validated algorithm, to EQ-5D to generate utility values to be used in a cost-effectiveness model. The company's approach using EPP-QoL, which included stratification of scores into mild, moderate and severe disease, and the use of a proxy condition potentially resulted in more uncertainty around the final estimates, even if the questionnaire itself was more responsive to changes in the condition. The committee considered that the DLQI may not be fully applicable to EPP. However, it thought that the DLQI could capture some of the key aspects of EPP that people with the condition report affect their quality of life, and allow for a more robust estimation of utility values. The committee concluded that results based on DLQI were relevant to its decision-making, alongside results based on EPP-QoL.

Cost to the NHS and value for money

Company's model

4.12 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. It noted that the modelled benefits were based on pooled trial data on EPP-QoL collected at 4 months. It also 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 uncertain (see section 4.10) and concluded that the company's arbitrary approach to stratifying disease severity added to this uncertainty.

- 4.13 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, because of the unique nature of the condition and because there was of a lack of available robust data from which to derive utility values, it did not support using utility values to quantify quality of life. Rather, the company noted it was more appropriate to consider the impact of EPP and afamelanotide on people's quality of life in terms of disability. 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. It 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 enough 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. The committee questioned further 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 4.15). 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.

4.14 At the second evaluation meeting, the company stated that it did not consider the DALY approach to be more appropriate than QALYs. Rather, it considered that no approach was entirely suitable to reflect the complexities in EPP, and that the DALY model was its attempt to present an alternative approach. 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 the one aligned with the NICE reference case.

4.15 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 4.12). 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

4.16 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, it 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 4.11). 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

4.17 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 some 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

4.18 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 (based on what had been seen in

expanded access and commercial distribution of the drug across the expected EPP population; this number is not reported because the company has deemed it to be commercial in confidence) but had provided no detail on 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

4.19 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 resources. 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 recalled that there was uncertainty around the utility estimates (and the disability estimates in the company's model), and that the full benefits of afamelanotide were not quantified. However, it concluded that accounting for this was unlikely to result in an incremental QALY gain of at least 10.

The committee concluded that the criteria for applying a QALY weight was not met.

4.20 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 simple QALY adaptation using utilities from the literature for the company's proxy condition: £1,726,802 per QALY gained
- the ERG's exploratory base case assuming 3 implants per year, gradual onset and 2-month attenuation of the relative treatment effect (see sections 4.17 and 4.18): £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 the relative 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. The committee noted that the ICERs based on EPP-QoL, and using the company's preferred proxy condition (but based on utility rather than disability weights from the literature) resulted in an ICER of £1,726,802 per QALY gained. The committee considered this to be very similar to the ERG's exploratory base-case ICERs.

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

4.21 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. Furthermore, the committee was unclear about the financial implications of these career choices. It 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. It also noted that only 1 scenario reduced the ICER from £278,471 per DALY averted in the company's base case to less than £100,000 per DALY averted. This was based on the assumption that people having afamelanotide receive 90% of the mean wage whereas people having standard care earned only 10% of the mean wage. The committee noted that this assumption was very strong and was not in keeping with the findings on choice of occupation from Holme et al. (2006; see section 4.2). The committee concluded that afamelanotide would have an impact beyond direct health benefits but that quantifying this was difficult. It concluded that it was highly unlikely the impact would be sufficient to overcome the committee's concerns about value for money

(see section 4.20), and also unlikely to bring the most plausible ICERs to a level considered to be an acceptable use of NHS resources.

Managed access agreement

4.22 Following consultation, the British Association of Dermatologists queried the possibility of developing a managed access agreement (MAA) to address the uncertainties. The committee noted that it could consider an MAA proposal if all stakeholders collaborated to develop and support it. The committee noted that it had not been presented with a proposal but discussed whether a proposal could potentially address the 2 main elements of an MAA:

- Data collection to reduce uncertainty at the end of the MAA: the committee was aware of the significant uncertainties in this evaluation and discussed whether further data collection would address the uncertainties. It heard from the company that there was a lack of appropriate instruments to enable robust data collection and it was not in support of redesigning clinical studies. The company also highlighted that the EMA considered it to be unethical to conduct further clinical trials in patients. Instead, the company stated that they intend to collect post-authorisation safety data and to validate the EPP-QoL tool and use it to collect further data in the UK. The committee accepted that data collection in the context of a MAA was unlikely to resolve the existing uncertainties in the evidence base because it was likely to face challenges similar to those faced in the trials.
- Sharing of financial risk during the MAA: the committee noted that an MAA would typically include financial components that would apply while it is in force to share the financial risk with the NHS. The company stated that it offered a single price across countries and there was no scope for this to differ in England. However, it 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. The committee was aware that these estimates (ranging between £1,343,359 and £1,785,957 per QALY gained) were very much above what could be considered an acceptable use of NHS resources, making it highly unlikely that afamelanotide has a plausible potential to be considered cost effective.

Conclusion

4.23 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 without a phototoxic reaction 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. 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 substantial difference between the trial results and the expert testimonies, anecdotal evidence of those present at the meeting, and the consultation comments. The committee agreed that afamelanotide was effective and that the true benefit had not been quantified. It was aware that its remit was to evaluate the value of afamelanotide, which includes consideration of cost effectiveness in addition to clinical effectiveness. The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. 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. 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.

- 4.24 The committee considered that, in both the company's base case and the ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources. It also considered that afamelanotide did not meet the criteria for QALY weighting to be applied, even if qualitative evidence on the extent of benefit and impact beyond direct health benefits was taken into account. 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. The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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

May 2018

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.

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