

Afamelanotide for treating erythropoietic protoporphyrria

Highly specialised technologies guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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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 severely painful and debilitating reactions in the body. There is no treatment, and the only way to avoid reactions is to avoid light. EPP has far-reaching effects on the lives of people with the condition and their families.

There is some evidence from clinical trials that afamelanotide provides benefits for people with EPP. Testimonies and evidence from people with EPP and clinical experts show that improvements in symptoms and quality of life would be of great importance to them. But it is very difficult to measure the effects of the condition and treatment and, although afamelanotide is an effective treatment, the size of its benefits is highly uncertain.

The cost-effectiveness analyses for afamelanotide are very challenging. Based on the available evidence provided by the company, the cost-effectiveness estimates are all substantially higher than the range normally considered acceptable for highly specialised technologies. Also, the benefits of afamelanotide may not have been captured adequately in the formal analysis. But, even when considering the scenario based on additional evidence from stakeholders, the most optimistic estimates of cost effectiveness are still higher than those considered acceptable for highly specialised technologies. So, it is not possible to conclude that afamelanotide provides appropriate value for money.

Taking into account all of the evidence and factors affecting the decision, afamelanotide is not recommended for use in the NHS.

2 The condition

- 2.1 Erythropoietic protoporphyria (EPP) is a genetic disorder. It results from mutations in genes involved in the haem production pathway, such as ferrochelatase and delta-aminolevulinate synthase 2. 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. The major symptom is phototoxicity (a chemical reaction underneath the skin) caused by sunlight and artificial light emitted along the visible spectrum above 400 nanometres. The skin can rapidly become severely painful, swollen, itchy and red, and skin erosions can also occur. A phototoxic reaction typically lasts between 2 days and 3 days. But it can last 10 or more days, with severe pain and loss of sleep. These symptoms, along with persisting anxiety and social isolation because of sun and light avoidance, can have a profound effect 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 melanocortin 1 receptor. Eumelanin contributes to photoprotection by:

- strongly absorbing UV and visible light (acting as a filter)
- antioxidant activity
- inactivating the superoxide anion and increasing the availability of superoxide dismutase to reduce oxidative stress.

Afamelanotide has a marketing authorisation in the UK 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. The marketing authorisation recommends 3 implants per year, depending on the length of protection needed. The maximum number of implants recommended in the marketing authorisation is 4 per year. 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 For full details of adverse reactions and contraindications, see [afamelanotide's summary of product characteristics](#).

3.3 Afamelanotide has not been launched in England, but the company has stated that the cost of an implant will be £13,209 (excluding VAT).

4 Consideration of the evidence

The [evaluation committee](#) considered evidence submitted by Clinuvel, 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 patient experts explained 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. They added that the reaction itself lasts from 2 to more than 10 days. They 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. The patient experts also reported an all-encompassing tiredness associated with a phototoxic reaction, which can take weeks to resolve. Sometimes, the phototoxic reactions are accompanied by redness and swelling resembling a second-degree burn, but often there are no external signs. The committee recognised that phototoxic reactions cause serious and severe symptoms, including intense pain and extreme tiredness, that last for days.

Effects on day-to-day activities

- 4.2 People with erythropoietic protoporphyria (EPP) describe the symptoms of phototoxic reactions as being debilitating, preventing them from being able to do day-to-day activities. They also highlight 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. They described how they need to constantly assess the light conditions and take measures to minimise the risk of a phototoxic reaction. They explained that various sources of light can cause phototoxic reactions, including some artificial lights and daylight through glass, which makes light avoidance very difficult. They also described how short light exposure triggers nerve stimulation (a prodromal phase) that prompts them to quickly withdraw from further exposure. They explained that assessing, avoiding and withdrawing from light becomes automatic and ingrained (or 'conditioned') behaviour. This, and the fear of a phototoxic reaction, are major and constant causes of anxiety. The committee understood the significant effect of EPP on day-to-day activities.

Psychological and stigmatising effects

- 4.3 The patient experts commented on further psychological effects of the condition, including post-traumatic stress, flashbacks and nightmares. They explained that suicidal ideation is not uncommon and can emerge from a young age. People with EPP also face difficult situations because other people do not understand the condition. They are often bullied or harassed. They may face hostility and disbelief about their symptoms. They often feel isolated. Also, other people may fail to make appropriate allowances for the condition. In response, people with EPP try to conceal their difficulties and their condition. The committee acknowledged that the psychological and stigmatising effects of the condition are striking and significant.

Far-reaching effects on the lives of people with EPP and their families

- 4.4 People with EPP report that they often turn down invitations to activities or events. This 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% (60 out of 127) of those in work felt their choice of occupation 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. One clinical expert explained 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, stigmatisation, psychological effects and social isolation from having to avoid light. The committee recognised that EPP is a serious, debilitating and disabling condition with far-reaching effects on the lives of people with EPP and their families.

Current treatments

- 4.5 There are no effective treatments used in England for the underlying cause of EPP, to protect against phototoxicity or to relieve the pain it causes. The only way people with EPP can avoid phototoxicity is to avoid light (see [section 4.2](#)). The clinical experts stated that beta carotene and narrow band UVB therapy have been tried as treatments to prevent phototoxicity. But they explained that these are used less and less because of a lack of clinical effectiveness and because of 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. One clinical expert noted that light-blocking creams like Dundee cream do not completely block 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

- 4.6 The committee highlighted that, like with 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, even though the age of onset of EPP is at birth or soon after for most people. One reason for this 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 the lack of understanding about the condition and their experiences (see [section 4.3](#)), and delayed diagnosis, have meant they have the condition without support for many years. The committee recognised that delay in the diagnosis of EPP is a problem.

Variation in symptoms

- 4.7 The committee explored the variation in symptom severity in people with EPP. One clinical expert stated that most people (around 70) under his care have 'classical' EPP, and that they could have between 2 minutes and 40 minutes of sun exposure before having a phototoxic reaction. But the pain severity and duration of a phototoxic reaction have less variation between people than the sun exposure times (that is, phototoxic reactions are similar in severity and duration across people with classical EPP). This expert also noted that he had treated mild EPP in around 16 people 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, nor 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 the experience of people with the condition was unclear because of a lack of data.

Features of EPP that make decision making difficult

- 4.8 The committee recognised that EPP is a unique condition with unique challenges and effects for people with it. As concluded at the appeal, the committee acknowledged that EPP meets the definition of a disability under the Equality

Act 2010, and understood its duties under the Equality Act 2010 (see [section 4.59](#)). It heard that there was an important lack of robust scientific instruments to measure the overall effect of the condition, and to generate data on efficacy and clinical benefit, as recognised by the European Medicines Agency (EMA). It considered in detail which features of the disability associated with EPP might cause people to be disadvantaged within a highly specialised technologies evaluation. It also considered how it would be reasonable to adjust its approach to avoid discrimination and promote equality. The committee considered that 1 of the main features that might affect its approach to decision making, and the need for reasonable adjustments, was the specific challenge in measuring the effect of the condition and its treatment on quality of life (QoL; see [sections 4.17 to 4.20](#)). It heard that there was an important lack of robust scientific instruments to measure such effects. It also heard in detail how the ingrained, automatic behaviours to avoid exposure to light ('conditioned light avoidance behaviours'; see [section 4.2](#)) further contribute to the substantial challenges in measuring and quantifying the effect of treatments for EPP in clinical studies. That is, even with treatment, people may continue to avoid light for some time because of these conditioned behaviours. It recognised that challenges of measuring treatment effect are seen in other conditions encountered in highly specialised technology evaluations. So, in that sense, such challenges are not unique to EPP, meaning that the committee should not deviate entirely from its normal approach. But, given the particular issues associated with EPP, it would nevertheless be appropriate to take these challenges into account. The committee concluded that it would take into account the nature of EPP as a disability throughout its decision making, and how it would be appropriate to adjust its approach in the context of this disability.

Impact of the new technology

Role of the committee

- 4.9 The committee explored in detail the clinical-effectiveness evidence for afamelanotide. The company highlighted that it had been through a long and complex regulatory process and that, 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 emphasised that it did not seek to re-examine the conclusions of the EMA. Instead, it considered the potential benefits (effectiveness), costs and uncertainties around recommending mandatory funding of a technology (in this case, afamelanotide) in clinical practice in England. It concluded that it was appropriate to consider the clinical effectiveness of afamelanotide and the uncertainties in the evidence base as part of its decision making.

Clinical-effectiveness evidence

4.10 The committee noted that there were 4 randomised placebo-controlled trials of afamelanotide:

- CUV017: 100 people and 12-month duration
- CUV029: 76 people and 9-month duration
- CUV030: 77 people and 6-month duration
- CUV039: 94 people and 6-month duration.

The trials were designed so that the people taking part would not know whether they were having afamelanotide or placebo. But the committee was aware that some people with EPP may have known they were having afamelanotide because it caused their skin to tan. The committee understood that CUV039 was the pivotal trial, and noted that it was carried out in the US. The other trials included people from the UK and other European countries. The clinical experts stated that the trial results were generalisable to clinical practice in England.

4.11 The committee was concerned to note that the company's 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 trials. The committee understood that the ERG had, when possible, extracted data from publications available to supplement the information available in the company's submission. The ERG pointed out that the Good Clinical Practice inspection done by the EMA and reported in the [EMA's public assessment report](#) highlighted concerns with CUV029 and CUV030, including unsatisfactory collection and analyses of data. The committee acknowledged that there were potential limitations in some of the clinical trials.

- 4.12 The committee also considered evidence from observational studies, testimonies from people with EPP and patient experts, and additional evidence described by the clinical experts.

Challenges of evidence collection

- 4.13 The company explained that quantifying the effects of afamelanotide was highly challenging. This was because of a lack of scientific tools to capture the true effect of EPP and so the benefit of afamelanotide, rather than problems with the trials. The committee understood that QoL was measured in the clinical trials using both generic tools (the short-form 36 [SF-36] and Dermatology Life Quality Index [DLQI]) and a novel condition-specific measure (EPP-QoL), but that all of these had limitations (see [sections 4.17 to 4.19](#)).
- 4.14 The committee was aware that measuring the effects of afamelanotide through light exposure times was affected by averaging – that is, the light exposure times reported in the clinical trials were averaged both between people and over time. So, exposure times were influenced by factors such as people's occupations, their daily activities, the weather and conditioned light behaviour. It agreed that this could have affected the trial results, but it was unclear to what extent.
- 4.15 The clinical and patient experts discussed how long it would take for people with EPP to begin to unlearn conditioned light avoidance behaviour. They explained that, for most people with the condition, it usually takes up to 2 to 3 implants to start to unlearn behaviour and increase the amount of time spent in light. For a few people with EPP, it may take only 5 to 6 weeks to start increasing light

exposure. A clinical expert stated that some of the trials (including CUV017 and CUV029) may have been too short for people with EPP to have changed their conditioned light avoidance behaviour. Also, the experts highlighted that some changes (including overcoming psychological barriers and changing employment) may take years to arise.

- 4.16 The committee acknowledged that there are challenges associated with measuring the effects of EPP and the benefits of afamelanotide, and that these contributed to uncertainties in the clinical trials.

Measuring QoL

- 4.17 Recognising the challenges in capturing the effect of EPP on QoL, the committee discussed in detail the QoL measures that were included in the clinical trials. The patient and clinical experts highlighted that factors such as fatigue particularly affect the lives of people with EPP and their families, and that the effects of stigma may not be fully reflected in any of the QoL measures.
- 4.18 The condition-specific QoL questionnaire, the EPP-QoL, was developed by the company with independent experts in EPP. The committee acknowledged that, to be appropriately validated, a questionnaire should be able to support labelling claims granted by the EMA and the US Food and Drug Administration. It also acknowledged that the EPP-QoL was modified while the trials were ongoing and data was being collected, and some questions were removed (although the clinical experts explained that there was evidence that removing some questions had not affected the results). The committee was particularly concerned that a question relating to capacity to go to work or school was removed from the EPP-QoL. It also worried that there were no questions relating to the effect of pain. People with EPP stated that these aspects are of great importance to them. The company stated that it had not included a question on how pain affected QoL because pain is not considered to be comprehensive in describing symptoms during a reaction. The company also stated that, because people with EPP avoid light, it is rare for them to experience pain, so measuring 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. One clinical expert added that,

because of the small numbers of people with EPP, there was a limit to how much the EPP-QoL could be optimised, and also that seasonal variations were important in interpreting the results. They explained that, ideally, a QoL assessment should be done during each of the 4 seasons to capture these variations. The committee considered that any QoL measure should capture the aspects of the condition that affect a person's QoL and, for EPP, this should capture QoL 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. But there was substantial feedback from stakeholders that the EPP-QoL is a relevant tool. Also, the clinical experts considered that the EPP-QoL was the best tool to date to capture the burden of EPP. After the second consultation, the committee was aware of a new study (Biolcati et al. 2021) which reported a validation of the EPP-QoL. This study provided evidence for the reliability and validity of the 10-item symptom score. But it did not find support for 2 questions on wellbeing, which the committee considered limited the tool. The committee concluded that the EPP-QoL provided relevant evidence that it would take into account in its consideration of the clinical effectiveness of afamelanotide. It also concluded that there was still some uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture all treatment benefits with afamelanotide. But it noted that it had been partially validated. The committee was also aware that the EPP-QoL had not been assigned preference weights and had not been mapped to an outcome measure that could provide preference weights. This meant that the measure could not be used to generate utility values (see [section 4.36](#)).

- 4.19 The committee noted that the SF-36 and DLQI had been used in some of the clinical trials. But the company stated that it had received advice from clinical experts that these measures were not appropriate for capturing the QoL of people with EPP. The DLQI is a validated QoL questionnaire, but is validated for conditions only affecting the skin and not for EPP. The ERG considered that, although not perfect, the DLQI addresses some factors that affect the QoL of a person with EPP, such as pain and ability to work or study. The patient experts explained 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 clinical experts explained 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 noted that, in a large observational study, Holme et al. (2006), DLQI had been shown to be sensitive to the effect of EPP on people with the condition. But the same issue that was seen with the EPP-QoL on seasonal variations (see [section 4.18](#)) applied to interpreting DLQI scores. In the third consultation, the company pointed out 2 more recent publications that recognised the challenges of studying photodermatoses and EPP. The ERG stated that both publications critically discuss the sensitivity of the DLQI in EPP, citing advantages and disadvantages of this measure. It added that the publications do not contradict the findings from Holme et al. (2006) about the sensitivity of the DLQI in EPP. The committee concluded that, although the DLQI had notable limitations, it had been one of the tools incorporated in the clinical trials at the outset to measure QoL and the results were relevant to its consideration of clinical effectiveness. The committee also stated that it was disappointed that available SF-36 data had not been provided by the company. This was because this measure can be used to generate utility values and includes questions on fatigue and anxiety that are not captured by the DLQI.

4.20 After the second consultation, the committee considered QoL evidence submitted by the International Porphyria Patient Network (IPPN) independently from the company. This consisted of EQ-5D data collected from a feasibility study carried out in Switzerland, and from an informal patient survey involving people with EPP from 4 European countries. Neither of these studies had been peer reviewed.

Feasibility study

4.21 The feasibility study included 5 people with EPP who had been having afamelanotide for more than 2 years. They completed the EQ-5D-5L and EPP-QoL for their current health status, and retrospectively for the period of a previous phototoxic reaction and treatment interruption. The IPPN highlighted that people in this study who were on long-term treatment (more than 2 years) with afamelanotide had a utility value comparable to the age-matched general population (0.965). In addition, the utility value for a phototoxic reaction (0.215) and for a treatment interruption (0.331) were similar to utility values seen in people with acute burn injuries and chronic neuropathic pain.

Informal patient survey

4.22 The IPPN informal patient survey included 18 people with EPP: 13 had been on afamelanotide for more than 2 years and 4 people for less than 2 years. One of them had not had any treatment. The utility value for people who had been on treatment for more than 2 years was similar to the feasibility study (0.975), but lower for people on treatment for less than 2 years (0.619). The survey estimated a utility value of 0.397 for no treatment. The committee recalled that clinical and patient experts had explained that time would be needed for the treatment effect of afamelanotide to be realised because people with EPP adapt and adjust their behaviour to avoid light. It considered that this may account for the difference in utility between people with more than 2 years of treatment and those with less than 2 years. But it also noted comments from the IPPN that unlearning of light avoidance behaviour may only need a few months. The ERG explained that both of these studies from the IPPN were subject to high levels of uncertainty. This was because the sample sizes were small and limited information was provided on the methods used. It was not clear how people were selected for inclusion, and the results may be subject to recall bias. The ERG said it was also not clear what time of the year the questionnaires were completed, or how EQ-5D values varied over the year. It noted that the German EQ-5D tariff was used. The ERG explained that the studies indicate that the EQ-5D may be appropriate for detecting QoL changes in EPP because they showed that each of its 5 domains was affected by the condition. The IPPN considered that this new evidence better addressed the uncertainty in the analysis about quantifying the quality-adjusted life year (QALY) gain associated with afamelanotide, and was comparable to methods previously accepted. But the committee considered that the IPPN's evidence was associated with substantial uncertainty. This was because of the points raised by the ERG and the absence of a concurrent comparator to account for the placebo effect on QoL shown in the clinical trials. The committee welcomed the studies' submission, especially as it raised the possibility that generic preference weighted measures of QoL were appropriate to measure the benefit of afamelanotide. It agreed that it would consider this evidence, despite its very high uncertainty, to aid its decision making as a part of a reasonable adjustment, given the nature of the condition (see [section 4.8](#)).

Clinical-effectiveness results

- 4.23 The clinical trial results showed a statistically significant increase with afamelanotide compared with placebo in the median amount of time a person could spend in daylight without pain (CUV029, between 10 am and 3 pm: 5.63 hours with afamelanotide and 0.75 hours with placebo, $p=0.006$; CUV039, between 10 am and 6 pm: 69.4 hours and 40.8 hours respectively, $p=0.044$). For CUV039, this equates to an average of 23.1 minutes per day in daylight for people having afamelanotide, compared with 13.6 minutes per day for people having placebo, between 10 am and 6 pm. For context, the committee understood that healthy indoor workers spend an average of 22 minutes outdoors between 10 am and 3 pm on summer weekdays. CUV029 also showed a statistically significant decrease in the number and severity of phototoxic reactions (77 reactions with afamelanotide and 146 with placebo, $p=0.04$; the data on severity is not reported because the company deemed it to be commercial in confidence). The clinical expert also described evidence on maximal light exposure durations (from an observational study), which further illustrated the size of the benefits associated with afamelanotide. The patient experts and the British Porphyria Association explained that being able to spend an extra few minutes in daylight or having fewer phototoxic reactions could have a large effect on people's lives. For example, a few minutes might 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 or shade. This would mean people with EPP would be in a much stronger position to manage their lives without being debilitated by the condition. The comments received following consultation strongly echoed these statements. For example, a patient expert at the meeting stated that afamelanotide had allowed him to increase the time he spent in light by hours and described this as life changing.
- 4.24 In 1 long-term observational study (Biolcati et al. 2015), QoL scores measured by the EPP-QoL increased from 32% to 74% of the maximum in the first 6 months of afamelanotide treatment. A clinical expert stated that this increase in the first 6 months was important. The committee also acknowledged that DLQI data from the clinical trials had shown a non-statistically significant improvement in QoL with afamelanotide. But the committee also noted that there was little further change in QoL (EPP-QoL) over the following 6 years in the observational study. This indicated that there was no marked improvement in QoL as measured by

EPP-QoL in people who had treatment beyond the duration of the controlled clinical trials. The clinical expert speculated that the climate in Switzerland and Italy may have contributed towards the stabilisation in scores beyond 6 months. The committee considered that these results were in contrast to the discussions around the slow resolution of conditioned light avoidance. The committee also noted that there was an improvement in QoL scores in the placebo arm of the clinical trials. The company explained that this was likely because EPP is a neglected disorder and the opportunity to enrol in a trial would have provided people with the condition hope for the first time. The committee recalled the testimony from clinical and patient experts highlighting the effect of the treatment benefits on QoL (see section 4.25). The committee concluded that afamelanotide was likely to improve QoL, but the true size of any improvement was uncertain.

- 4.25 The company and experts stated that another indicator of the effectiveness of afamelanotide was the adherence rate in 2018 of 98.5%, despite the cost and time associated with travel for treatment. A patient organisation also highlighted a survey showing that 93% of people surveyed would want to try afamelanotide. The committee appreciated that the adherence rate was high, but noted that it was not a direct marker of effectiveness and did not quantify the size of the treatment benefit.
- 4.26 The committee asked if there was any evidence about how the severity of EPP affected outcomes with afamelanotide, and heard that there was no specific data on this. But the clinical experts suggested that, anecdotally, afamelanotide had been effective across the whole trial population.
- 4.27 After the second evaluation consultation, the committee considered some more recently published studies, which were highlighted by stakeholders:
- Wensink et al. (2020) reported results for a 3-year single-centre (Netherlands) prospective postauthorisation observational study. This study included 117 people and reported outcomes for safety, efficacy and QoL. It reported that people taking afamelanotide increased their time spent outside over time. This increase was by 1.85 hours in week 1 (95% confidence interval [CI], -0.07 to 3.78 hours; $p=0.06$) and 6.14 hours in week 5 (95% CI 3.62 to 8.67 hours; $p<0.001$). Time spent outdoors increased during the observational period 2016 to 2018, increasing by 1.41 hours per week per

year on treatment (95% CI 0.04 to 2.77 hours; $p=0.04$). EPP-QoL scores also increased by 14.01% (95% CI 4.53% to 23.50%; $p<0.001$). The ERG said that there was substantial uncertainty over the results. They have wide confidence intervals and there are limitations in reporting. The ERG also considered that there was a high likelihood of recall bias. Overall, the ERG concluded that the study did not provide convincing new evidence. In the third consultation, the company noted that Wensink et al. (2020) was the largest single cohort study of EPP ever published and was peer reviewed. But the ERG maintained its conclusions, in the absence of any alternative critical interpretation of Wensink et al. (2020) provided by the company.

- Barman-Aksozen et al. (2020) reported a single-centre (Switzerland) retrospective chart review study. It included 39 people and reported outcomes for the maximum time spent in sunlight without a phototoxic reaction. People having afamelanotide had a median phototoxic reaction time of 180 minutes (range 15 to 420 minutes) compared with 10 minutes for those not on treatment (range 2 to 120 minutes), $p<0.0001$. The ERG said that the study lacked clarity around important aspects of participant recall and that the results could be at high risk of recall bias. It also noted that population characteristics had not been reported. The ERG considered the results of the study to be uncertain.
- Wensink et al. (2021) reported 2 retrospective studies for prodromal symptoms (reversible warning symptoms that precede phototoxic reactions to sunlight in people with EPP). The studies included 31 people from the US and 58 people from the Netherlands. In both studies, afamelanotide statistically significantly increased the time to the first prodromal symptom. The ERG again noted a lack of clarity in the study over participant recall. It also pointed out that the instrument used to measure results had not been validated.
- Wensink et al. (2022) was an open-label single-centre longitudinal case-control study. It looked at 26 people before and during their afamelanotide treatment and 23 healthy controls. It reported outcomes for white light exposure and activity levels. The results showed that people on afamelanotide had 71.6% more light exposure during spring compared with people off treatment ($p<0.01$). People on afamelanotide had fewer painful moments in the morning (6.5% decrease; $p=0.005$), and the afternoon and

evening (8.1% decrease; $p=0.004$). The ERG said that a strength of the study was the use of an actigraph to measure light exposure, meaning this measurement was not subject to recall bias. It did note that there were several limitations with the study, for example, there were differences between the groups and missing data was excluded.

- Minder et al. (2021) was a single-centre (Switzerland) retrospective chart review. It included 38 people and reported outcomes relating to liver damage. The results showed that mean aspartate transaminase (AST) levels decreased statistically significantly (improved). But while 24 out of 38 people (63%) had a decrease in AST on treatment with afamelanotide, 14 out of 38 people (37%) had a slight increase. The committee recalled that a small proportion of people with EPP will have liver damage related to their condition. The ERG said that the Minder et al. (2021) study results may have suggested positive results in relation to liver damage. But it added that, in clinical practice, tests other than those used in the study are likely to be used to assess liver damage. In the third consultation, the company stated that it disagreed with the ERG's assessment, and that protoporphyrin IX (PPIX) and AST are primary biochemical markers of liver function in people with EPP. It stated that these markers are used in routine UK and EU clinical practice to monitor for potential liver damage. It added that both markers, along with 13 other laboratory measures, were reported in the study. In response, the ERG noted that the focus of interest in the study was detecting the presence or absence of liver damage. It stated that, in light of this, it was unclear why standard liver function tests such as ALT and bilirubin were not also done to provide a more complete picture of liver health. It added that the 13 other laboratory measures referred to by the company did not include any liver-specific markers. The committee considered that afamelanotide may provide some liver protection benefits but the extent was unknown.

4.28 The patient experts said that the recently published studies provided additional evidence to quantify the benefits of afamelanotide treatment. They also said that they did not think recall bias concerns in the studies were necessarily valid because people with EPP can usually recall events such as a phototoxic reaction accurately. The committee acknowledged that the recently published evidence provided more information on the treatment effects of afamelanotide. But it noted the limitations of the data outlined by the ERG, and was aware that none of the

data provided could be used to inform the economic model. The committee concluded that it would take the study results into account in its decision making.

Nature of the qualitative evidence

- 4.29 The committee discussed at length the nature of the testimonies from people with EPP and their carers as evidence. It found the qualitative evidence from patient and carer testimonies particularly persuasive, and it was the major factor in the committee questioning the clinical trial results. But it recognised that the current state of science does not allow for data collected in this way to be used to quantify the burden of EPP or the benefit of the technology. What the data was able to do was contribute to the understanding of the nature of EPP, and to interpreting the clinical evidence. The committee understood that qualitative evidence collected systematically and analysed using standard techniques could potentially have provided more scientifically robust information about the clinical effectiveness of afamelanotide (see [section 4.48](#)). It also highlighted the use of the [NICE real-world evidence framework](#), which could be used to generate real-world evidence prospectively. It recognised that the qualitative information it had been presented with on the clinical effectiveness of afamelanotide could not feed into QALY calculations. But it noted that it was highly valuable in informing the nature of the condition, the benefits of the treatment and the meaning of those benefits for people with EPP and their families. Given the specific challenges associated with EPP, the committee concluded that it was important to take into account testimonies from people with EPP and other qualitative evidence as part of its decision making.
- 4.30 The committee understood that, because of the nature of EPP, measuring health-related (HR) QoL was difficult for people with the condition (see [section 4.8](#)). The committee highlighted that the [NICE decision support unit](#) had issued updated guidance on alternative methods for measuring and valuing HRQoL when the available EQ-5D data from clinical studies is insufficient for the needs of the economic evaluation. It noted that qualitative descriptions of health states associated with EPP could be used to elicit quantitative utility values when using a vignette study methodology (see [section 4.48](#)). Such a study would collect the experiences of people with EPP or experts to form a detailed description of each disease health state (a 'vignette') as a way of capturing the qualitative dimension

of the condition. The QoL associated with each vignette could then be quantified using established methods. Preferably, these would involve the general population or, alternatively, clinical experts to provide an objective estimate of utility. This was one of the alternative methods discussed in the decision support unit guidance. The committee concluded that qualitative descriptions of EPP could be used to inform the economic model if a vignette study approach was taken to estimate utilities.

Clinical-effectiveness conclusions

4.31 The committee considered the breadth of the clinical-effectiveness evidence, including the clinical trials, observational studies, stakeholder-submitted evidence and testimonies. It acknowledged the challenges in measuring the benefits of afamelanotide, and that these influenced the limitations in the clinical-effectiveness evidence for the drug. It also accepted that the clinical trial results may not have adequately represented the benefits of afamelanotide. It highlighted the influence of qualitative evidence, in particular, to help further clarify the clinical significance and practical meaning of the treatment effect for people with EPP and their families. The committee noted the benefits associated with afamelanotide in clinical trials, and recalled the importance and value of those benefits for people with EPP and their families. Nevertheless, the committee considered it important to take into account the uncertainties in the evidence and in the quantification of the benefits. It considered that, although it thought that afamelanotide did offer a clinical benefit, the size of the benefit remained uncertain. Overall, the committee concluded that afamelanotide is effective and provides important benefits for people with EPP. But it further concluded that there are important uncertainties in the evidence and the size of the clinical benefits because of the challenges specifically associated with collecting data in EPP.

Cost to the NHS and value for money

Company's model

- 4.32 A large amount of information relating to the company's model structure and assumptions was considered confidential by the company. The committee was disappointed because this meant that its discussions and decisions on the model could not be fully described publicly. 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's model stratified the condition into mild, moderate and severe disease, based on EPP-QoL scores divided into 3 equal ranges (that is, 67 to 100, 33 to 67 and 0 to 33 respectively), and each range was assigned a disability weight to generate DALYs. The effectiveness of afamelanotide and standard care was based on the proportion of people in the 3 ranges, using pooled clinical trial data on the EPP-QoL collected at 4 months. The ERG presented several exploratory analyses, including direct conversion of the company's approach to generate QALYs instead of DALYs and an alternative modelling approach.
- 4.33 The committee discussed the company's stratification of the condition into mild, moderate and severe disease. The company considered that arbitrary division of the EPP-QoL into thirds was the fairest approach in the absence of validated cut-offs for EPP severity using the EPP-QoL. The committee recalled the challenges associated with measuring QoL in EPP using EPP-QoL (see [section 4.18](#)). It concluded that the company's approach to stratifying disease severity according to arbitrary quantiles contributed to the uncertainties in the economic modelling.

Disability-adjusted life year framework

- 4.34 The company stated that it did not support using utility values to quantify QoL in EPP 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. Rather, the company considered that it was more appropriate to consider the effect of EPP and afamelanotide on people's QoL in terms of disability. At the second evaluation committee meeting, the company stated that it did not consider the

DALY approach to be more appropriate than QALYs. It considered that no approach entirely reflected the complexities in EPP, and that the DALY model was its attempt to present an alternative approach. The committee noted that the NICE interim process and methods guide of the Highly Specialised Technologies Programme states that, as part of the consideration of value for money, the committee will consider the ICER expressed as an incremental cost per QALY gained. It stated that using QALYs was in the NICE reference case (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. But the committee can consider non-reference case methods alongside those in the reference case if there is a strong enough case for it. But the committee was not persuaded by the argument for preferring an analysis based on the DALY rather than the QALY. The committee was aware that the ERG had provided a simple adaptation of the company's model, which showed that the DALY and the QALY approaches produced similar ICERs. The committee concluded that, although it would take the DALY-based model into account in its decision making, its preferred approach was the one aligned with the NICE reference case.

Generating DALYs and QALYs

4.35 In its DALY-based framework, the company 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. But because the GBD survey did not ask about EPP, the company used weights for a proxy condition it considered similar to EPP in its modelling. The company considered the proxy condition to be confidential. The committee appreciated similarities between some important aspects of EPP and the proxy condition, but was aware of other important aspects that were quite different. 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 4.18](#)). The committee questioned further why the company preferred to map from other conditions that may not be fully representative of EPP rather than directly using patient-level QoL 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. But 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 concluded that the proxy condition used by the company may not fully capture the experience of people with EPP. It also concluded that the assumption that it is similar to EPP in general and at different levels of severity was not sufficiently robust.

- 4.36 The committee queried whether it would be possible to generate utility weights (and hence QALYs) from the EPP-QoL data (for example, by mapping to the EQ-5D). It noted that the EPP-QoL has not been assigned preference weights or mapped to a tool such as the EQ-5D. The committee understood that it was not possible to generate utility weights directly from the EPP-QoL data. After the committee meeting, 1 clinical expert suggested that EPP-QoL visual analogue scale (VAS) data could be used to infer utility values. But the ERG highlighted that there were several problems in using VAS data in this way. In particular it noted that, fundamentally, VAS data represented health status and not utility.
- 4.37 At the first meeting, the ERG presented alternative methods to generate QALYs in exploratory analyses. It presented 2 analyses in which the company's modelling approach was directly converted to generate QALYs. One approach involved converting the disability weights to utilities, the other involved sourcing utilities rather than disability weights for the same proxy condition from a published source. These approaches both used the same disease stratification and proxy condition as the company's base case. The ERG also presented an alternative approach in its exploratory base case, in which it used DLQI data for afamelanotide and standard care from 1 clinical trial (in place of the disease stratification approach in the company's model). The DLQI scores were mapped to the EQ-5D to derive utility values using a published, validated algorithm. The committee considered that this approach provided a more direct link between QoL measured in the clinical trials and the modelled benefits, with fewer assumptions than the company's proxy condition base-case approach. But it

reiterated questions about whether the DLQI measured in the trials adequately captured the QoL associated with EPP and the benefits of afamelanotide (see [section 4.19](#)). So, the committee considered that the ERG's approach may have underestimated the real-life benefits of afamelanotide because these may have been underestimated in the trials and may not have been captured in the DLQI. But the committee noted that it was not possible to quantify the underestimation.

- 4.38 Overall, the committee acknowledged important limitations in all the presented modelling approaches. It considered that quantifying the effects of the condition and benefits associated with afamelanotide, and translating those into QALYs, was a crucial uncertainty in the economic modelling. It highlighted that, even if the EPP-QoL is the best available tool for capturing the burden of EPP, it still had uncertainties (see [section 4.18](#)), and the modelling based on EPP-QoL still relied on the disease stratification and proxy condition. The committee recognised that the appropriateness of DLQI and its sensitivity to the effects of EPP and treatment have been questioned. But it acknowledged that it would capture some relevant aspects (see [section 4.19](#)), and that the modelling based on it provided a more direct link between QoL measured in the clinical trials and the modelled benefits. The committee concluded that on balance all the modelling approaches had limitations.

Additional assumptions

- 4.39 The committee noted that the modelling was based on EPP-QoL data collected at 4 months, but that this data was also collected at 6 months, although from a smaller proportion of the trial population. This data had not been provided by the company. The committee considered that, if the EPP-QoL data was to be used, the longer follow-up data could have been useful to see. This was particularly because 1 clinical expert explained that the benefits of afamelanotide may take time to become apparent if people adapt their conditioned behaviour gradually.
- 4.40 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. The ERG 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 people with EPP 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 effects of afamelanotide (melanisation and presumed antioxidant effect) need 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. But on balance, it concluded that the ERG's analyses assuming that the effect of afamelanotide would build up over the first 2 months (as modelled in its base case), and that the treatment effect would slowly decrease over 6 months after the last implant, used plausible assumptions.

- 4.41 The committee discussed the likely dosage 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 often be used, but that some people may not need the maximum number. The company provided an estimate of the average number of implants people with EPP may have. This was 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 deemed it to be commercial in confidence. The company did not provide any detail on whether its estimate 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 per year in its decision making, and noted that the data from the Wensink et al. (2020) study supported this.

Role of ICERs in decision making

- 4.42 The company challenged the use of the ICER in the committee's decision. It, and other stakeholders, considered that the ICER alone had determined the initial decisions, and that inherent problems had not been taken into account. In particular, the company emphasised the significant challenges in measuring the

effects of EPP and the benefits of afamelanotide. It considered that the QALY estimates, and hence the ICERs, were not appropriate to use for decision making in this case. The committee was aware of its remit as reflected in [NICE's principles](#) and the [NICE constitution](#), which requires it:

- to consider the broad balance between the benefits and costs of providing health services of social care in England
- take account of NICE's commitment under the NHS Constitution to provide 'the best value for taxpayers' money and the most effective, fair and sustainable use of finite resources.

The committee recalled the crucial importance of considering value for money in a fair and consistent way as part of this remit. It emphasised that an important part of NICE's approach to achieving a fair and consistent health technology evaluation programme was to use QALYs as a measure of treatment benefit and noted that this is enshrined in [NICE's principles](#). This states that, if possible, NICE considers value for money by calculating the ICER. This is based on an assessment of the intervention's costs and how much benefit it produces compared with the next best alternative. It is expressed as the 'cost (in £) per QALY gained'. This takes into account the 'opportunity cost' of recommending one intervention instead of another, highlighting that there would have been other potential uses of the resource. It includes the needs of other people using services now or in the future who are not known and not represented. The primary consideration underpinning NICE's guidance and standards is the overall population need. This means that sometimes NICE does not recommend an intervention because it does not provide enough benefit to justify its cost. It also means that NICE cannot apply the 'rule of rescue', which refers to the desire to help an identifiable person whose life is in danger no matter how much it costs. The committee emphasised that value for money must remain an important (but not the only) part of the decision in this case, and that the ICER was not the only contributor to its view on value for money (see [section 4.58](#)). It explained that all its decisions on highly specialised technologies are reached by in-depth committee deliberation. The committee considered that the methods for establishing ICERs in this population were not so uncertain as to be unreasonable for them to contribute to decision making, provided those ICERs are considered in the context of the associated challenges, limitations

and uncertainties. It concluded that it was appropriate to consider the ICERs for afamelanotide as part of its consideration of value for money.

QALY weight

- 4.43 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 size of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained. For a QALY weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. The committee discussed the QALY gains associated with afamelanotide. The QALY gains were driven by improvements in QoL. The committee considered the size of the treatment benefits predicted by the models in both the company's base case and the 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 lifetime of someone with EPP, the undiscounted QALYs gained with afamelanotide in the ERG's original exploratory base case were 0.56, and did not exceed 0.8 in the ERG's sensitivity analyses. The committee noted that the ERG's original analysis may have underestimated the QALY gains associated with afamelanotide. The committee recalled that there was uncertainty around the utility estimates (and the disability estimates in the company's model), and also recalled that the quantification of the benefits of afamelanotide was a critical uncertainty in this evaluation. Taking into account the clinical trial results, observational studies and qualitative evidence including testimonies from people with EPP and clinicians, it recognised that the original economic modelling was likely to have fallen short in capturing the full benefits of treatment in the QALY estimates.
- 4.44 The committee considered the impact of the time horizon on the economic analysis and the undiscounted QALYs. In the second consultation, the IPPN

responded to the approach taken in this evaluation. It commented that the time horizon used in the original modelling was 35 years, which was not a lifetime horizon. It said it thought a longer time horizon was more appropriate and in line with previous highly specialised technology evaluations. The IPPN noted that the incremental QALY gain estimated by the ERG's analysis was smaller than the utility benefit associated with oral administration that had been accepted by the committee for a previous evaluation ([NICE's highly specialised technologies guidance on eliglustat for treating type 1 Gaucher disease](#)). It highlighted that this did not appear to be valid. The committee acknowledged that the IPPN's comments were in line with its own concerns that the ERG's analysis may not have captured all the benefits associated with afamelanotide treatment. After the second consultation, the ERG's exploratory analyses were done using the new information provided by stakeholders. Because these used the original model structure, they incorporated a 60-year time horizon. The committee also considered comments from the IPPN in the third consultation concerning the time horizon. The IPPN stated that most time horizons assumed for conditions that start in childhood and have a near normal life expectancy, with technologies recommended for funding, are at least 80 years. The IPPN stated that a 70-year time horizon, which it thought to be more appropriate, would increase the QALY gains and potentially qualify afamelanotide for QALY weighting. The ERG noted that a 70-year time horizon would increase the ICER and would not reduce the uncertainty in the cost-effectiveness analysis. It explained that the increase in ICER was because utility declines with age because of the age-adjustment of utility values, but the cost is constant each year. As per the [NICE process and methods guide](#), in some circumstances, adjustments to utility values (for example, for age or comorbidities) may be needed. The committee recalled that, because of limited data in treatment for older people, afamelanotide use is not recommended in people over 70, as per [afamelanotide's summary of product characteristics](#). It considered that, if afamelanotide is used in line with this recommendation, a 70-year time horizon assumes diagnosis and treatment at birth. It recalled that the British Porphyria Association stated that the median age of diagnosis is 22 years (see [section 4.6](#)).

- 4.45 The committee considered whether to apply the QALY weighting. It recalled that for a QALY weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. The committee noted that the HRQoL evidence used to underpin the updated analyses was subject to considerable

uncertainty (see [section 4.50](#)). But, given the nature of EPP, it was considered in the decision making as a part of a reasonable adjustment. It also noted that the analyses using this HRQoL evidence was considered to determine whether afamelanotide could be considered plausibly cost effective for a recommendation with managed access rather than for routine commissioning. The committee concluded that, because of the uncertainty in the HRQoL evidence, there was not enough compelling evidence underpinning the analysis using the additional data submitted by the IPPN at the second consultation to apply a QALY weight. It further concluded that the criteria for applying a QALY weight were not met.

Cost-effectiveness results: ICERs

4.46 The committee considered the results of the original company and ERG exploratory base case and scenarios presented at the first evaluation committee meeting. It noted that the ICERs were updated after the third consultation with the new list price for afamelanotide. It also noted that the following ICERs were all over £100,000 per QALY gained:

- the company's base case: £305,244 per DALY averted (£305,151 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: £1,892,822 per QALY gained
- the ERG's exploratory base case (3 implants per year, gradual onset and 2-month attenuation of the relative treatment effect): £1,759,833 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 (see [section 4.40](#)): £1,472,513 per QALY gained
- the ERG's exploratory base case assuming 2 implants per year: £1,465,343 per QALY gained
- the ERG's exploratory base case assuming a maximum of 4 implants per year: £1,958,162 per QALY gained.

The committee noted that the ICER was £1,892,822 per QALY gained using the EPP-QoL data and disease stratification, and the company's preferred proxy condition (based on utilities from the literature rather than disability weights). It considered this to be very similar to the ERG's exploratory base-case ICERs. The committee preferred the assumptions used by the ERG to those used by the company. But it concluded that the ICERs based on the ERG's exploratory base case were unlikely to be plausible. This was because the base case may have underestimated the QALY gains associated with afamelanotide.

Challenges in quantifying treatment benefits in the economic modelling

- 4.47 The committee was aware that a critical uncertainty for the evaluation was in the quantification of treatment benefits and the translation of the benefits into QALYs (see [section 4.38](#)). The committee recalled its consideration of the importance of value for money as part of its remit (see [section 4.42](#)). It also recalled that, taking into account the clinical trial results, observational studies and qualitative evidence, it recognised that the economic evaluations before the second consultation were likely to have fallen short in capturing the full benefits of treatment in the QALYs (see [section 4.13](#)). The committee recognised that some of the problems with the economic modelling were influenced by the challenges of measuring the effects of the condition and treatment (see [section 4.8](#)). So, the committee considered that it would be reasonable to consider alternative methods to capture the benefits of afamelanotide.
- 4.48 Before the second consultation the committee explored ways to quantify the health benefits described by testimonies from people with EPP and clinical experts in terms of QALYs. It suggested that utility scores for the economic model could be estimated through an indirect method such as a 'vignette' study. Such a study would collect experiences of people with EPP or experts to form a detailed, description of each disease health state (a 'vignette'), in this way capturing the qualitative dimension of the condition. The QoL associated with each vignette could then be quantified, using established methods, preferably by the general

population or alternatively by clinical experts, to provide an objective estimate of utility. The committee suggested that such a study should consider the effects of all aspects of the condition and the treatment on HRQoL, including the totality of the experience of people with EPP and, for example, effects on employment and effects on the health of family members.

- 4.49 After the second and third consultations, the committee was disappointed that the company had chosen not to do a vignette study. The company questioned the value of a vignette study and stated that it did not believe a vignette study would adequately capture the effects of EPP. The company further stated that the vignette methodology had not been validated for EPP and that it consulted with EPP experts who did not believe a vignette study would be suitable in EPP. The patient experts added that they were concerned that the qualitative descriptions of health states needed for a vignette study would understate the severity of EPP. They emphasised that it would be very difficult for members of the public and clinicians to fully understand the real burden on a person's QoL with EPP. The patient experts noted that, in their experience, the condition is often underestimated or not taken seriously. This was primarily because avoiding light becomes automatic and ingrained (or 'conditioned') behaviour. They were concerned that any qualitative description of EPP could result in an underestimate of the true burden on their QoL. The committee explained that similar approaches had previously been considered in other highly specialised technologies evaluations when direct measurement was not possible, as recommended by the [decision support unit guidance on the use of qualitative evidence to inform generation of utility values in health technology assessment](#). The committee also recalled that testimonies from people with EPP at committee meetings effectively highlighted the serious, debilitating and disabling nature of EPP. The committee also clarified that people with EPP could be directly involved in the wording of the vignette, with input from clinical experts to ensure states had been described appropriately. It acknowledged that such approaches are not necessarily as robust as the preferred approaches specified in the NICE reference case, but that it would be reasonable to consider given the challenges associated with this condition. The committee considered that, if such a study was submitted, it may be possible to refine the QALY estimates and then reconsider with a higher degree of certainty the QALY gains and value for money of afamelanotide.

4.50 The committee took into account responses from other stakeholders and the new QoL evidence they submitted after the second consultation (see [section 4.20](#)). The committee accepted the new evidence, despite the limitations, because capturing the HRQoL in EPP is challenging. Such data provided evidence that EQ-5D may be responsive to EPP, and about the effect of afamelanotide on QoL. The committee agreed that the new QoL evidence submitted by the patient groups provided more information on the experiences of people with EPP. But it concluded that the evidence was still highly uncertain.

Cost-effectiveness scenarios after the second consultation

4.51 After the second consultation, the committee considered further exploratory cost-effectiveness scenarios based on the new QoL data submitted by stakeholders (see [section 4.20](#)). The committee considered the following exploratory scenarios:

- Using the IPPN's Swiss EQ-5D feasibility study to inform the utility value for people with EPP on afamelanotide and the utility value estimated from Holme et al. (2006) for baseline utility. Two different mapping algorithms were explored in Holme et al., but the resulting utilities were very similar for both algorithms (0.6). The committee noted that the utility estimated in the IPPN's Swiss EQ-5D feasibility study for people on afamelanotide was higher than that of the general population for the average age in the model. So, the committee chose to adjust this utility value to match that for the UK general population for a person of that age.
- Using the IPPN's EQ-5D patient survey results to inform the utility value for people with EPP on afamelanotide and the utility estimated from a treatment interruption for people having standard care. The committee chose to adjust the utility value for people on afamelanotide to match the utility value for the UK general population for a person of the assumed starting age in the company's model.
- Both analyses assumed a dosage of 4 implants per year of afamelanotide to reflect clinical expert opinion (see [section 4.41](#)) and Wensink et al. (2020), a gradual onset of effect over 2 months and a 4-month attenuation of the relative treatment effect after the fourth implant. The committee chose

adjusting utilities by age over the time horizon of the model.

Using these assumptions in the model and the updated list price for afamelanotide resulted in ICERs that ranged from £133,748 per QALY gained (using the IPPN's EQ-5D patient survey utility values) to £253,676 per QALY gained (using the IPPN's Swiss feasibility study utility values). The committee considered these to be optimistic scenarios in light of the range of ICERs presented during the course of the evaluation and the associated uncertainty with the QoL data submitted by the IPPN.

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

4.52 The committee discussed the impact of afamelanotide beyond its direct health benefits, mainly based on the testimony of the patient experts. It noted that people with EPP often alter their career plans to accommodate the effects of their condition, and might be unable to take up enhanced career opportunities. But the clinical experts explained that, after treatment with afamelanotide, people with EPP may feel confident enough to move to a career with a higher level of light exposure and a higher income. The clinical experts also acknowledged that this process might take 2 to 3 years, or perhaps longer in older people for whom a career change is more difficult. 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, although it was not provided with any data on this. The company provided exploratory analyses on loss of earnings associated with EPP, but the committee was unclear what the data underpinning the company's assumptions was. It also noted that the most optimistic scenario reduced the company's original ICER from £305,244 per DALY averted in the company's base case to £124,397 per DALY averted. This was based on the assumption that people having afamelanotide receive 90% of the mean wage whereas people having standard care earn only 10% of the mean wage. The committee considered 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 4.4](#)). The committee recalled the far-reaching effects of EPP on families of people with the condition, and heard that treatment with afamelanotide has substantial social, educational, financial and psychological benefits for families. The committee concluded that afamelanotide would have an impact beyond direct health benefits but that quantifying this was difficult.

Cost-effectiveness conclusions

4.53 The committee considered the cost-effectiveness estimates from the ERG's exploratory analysis and from the analysis based on the additional evidence submitted by the IPPN at the second consultation. The results were updated after the third consultation to incorporate the company's new list price. Using the original model and the ERG's exploratory base-case assumptions, the ICERs were between £1.46 million and £1.89 million per QALY gained. The committee considered that these ICERs may be overestimates if the QALY gains associated with afamelanotide were underestimated. In the absence of the company providing any additional HRQoL evidence that could be used in the economic model, the committee also considered the exploratory analysis based on the IPPN evidence submitted at the second consultation. It considered that the evidence underpinning this analysis (see [section 4.20](#)) was extremely uncertain, but that it may better reflect the range of experiences with the treatment of people with the condition and clinical experts. The committee used these analyses for the basis of its decision making as a part of a reasonable adjustment given the nature of the condition. The ICERs associated with these analyses ranged from £133,748 to £253,676 per QALY gained. The committee considered that £133,748 per QALY gained was a potentially plausible ICER although this was the most optimistic scenario it had been presented with. It recalled that it had decided not to apply a QALY weighting (see [section 4.45](#)), and noted that the ICER from this most optimistic scenario was above what could be acceptable for a highly specialised technology. It also considered that the current evidence for afamelanotide was too uncertain to make a recommendation for routine use.

Managed access

- 4.54 Having considered that a recommendation for routine use could not be made (see [section 4.53](#)), the committee considered the potential for a recommendation with managed access. It noted that the [Innovative Medicines Fund](#) had launched during the evaluation. This created a new opportunity for a managed access agreement to be considered by the company and NHS England. The aim of such an agreement would be to resolve some of the uncertainties and to potentially support a recommendation for routine funding in the future.
- 4.55 After the third consultation, the company submitted its proposal to collect data as part of a managed access agreement. The proposal considered that data collected within the ongoing European EPP disease registry, operational since 2016, could sufficiently resolve the key uncertainties if extended to England. The proposal included:
- using the EPP-QoL and exploring whether it was possible to map to standard HRQoL measures and tools
 - using an EPP-specific Inventory of Daily Activities (IDA) tool, which has been in use post authorisation since 2016, and exploring whether this can be mapped to standard HRQoL measures and tools; the IDA captures information on the overall disability and restrictions placed on people with EPP, and changes to these over time
 - extending the registry to capture data on the number of implants per patient per year in England
 - investigating a possible hepatoprotective effect with afamelanotide in people with EPP
 - a statement that the company considered that a 5-year window for data collection and analysis would provide sufficient time to capture data to resolve the uncertainties
 - committing to the principles of the [Innovative Medicines Fund](#).

The committee was presented with the NICE managed access team's initial assessment of the data collection proposals. It noted that the company had

stated it plans to explore whether the EPP-QoL and IDA tool can be mapped to accepted HRQoL measures and tools. But it thought that this could potentially be explored with the currently available EPP-QoL and IDA data. The company did not provide any further detail on how it would develop a mapping algorithm, so it was not possible to assess whether this would be feasible. The ERG noted that, for a mapping approach to contribute to the reduction in uncertainty over cost effectiveness, it would be essential to administer an accepted instrument for utility assessment with a preference-based UK value set (preferably the EQ-5D in line with the NICE reference case). This would need to be done alongside the disease-specific outcome measures in a representative sample of people with EPP. It also noted that, to reduce uncertainty, it would be necessary to collect data on all important prognostic factors, including the season and weather at the times of assessment. The mapping algorithm should be capable of retrospectively estimating utility outcomes from the trial data, in addition to assessing utilities from the real-world data sources.

4.56 The committee discussed the company's proposal, and the NICE managed access team and ERG assessments. It noted that the vignette study remained its preferred method for the quantification of QALYs. But it also thought that alternative approaches like those proposed by the company could also generate utility values. The committee thought that the feasibility of generating a robust mapping algorithm may be limited by the sample size available. It noted that generating preference weights or mapping to an outcome measure that could provide preference weights would likely need a longer time window, and substantially more data compared with a vignette study. But the committee considered that these methods could also be explored as options to generate utility values.

4.57 The committee concluded that the company's data collection proposals were potentially valid, but that it would have needed to see further details on how the company planned to generate preference weights. It noted that, for a technology to be considered for managed access, it needs to have plausible potential to be considered cost effective by the committee. The most optimistic potentially plausible ICER that the committee considered after the third consultation remained in excess of £100,000 per QALY gained. The company reconfirmed its commitment to uniform pricing, which meant the ICER remained above £100,000

per QALY gained. So, the committee concluded that afamelanotide could not be considered for managed access.

Other factors

4.58 In line with [NICE's principles](#), the committee acknowledged that its recommendations should not be based on evidence of costs and benefit alone, and that other factors should be taken into account when developing guidance. The committee considered whether any other factors would affect its decision. It was aware of the full range of factors affecting decision making in the Highly Specialised Technologies Programme (including the nature of the condition, clinical evidence, value for money and the impact of the technology beyond direct health benefits). It concluded that all relevant factors had already been taken into account in its considerations, and that no specific additional considerations were needed.

Equality considerations

4.59 The committee considered whether there were any equality issues. It recalled its recognition that EPP is a disability and understood its duties under the Equality Act 2010 (see [section 4.8](#)). It emphasised that it had taken this disability into account throughout its deliberations, and whether and how it would be reasonable to adjust its approach to avoid discrimination and promote equality. Throughout the process, the committee considered the challenges of measuring the benefits of treatment. As part of its reasonable adjustments to the usual highly specialised technologies process, it made several amendments to the usual process. The first adjustment was to take into account the company's non-reference case economic model, based on a DALY framework, as part of the committee's decision making (see [section 4.32](#)). The committee concluded that, although it would take the DALY-based model into account in its decision making, its preferred approach was the one aligned with the NICE reference case. The ERG converted the company's model to a QALY model to generate an ICER, in line with the NICE reference case. It also explored the use of proxy conditions to measure HRQoL to aid the committee's decision making (see [section 4.34](#)). The

committee concluded that the clinical trials and original company model and ERG amendments might have underestimated the treatment benefits. This was based mainly on its considerations of patient and expert testimonies informing the clinical effectiveness of afamelanotide. This led the committee to request further data on improvement in HRQoL. This was so it could investigate whether refined values would reduce the initial ICERs, which were well above the threshold representing good use of NHS resources. The committee made suggestions to the company and stakeholders for alternative methods of capturing HRQoL. It gave the company additional time to collect this evidence after the third committee meeting. The committee accepted evidence from the IPPN after the second consultation that was highly uncertain but useful for exploring the plausible range of improvements in QoL for people having afamelanotide. The committee also explored increasing the time horizon to explore the impact on the incremental costs and benefits. The committee concluded that it had fully taken into account the disadvantages encountered by people with EPP and the difficulties in quantifying the benefit of treatment with afamelanotide. It also concluded that there had been sufficient and many reasonable adjustments made to the highly specialised technologies guidance process to promote equality between people with EPP and people with other rare and disabling conditions considered by the Highly Specialised Technologies Programme.

Conclusion

- 4.60 The committee recognised that EPP is a serious, debilitating and disabling condition with far-reaching effects on the lives of people with the condition and their families. It understood the important challenges in measuring the effects of the condition and the benefits of treatment, including the lack of scientific instruments and the effect of conditioned light avoidance behaviours. Bearing in mind the full breadth of clinical-effectiveness evidence, including the clinical trials, observational studies and evidence from people with the condition and their families, it was convinced that afamelanotide is an effective medicine that provides valuable benefits. It also acknowledged that the clinical trial results may not have fully captured the benefits of afamelanotide. It also considered that afamelanotide was innovative and had non-health-related benefits.
- 4.61 The committee recognised that the original economic modelling had significant

uncertainties, influenced by the important challenges in measuring the effects of the condition and the benefits of treatment. It considered that quantifying the benefits associated with afamelanotide and translating those benefits into QALYs was a crucial uncertainty in the economic modelling. It further considered that it was appropriate to make a decision taking into account the QALYs and ICERs as part of its consideration of value for money, in the context of the associated challenges, limitations and uncertainties. It recalled that the ERG's ICERs based on the original model ranged between £1.46 million and £1.89 million per QALY gained, but that these ICERs were unlikely to be plausible. This was because they may have underestimated the QALY gains associated with afamelanotide.

- 4.62 The committee discussed the QoL evidence submitted by the IPPN after the second consultation and how it could be used to estimate ICERs. It considered that the evidence provided (see [section 4.20](#)) was highly uncertain. But it thought that it could be taken into account in this instance as part of its reasonable adjustments because of the nature of the condition and the challenges in quantifying QALY benefits (see [section 4.8](#)). The ICERs using the committee's preferred scenarios and based on the evidence submitted by the IPPN were between £133,748 and £253,676 per QALY gained. These analyses estimated substantially higher QALY gains than those estimated from the clinical trial data. The committee considered that these QALY gains, although highly uncertain, were still potentially plausible. This was because they may better reflect the range of experiences with the treatment of people with EPP and clinical expert experiences. The committee considered that the most optimistic potentially plausible ICER it had been presented with was £133,748 per QALY gained. But it also noted that the evidence underpinning this scenario was associated with substantial uncertainty.
- 4.63 Based on all of the information that it had considered, including the economic analyses, patient and clinical expert testimonies and the significant uncertainties in the evidence, the committee concluded that afamelanotide would not currently provide value for money. The committee also concluded that, despite the other factors that it had considered, it could not recommend afamelanotide for routine commissioning in the NHS in England.
- 4.64 The committee considered that there remained a critical uncertainty in the evaluation in how the effects of the condition and treatment benefits were

quantified and translated into QALYs. It considered that it would be possible to gather better information to try to address this uncertainty, for example, a vignette study or a study to map between a condition-specific tool (EPP-QoL or IDA) and EQ-5D. The committee considered that these approaches might allow it to reconsider with a greater degree of certainty the QALY benefits and so the value for money of afamelanotide. It also thought that it may be possible to do this research within the timeframe of a managed access agreement.

- 4.65 The committee considered that afamelanotide could not be considered to plausibly provide value for money at its current price. It noted that the company has a uniform pricing policy so did not propose a simple confidential patient access scheme discount. The committee also noted that, while there had been discussion between the company and NHS England, this had not led to agreement on any other commercial arrangement that could be considered. So, it concluded that the criteria for managed access had not been met. Taking into account all the available evidence, including all its reasonable adjustments to avoid discrimination and promote equality for people with EPP, the committee concluded that afamelanotide was not recommended.

5 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.

Chair

Peter Jackson

Chair, highly specialised technologies evaluation committee

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, Alan Moore, Dilan Savani

Technical Leads

Ian Watson, Victoria Kelly

Technical Advisers

Joanne Ekeledo, Daniel Davies

Project Managers

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