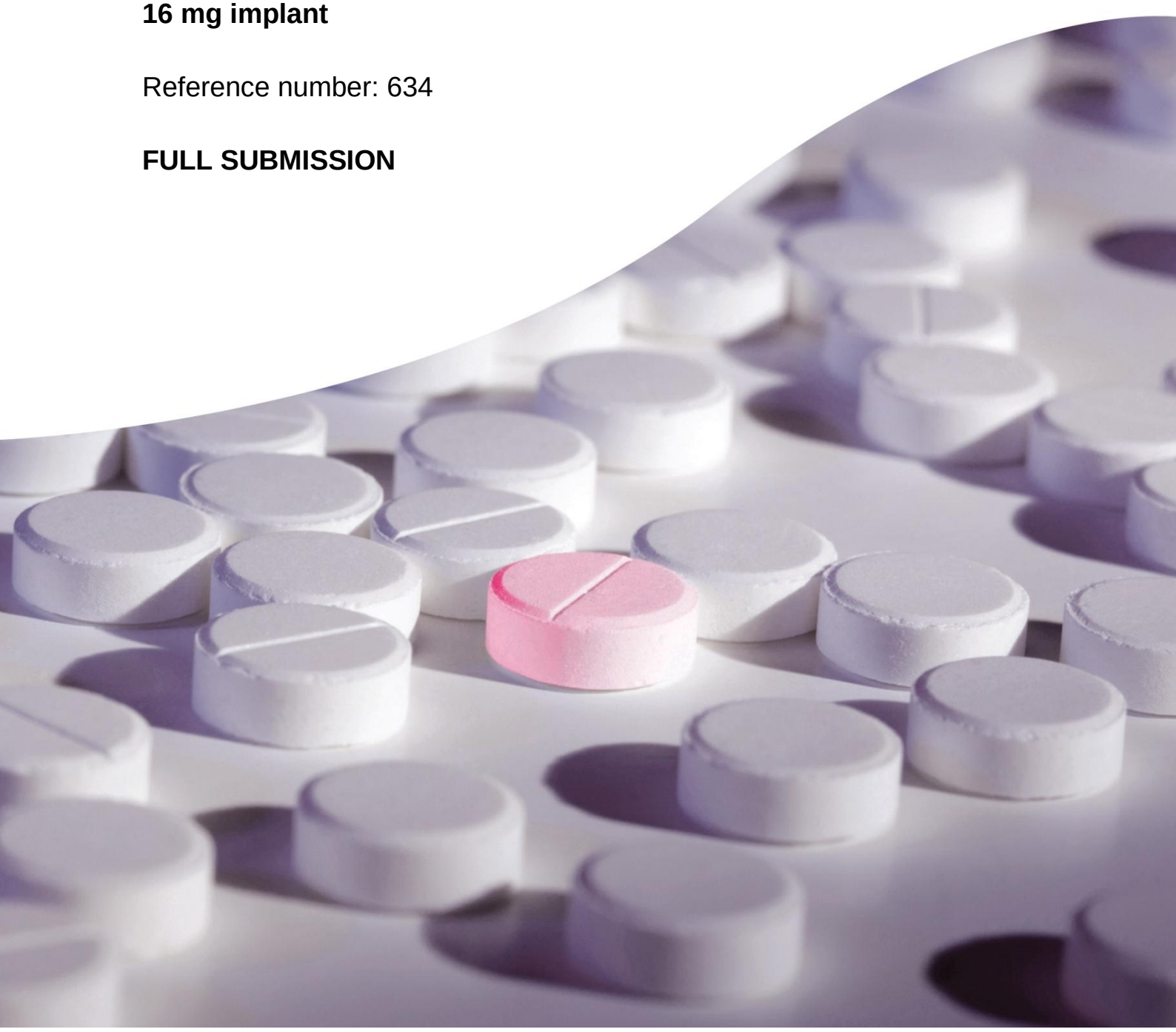
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Afamelanotide (Scenesse®)
16 mg implant

Reference number: 634

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Afamelanotide (Scenesse®▼) 16 mg implant

This assessment report is based on evidence submitted by Clinuvel Pharmaceuticals Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Afamelanotide (Scenesse®▼) for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP)[2]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Dosing	One implant administered subcutaneously every two months before expected or during increased sunlight exposure, such as from early spring to autumn. Three implants per year are recommended, depending on the length of protection required. The recommended maximum is four implants per year. Overall duration of treatment is at the specialist physician's discretion. Refer to the Summary of Product Characteristics for further dosing information[2].
Marketing authorisation date	22 December 2014[3]
UK launch date	1 April 2017[1]

2.0 DECISION CONTEXT

2.1 Background

Erythropoietic protoporphyria (EPP) is a rare cutaneous porphyria that affects approximately 25 per 1,000,000 people in the UK[4-6]. EPP results from a partial deficiency of ferrochelatase, the final enzyme in the haem biosynthetic pathway[5]. This leads to the accumulation of protoporphyrin in red blood cells, plasma, liver and skin[5,7]. When exposed to artificial light or sunlight, protoporphyrins produce free radicals that can cause painful skin damage[5].

People with EPP experience life-long photosensitivity and phototoxicity[5]. Effects include tingling, itching, painful burning (immediate or delayed), as well as reddening and swelling of the affected area[5]. In the most severe cases people with EPP experience absolute intolerance to light and intolerable burning pain on the exposed skin[5]. People with EPP are therefore severely limited in their outdoor activities and develop photoprotective behaviours with a marked impact on quality of life[5].

Management of EPP is based mainly on protective measures, such as use of sunscreens, wearing sun protective clothing, and avoiding bright light and sun exposure[5]. Treatment can also include dietary supplements (beta-carotene or cysteine), but these have been found to have limited efficacy[5,7]. Further supportive care includes the use of analgesics, anti-histamines, topical corticosteroids and cold compress[5].

Afamelanotide is a synthetic analogue of the physiologically occurring alpha-melanocyte stimulating hormone[5]. It acts by directly stimulating melanocytes to produce eumelanin, which pigments the skin. The intended action of this pigmentation is to protect against phototoxic reactions caused by sunlight[5].

2.2 Comparators

The comparator included in the company submission, for the economic analyses only, was standard of care: afamelanotide is the first licensed medicine for the prevention of phototoxicity in adult patients with EPP[1].

2.3 Guidance and related advice

- European Dermatology Forum. Guidelines in the classification, diagnosis and treatment of the photodermatoses. 7. Endogenous: The (cutaneous) porphyrias (accessed 10 Feb 2017)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes a brief overview of five clinical trials:

- CUV039, the pivotal phase III trial to confirm the safety and efficacy of afamelanotide in patients with EPP[5,8]. A good clinical practice (GCP) inspection was performed on CUV039 in 2014 and revealed one major finding regarding safety/adverse event reporting, but did not reveal any critical issues that would prevent efficacy assessment[5].
- CUV030 and CUV029, phase II and phase III studies that were submitted as pivotal studies to support the marketing authorisation of afamelanotide in 2009, prior to CUV039. However, following a GCP inspection the Committee for Medicinal Products for Human Use (CHMP) concluded that these studies were not pivotal and excluded from the European Public Assessment Report (EPAR) efficacy evaluation[5,8].
- CUV017, a phase III study was also initially intended to be submitted as the pivotal study for the marketing authorisation of afamelanotide[5]. However, CHMP assessed the crossover design as unsuitable for a pivotal study and it will not be discussed further[5].
- CUV010[9], a phase II open-label, uncontrolled study. This lead to the studies listed above and will not be discussed further.

3.1 CUV039

CUV039 was a pivotal phase III, multicentre, double-blind, randomised, placebo-controlled study to confirm the safety and efficacy of afamelanotide implants in patients with EPP[5,8]. The study took place over a six month period at centres in the US[5,8]. Patients included in the study were aged 18 years or older with biochemically confirmed EPP[5,8]. Patients were not eligible if they had clinically significant hepatic or other organ dysfunction, skin cancer, premalignant lesions or other photodermatoses[8].

Patients (n = 94) were randomised 1:1 to receive either afamelanotide or placebo implant[8]. Placebo implants were identical to the afamelanotide implants[8]. Implants were inserted on days 0, 60 and 120 of the trial[8].

The primary endpoint of the study was the duration (total hours) of direct exposure to sunlight without 'pain' between 10 am and 6 pm in the intent-to-treat population (n = 89)[8]. This was evaluated based on a patient diary where the intensity and duration of pain and exposure to sunlight and shade were recorded daily[8]. Time spent outdoors was recorded in 15 minute intervals as "direct sunlight" or "shade"[8]. Pain was scored using an 11-point Likert pain intensity scale, with scores ranging from 0 to 10 and higher scores indicating greater severity of symptoms[8]. As shown in Table 1, the total number of hours spent in direct sunlight without pain was significantly higher in the

afamelanotide group compared to the placebo group (median 69.4 versus 40.8; p = 0.044).

Table 1. Primary and some secondary efficacy endpoints of the CUV039 trial[5,8]

	Afamelanotide (n = 46)	Placebo (n = 43)	p-value
Primary endpoint: total no. of hours in direct sunlight between 10 am and 6 pm without pain (Likert score of 0)			
Median per patient (range)	69.4 (0–650.5)	40.8 (0–224.0)	0.044
Mean per patient (SD)	115.6 (140.6)	60.6 (60.6)	
Secondary endpoints:			
No. of hours in direct sunlight between 10 am and 6 pm on days with no pain or mild pain (Likert score of 0–3)			
Median per patient (range)	80.0 (0.5–825.0)	51.0 (1.25– 251.0)	0.053
Mean per patient (SD)	141.1 (165.1)	74.6 (67.5)	
No. of hours in direct sunlight between 10 am and 6 pm regardless of pain score			
Median per patient (range)	83.5 (0.5–825.0)	65.3 (3.5–278.5)	0.066
Mean per patient (SD)	145.0 (164.1)	81.8 (71.2)	
No. of hours in direct sunlight between 10 am and 3 pm without pain (Likert score of 0)			
Median per patient (range)	39.6 (0–419.0)	31.8 (0–198.8)	0.092
Mean per patient (SD)	71.2 (89.2)	41.6 (45.3)	
n: number of patients; SD: standard deviation.			

To provide an objective measure of light tolerance, photoprovocation was also included as a secondary endpoint. Patients (n = 21) were exposed to visible light on two small areas on the back of the hand and on the lower back[5,8]. The minimum irradiation dose of visible light needed to provoke symptoms was determined at baseline (day 0) and on days 30, 60, 90 and 120. Patients treated with afamelanotide (n = 11) demonstrated higher tolerance to light compared with patients treated with placebo on both the hand and back (n = 10). The differences were statistically significant on days 90 and 120[5,8].

Quality of life (QoL) was also assessed as a secondary endpoint[5,8]. This study included the Dermatology Life Quality Index (DLQI), a questionnaire that is not specific for people with EPP but is widely used in dermatology to assess QoL[5]. There were no clinically relevant or statistically significant differences between groups in QoL at any time point when assessed using the DLQI questionnaire[5].

A new disease specific EPP-QoL questionnaire was developed and then revised following validation prior to the CUV039 study[8]. Both the original and revised EPP-QoL assessments showed a significantly improved QoL from baseline in the CUV039 study[5]. The results for the revised EPP-QoL are shown in Table 2.

Table 2. EPP-QoL questionnaire scores (revised version)[5,8]

	Afamelanotide		Placebo		p-value
	Mean score (SD)	n	Mean score (SD)	n	
Baseline score at day 0, before dose 1	26.6 (19.9)	47	26.2 (19.4)	43	
Change at day 60, before dose 2	44.0 (25.8)	47	23.4 (24.6)	43	< 0.001
Change at day 120, before dose 3	49.8 (26.4)	46	30.4 (25.4)	42	< 0.001
Change at day 180, after dose 3	51.1 (29.1)	46	36.8 (25.7)	43	0.02
Scores at day 360, 240 days after last dose	38.4 (27.0)	44	45.4 (29.6)	40	
n: number of patients; SD: standard deviation.					

The results of the secondary endpoints related to sun exposure, phototoxic events, quality of life and photoprovocation testing all numerically favour the afamelanotide group, though differences between groups only inconsistently achieve statistical significance[5].

3.2 CUV029 and CUV030

CUV029 and CUV030 were similar studies designed at the same time in order to evaluate the efficacy and safety of afamelanotide[1]. Both studies were finalised before data analysis for the CUV017 crossover study was available[1]. CUV029 was a phase III, double-blind, placebo-controlled study that took place over a nine month period in Europe[5,8]. CUV030 was a phase II, double-blind, placebo-controlled trial that took place over a six month period in the US[1,5]. Inclusion and exclusion criteria were similar to CUV039[5,8].

Due to results from CUV017, the objectives for CUV029 and CUV030 were changed whilst the studies were still ongoing[5]. The primary endpoint of both studies was changed to exposure to sunlight without pain between 10 am and 3 pm (this was included as a secondary endpoint in the pivotal CUV039 study [see Table 1])[5]. This was evaluated by a patient diary where the intensity and duration of pain and exposure to sunlight and shade were recorded daily[8]. Time spent outdoors was recorded in 15 minute intervals as mainly in direct sunlight, mainly in shade, or a combination of both[5,8]. Although the trends in both studies were considered consistent with the CUV039 trial, CUV029 and CUV030 were excluded from the efficacy evaluation due to GCP noncompliance[5].

3.3 Safety

In the afamelanotide arm of the pivotal study (CUV039; n = 48), 45 patients (94%) reported at least one adverse event of any severity[8]. The majority of adverse events were mild to moderate, with three patients (6%) reporting at least one severe adverse event. The serious adverse events were considered by the principal investigator to be unrelated to the study drug. The most common adverse events included headache (n = 19 [40%]), nausea (n = 9 [19%]), nasopharyngitis (n = 6 [13%]), and back pain (n = 6 [13%]). There were no clinically relevant differences between the afamelanotide and placebo groups, with the exception of mild skin discolouration at the implant site in nine patients (19%) from the afamelanotide arm. No deaths were reported during the study[8].

At the time of licensing, CHMP considered safety data from all five EPP trials (CUV010, CUV017, CUV029, CUV030, CUV039) involving a total of 231 patients with EPP who had been treated with afamelanotide[5]. The most common adverse events based on number of reports and assessed as related to afamelanotide were headache (n = 54 [23%]), nausea (n = 53 [23%]), migraine (n = 6 [3%]) and back pain (n = 4 [2%]). Most adverse events were mild in severity[5].

Due to the short treatment periods (maximum up to one year), the safety data provided by the EPP trials are limited. The safety data set included additional long-term safety data from expanded access/compassionate use programmes in Italy and Switzerland (73 patients)[5]. These programmes observed relatively high long-term adherence to afamelanotide, with few withdrawals based on lack of efficacy or tolerability. Reasons for discontinuation included heart disease (n = 1; patient deceased), pregnancy (n = 5) and weight gain (n = 1). Discontinuation due to lack of efficacy was reported in three patients[5].

CHMP concluded that there were no indications for safety signals that would prevent granting marketing authorisation[5]. CHMP also determined that the most relevant safety concern is the lack of long term data (less than two years) and that further characterisation of the long term safety profile of afamelanotide is needed[5]. This included a specific obligation for the marketing authorisation holder to establish a disease registry prior to launch in order to gather long term safety data and endpoints, from both patients and physicians[5]. A retrospective study was also imposed to assess the long term safety data and outcome endpoints, in addition to assessing compliance to the risk minimisation recommendations and controlled access program for patients receiving afamelanotide[5].

3.4 AWTTC critique

- Afamelanotide is considered a first-in-class treatment licensed for the prevention of phototoxicity in adult patients with EPP[5].
- The findings from available data are limited due to the various deficiencies identified in trial design and data analyses. Even when regarding the statistical significant difference in the primary endpoint as valid from the pivotal trial CUV039, CHMP acknowledged it is not clearly evident from the clinical trials whether the apparently small increase in sunlight would translate into a meaningful change in the patients' life[5]. However, with no authorised medicinal products for EPP, there was a clear unmet medical need for treatment[5]. CHMP granted marketing authorisation of afamelanotide under exceptional circumstances with the obligation of the market authorisation holder to complete post-authorisation measures[5].
- Studies (CUV029, CUV030 and CUV039) included in the company submission compare afamelanotide versus placebo and do not include an active comparator. The company has only highlighted a comparator (standard of care) for the economic analyses[1]. [Commercial in confidence information removed]. Compliance with sunscreen was also reported to be poor[1,5].
- Due to the absence of an appropriate active comparator, the increased pigmentation (tanning) caused by afamelanotide could have resulted in the unblinding of patients[5]. This could therefore lead to bias within the studies, especially due to the inclusion of subjective efficacy endpoints (based on patient diary) and QoL surveys.
- The EPP-QoL survey indicated a benefit for patients treated with afamelanotide versus placebo. EPP-QoL is not a verified measurement of QoL, but was developed specifically for the EPP trials to try and capture the specifics of the disease, with input from EPP clinical experts[1]. The only validated QoL instrument used, DLQI, did not demonstrate statistically significant differences in QoL between afamelanotide and placebo[5].
- A key limitation in all the EPP trials is the life-long sun avoidance behaviours of patients with EPP[5]. Due to the phototoxicity and pain patients usually experience, they are often reluctant to modify these behaviours[5]. CHMP stated that it is therefore challenging to show significant efficacy of afamelanotide, particularly in short studies (six and nine months) that do not give patients enough time to 'trust' the treatment and risk light exposure[5].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost-effectiveness analysis of afamelanotide (a 16 mg subcutaneous implant; with a maximum of four implants per year) compared to standard of care (no treatment) for the prevention of phototoxicity in adults diagnosed with EPP[1].

[Commercial in confidence information removed]. The cost of tests and healthcare was taken from published unit costs[10,11].

[Commercial in confidence information removed].

4.1.2 Results

[Commercial in confidence information removed].

AWMSG guidance stipulates that economic evaluations should take the form of cost-utility analyses, with results expressed as incremental costs per QALY gained. The QALY provides a 'common currency' which allows different medicines to be compared for different conditions. This allows AWMSG to make its decisions consistently, transparently and fairly. [Commercial in confidence information removed].

Table 3. Results of the base case analysis

	Afamelanotide + SOC	SOC	Difference
Base case presented by the company			
Total cost per patient	¶¶	¶¶	¶¶
Total DALYs per patient	¶¶	¶¶	¶¶
ICER (£/DALY averted)	¶¶		
Base case as per AWMSG guidance			
Total cost per patient	¶¶	¶¶	¶¶
Total QALYs per patient	¶¶	¶¶	¶¶
ICER (£/QALY gained)	¶¶		

¶¶: Commercial in confidence figures removed.

AWMSG: All Wales Medicines Strategy Group; DALY: disability-adjusted life-year; ICER: incremental cost-effectiveness ratio; SOC: standard of care; QALY: quality-adjusted life-year.

Table 4 summarises the scenarios provided by the company in order to address uncertainty around the key input parameters. Several scenario analyses were tested using alternative data sources. [Commercial in confidence information removed].

Table 4. Results of the scenario analyses

Scenarios	ICER	Plausibility
Scenario 1: Number of afamelanotide implants per year increased	¶¶	These scenarios are plausible as, in the SPC, the recommended dose is 3 implants and the maximum dose is 4 implants per year.
Scenario 2: Starting age of 18 years	¶¶	This scenario is plausible as EPP is a life-long, hereditary condition.
Scenario 3: Alternative utility values in CUA. Weighted average calculated using "in between" attacks instead of "mild attacks". *Note: QALYs are based on values for* [Commercial in confidence information removed] *as a proxy.*	¶¶	The plausibility of this scenario depends on whether [Commercial in confidence information removed] is an appropriate proxy for EPP and whether the condition is intermittent or always active.
Scenario 4: CUA utility values extrapolated from SF-36 scores of the CUV017 trial using logarithmic function.	¶¶	The plausibility of this scenario is uncertain as the company states that none of the statistical models fit the trial data well as a result of the crossover study design and the characteristics of the disease.
Scenario 5: CUA utility values extrapolated from SF-36 scores of the CUV017 trial using linear function.	¶¶	The plausibility of this scenario is uncertain as the company states that none of the statistical models fit the trial data well as a result of the crossover study design and the characteristics of the disease.
Scenario 6: CUA utility values extrapolated from SF-36 scores of the CUV017 trial using exponential function.	¶¶	The plausibility of this scenario is uncertain as the company states that none of the statistical models fit the trial data well as a result of the crossover study design and the characteristics of the disease.
Scenario 7: Different multiplying factors for moderate and severe weights from the disability weights of anxiety disorders.	¶¶	The plausibility of these scenarios is uncertain as the methods and rational of the approach are unclear.
Scenario 8: Alternative DALY proxy used for DALY weighting: [Commercial in confidence information removed].	¶¶	The plausibility of this scenario depends on whether [Commercial in confidence information removed] is an appropriate proxy for EPP.
Scenario 9: Inclusion of loss of earnings for patients based on different employment capacities.	¶¶	This scenario is irrelevant to the assessment context as AWMSG will only consider NHS costs.

¶¶: Commercial in confidence figures removed.

AWMSG: All Wales Medicines Strategy Group; CUA: cost-utility analysis; DALY: disability-adjusted life-year; EPP: erythropoietic protoporphyria; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SF-36: 36-Item Short Form Survey; SPC: Summary of Product Characteristics.

The results of the deterministic sensitivity analyses suggest large fluctuations in the ICER that are very sensitive to changes in the utility and disutility extrapolations, the proxy used and the number of implants per year.

No probabilistic sensitivity analysis was provided by the company.

4.1.3 AWTTC critique

The results of the base case cost-effectiveness analysis indicate that the preventative use of afamelanotide is considerably more costly but produces decreased QoL-loss compared to standard of care alone in adult EPP patients. [Commercial in confidence information removed]. The sensitivity analyses show that the results are not robust and very sensitive to changes in the utility and disutility extrapolations, the proxy used and the number of implants per year. [Commercial in confidence information removed].

Strengths of the economic analysis:

- In the absence of other licensed treatments, standard of care appears to be the appropriate comparator for this patient group.
- The company has made a clear effort to estimate utility and disutility values in the absence of published utility data for EPP patients.

Limitations of the economic analysis:

- While the company makes a clear effort to estimate utility and disutility data through weighting, appropriate proxies and extrapolation of trial data, the analyses are severely limited by the lack of robust utility data. [Commercial in confidence information removed]. It is unclear how much bias will be introduced by the amount of data manipulation involved and how accurately the obtained utility and disutility scores reflect the QoL of EPP patients.
- The model only includes two health states (alive and dead) with mortality assumed to be that of the general population (and hence equal) for both arms. The model does not consider adverse events and disease-specific mortality. This means that the only two data inputs that are different between the groups are cost of treatment and utility values. Costs are added into the calculations as an annual total (stable over lifetime) and utilities are entered as a weighted annual average (identical for every year of life). This means that the ratio of costs and effects becomes linear and remains constant over time without taking account of individual transition probabilities. Therefore, the ICERs are identical irrespective of the chosen time horizon and starting age of the population. Calculating the ICER from the total costs and weighted mean utilities results in the same ICER as computed for the lifetime horizon. This oversimplification severely limits the usefulness of the model, making it redundant, and will cause considerable bias. It would have been preferable to use a more complex Markov model with five health states (in-between attacks, mild, moderate, severe attacks and dead) and to include adverse events.
- The company's base case presents a cost-effectiveness analysis using DALYs instead of QALYs as outcome measure. The rationale for this decision was the lack of robust utility data on which to inform a cost-utility analysis approach and the fact that the company considers a cost per DALY averted framework to be a better fit for the condition and treatment provided. The company states that the usual generic questionnaires were deemed inappropriate in identifying the nuances of the underlying condition and quantifying their impact on health related QoL. Studies CUV029, CUV030 and CUV039 therefore collected QoL data using the EPP-QoL questionnaire that the company developed in cooperation with leading clinical experts. There is no mapping algorithm to map EPP-QoL to a utility measure. [Commercial in confidence information removed]. The approach taken is not well described and it is unclear how much uncertainty this complex approach introduces. [Commercial in confidence information removed]. It is therefore unclear why the company has chosen to

use DALYs in the base case. Based on this evidence and the AWMSG preference for a cost-utility approach, AWTTC considers that the sensitivity analysis using QALYs is the most plausible estimation of cost-effectiveness [Commercial in confidence information removed].

- The company state that the model uses a lifetime horizon, but this is not the case. [Commercial in confidence information removed]. The rationale for this approach is unclear.
- The company suggests that no extrapolation method tested was a good fit for the utility data available. Sensitivity analysis of the cost-utility analysis shows that different extrapolation methods cause large variations in the ICER [Commercial in confidence information removed], with the linear extrapolation resulting in the lowest ICER. No extrapolation method is used in the cost-utility analysis base case. It is unclear which ICER is the most plausible.
- The company states that hepatic disease affects 10–15% of people with EPP[1]. However, for simplification purposes, the economic model assumes that life expectancy is normal and that normal hepatic function is maintained for all patients. This omission will underestimate the costs and overestimate the benefits calculated by the model, artificially reducing the ICER.
- [Commercial in confidence information removed]. This is based on an assumption considered plausible by the company (data on file unavailable to the AWTTC for review). The maximum licensed dose is 4 implants per year. The largest European study to date found an average dose of 2.6 implants[12]. It is therefore likely that the base case underestimates the cost of treatment. [Commercial in confidence information removed].
- Costing of implantation and follow-up visits is based on clinical practice of single centres in Rotterdam and Dusseldorf. It is unclear how generalisable these practices are to the Welsh setting and how accurately these costs reflect costs accrued in Welsh clinical practice.
- The model assumes sustained efficacy of afamelanotide over a patient's lifetime. To date, available data are restricted to 12 months. Therefore, there is no longer term data to support this assumption. The company suggest that antibodies against afamelanotide did not develop in 26 Swiss patients after up to six years of exposure[13]. However, it is unclear how this relates to sustained efficacy.
- The oversimplified model reduces the economic analysis to a simple ICER calculation based on annual total costs and weighted mean utilities. Furthermore, the severe limitations of the utility values further restrict the usefulness of the analysis. AWTTC therefore believes that the economic analysis presented by the company cannot accurately reflect the cost-effectiveness of afamelanotide over a life time horizon.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-utility of afamelanotide for the treatment of adult patients with EPP.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The overall prevalence of EPP in the UK is estimated to be 25 in 1,000,000[4], with reports of a specific prevalence in Wales of 1 in 200,000[14]. This equates to between 15 and 79 EPP patients of all ages in Wales. The budget impact model assumes a prevalence number of 17 to 27 based on data provided by the Cardiff Porphyria Service (data on company file, not verified). Incidence of EPP in the UK is reported to be 0.33 in 1,000,000 per year[4], without Wales-specific data available. [Commercial in confidence information removed].

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 5. [Commercial in confidence information removed].

Table 5. Company-reported costs associated with use of afamelanotide

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Number of eligible patients (Adult EPP patients)	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving treatment	¶¶	¶¶	¶¶	¶¶	¶¶
Afamelanotide acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Replaced medicine cost (SOC only, includes laboratory tests, screening and photoprovocation tests))	¶¶	¶¶	¶¶	¶¶	¶¶
Afamelanotide administration costs	¶¶	¶¶	¶¶	¶¶	¶¶
Afamelanotide laboratory tests, screening and photoprovocation tests	¶¶	¶¶	¶¶	¶¶	¶¶
Net resource implications	¶¶	¶¶	¶¶	¶¶	¶¶
Net financial costs	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶: Commercial in confidence figures removed.

EPP: erythropoietic protoporphyria; SOC: standard of care.

[Commercial in confidence information removed].

5.1.3 AWTTC critique

- The data sources and calculations used for the budget impact model provided by the company are poorly described and only limited sensitivity analyses are undertaken.
- It is unclear how the number of eligible patients was derived. The methods are not described and no calculations are provided in the model. AWTTC can therefore not verify these numbers.
- Uptake rates are estimates based on the company's experience and data on file not available for review. Any changes to the uptake rate will affect the budget impact of afamelanotide.

5.2 Comparative unit costs

Annual acquisition costs of afamelanotide are described in Table 6. To date, no other treatment options are licensed in the UK for the treatment and prevention of phototoxic effects in patients with EPP.

Table 6. Examples of acquisition costs of specific treatment for patients with EPP

Regimens	Example doses	Approximate annual costs
Afamelanotide (Scenesse®) 16 mg subcutaneous implant	Maximum of 4 implants per annum.	¶¶

¶¶: Commercial in confidence figures removed

No other regimens are licensed for use in this patient population.
Costs and doses provided by company[1]. Costs of administration are not included.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, afamelanotide (Scenesse®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The Summary of Product Characteristics states that Scenesse® should only be prescribed by specialist physicians in recognised porphyria centres[2]. Administration should be performed by a physician trained and accredited by the marketing authorisation holder to administer the implant[2].

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months. Patients in the Netherlands, Switzerland (non-EC), Italy, Austria and Germany are being treated under the Post Authorisation Safety Study (PASS) protocol. Longitudinal data on safety and effectiveness (continuation data) are being collected under conditions of use. Safety data have already been generated from these studies and effectiveness data are expected at the end of 2017.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7 February 2017
Date range of evidence search: No date limits were applied to database searches.

6.6 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that afamelanotide (Scenesse®) in the given population meets the AWMSG criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted European Medicines Agency (EMA) designated ultra-orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[15].

[Nle4, D-Phe7]-alpha-melanocyte stimulating hormone (afamelanotide) is designated an orphan medicine by the EMA for the treatment of EPP[16]. The EMA suggest a prevalence of 0.2 per 10,000 people in the European Union, thus meeting orphan status[16]. The company suggest an overall prevalence of 25.4 per 1,000,000 in the UK[4] and a specific prevalence in Wales of 1 per 200,000 population[14] based on published reports. This would result in between 15 and 79 patients of all ages in Wales of which only adult patients would be considered for treatment with afamelanotide. Data

provided to the company by the Cardiff Porphyria Service, which is the leading expert centre in Wales, suggests that 15 adult patients are currently known to the service (personal correspondence with the company, not available for AWTTC review).

The criteria for assessing clinical effectiveness and cost-effectiveness of ultra-orphan medicines are the same as those applied to other medicines, but recognising that the evidence base may be weaker. NMG/AWMSG will consider evidence on the following to inform their decisions (see Table 7).

Table 7. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG.

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	EPP is a genetic disorder that can result in phototoxic reactions upon exposure to both environmental and artificial visible light, which may last for days or weeks[17] and are unresponsive to medication (including regular analgesics). During a reaction, any subsequent exposure to light, heat variation, pressure or air movement can exacerbate and prolong symptoms. This causes severe anxiety, with recent reports of suicidal ideations[18]. People with EPP will avoid all forms of light exposure. This leads to an indoors existence, lifelong isolation and deprivation of social interaction. Long-term scarring, particularly of the face, lips and hands, is common[7]. Studies suggest that EPP is "a persistent, severely painful, socially disabling disease with a marked impact on QoL"[7] that severely restricts people's lives[19].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	Afamelanotide is the only licensed medicine for the prevention of phototoxicity in people with EPP. Light avoidance (including avoidance of transmission through glass) is reported as the only other effective preventative treatment[20]. There is no current guidance from NHS Wales or NHS England on the treatment or management of EPP and current standard of care varies between UK clinics[7].
Whether the medicine can reverse, rather than stabilise the condition.	Afamelanotide does not reverse or cure the condition. It reduces the length and severity of anaphylactoid and phototoxic reactions and increases the amount of time people with EPP are able to tolerate exposure to light with either limited or no phototoxicity that improves people's QoL[20].
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	Afamelanotide does not bridge a gap to definitive therapy. No curative therapy for the gene defect exists or is in development for EPP.
The innovative nature of the medicine.	The company suggests that afamelanotide is a new molecular entity in a specially designed novel subcutaneous formulation[1]. It is the first pharmaceutical product developed to provide therapeutic and endogenous photoprotection in the visible spectrum of light for people with EPP[1].

Table 7 continued

NMG/AWMSG considerations	AWTTC comments
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	The company suggests that the impact of EPP on people's QoL is substantive but impossible to quantify due to the unique nature of the disease and the lack of specific enough tools to accurately measure the impact of EPP on people's lives. Also, patient feedback on the effectiveness of afamelanotide was often more positive than the statistical results from clinical trials, as the study outcome of time in direct sunlight did not include indirect or incidental light exposure[20]. People with EPP often show signs of mental distress and anxiety throughout their lives, based on the awareness that light exposure (sunlight, ambient and artificial light sources) will be followed by anaphylactoid reactions and second-degree burns. This leads to isolation, social withdrawal and depression[19]. Furthermore, EPP has a significant impact on people's ability to participate in normal activities, such as schooling or work, with significantly higher rates of unemployment in people with EPP compared to the healthy population[21]. Most people with EPP also suffer from low vitamin D levels due to their inability to expose to sunlight[22].
Added value to the patient's family (e.g. impact on a carer or family life).	People with EPP are unable to engage with society, including participating in normal family life (such as caring for children or participating in outdoor activities at home or work)[12].
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; EPP: erythropoietic protoporphyria; NMG: New Medicines Group; QALY: quality-adjusted life-year; QoL: quality of life.	

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