Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Dr Alan G MacDonald

afamelanotide 16mg implant (Scenesse®) SMC No (1251/17)

Clinuvel (UK) Ltd

07 July 2017 (*Issued 15 January 2021*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra-orphan process

afamelanotide (Scenesse®) is not recommended for use within NHS Scotland.

Indication under review: prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

In a phase III study, afamelanotide increased the duration of time, over a six-month period, that patients with EPP spent in direct sunlight on pain-free days compared with placebo.

The submitting company's justification of the treatment's cost in relation to its benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).[1]

Dosing Information

One 16mg implant is administered subcutaneously every two months prior to expected and during increased sunlight exposure, e.g. from spring to early autumn.

Three implants per year are recommended, depending on the length of protection required. The recommended maximum number of implants is four per year. The overall duration of treatment is at the specialist physician's discretion.

Afamelanotide should only be prescribed by specialist physicians in recognised porphyria centres and administration should be performed by a physician trained and accredited by the marketing authorisation holder to administer the implant.[1]

Product availability date

16 November 2020
Afamelanotide meets SMC ultra-orphan criteria.

Background

Afamelanotide is considered a first-in-class melanocortin receptor agonist and binds mainly to the melanocortin-1 receptor. Afamelanotide is a structural analogue of α-melanocyte stimulating hormone (α-MSH) and is thought to mimic the pharmacological activity of α-MSH by activating the production of eumelanin which contributes to photoprotection.[1, 2]

EPP is caused by a partial deficiency of the last enzyme in the haem biosynthesis pathway, ferrochelatase. This results in the accumulation of protoporphyrin IX in erythrocytes, plasma, liver and other tissues. Exposure to light (sunlight and strong artificial light) causes pain related to cutaneous damage in patients with EPP. [2, 3]

Afamelanotide for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

EPP is a rare socially disabling condition that has a substantial and persistent impact on the quality of life of affected patients.[4] Exposure to light (sunlight and strong artificial light) can cause phototoxicity in patients with EPP resulting in pain related to cutaneous damage. This may occur after less than 30 minutes of light exposure. Initial symptoms would be itching and tingling and continued exposure results in erythema, oedema and painful burning. The pain typically lasts for three days but symptoms may continue for up to four weeks.[2] The current management of EPP involves avoidance of sunlight and strong light, covering the skin with sun-

protective clothing and application of mineral sunscreens containing zinc oxide or titanium oxide. Pain relief, anti-histamines, topical corticosteroids and a cold compress may be used as supportive care for photoreactive symptoms. Ultra-violet B (UVB) phototherapy may be used to prevent phototoxicity in patients with EPP.[2] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely prevention of phototoxicity in patients with EPP.

A patient and clinician engagement (PACE) meeting was held to consider the added value of afamelanotide in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the severity of the pain experienced during phototoxic reactions. This was described as 'intense, shooting and unrelenting'. Clothing and touch exacerbates the pain and painkillers often have little or no benefit. During a phototoxic episode the patient may be incapacitated and unable to concentrate, impacting on ability to be fully effective at work. Once a phototoxic episode has commenced, any further exposure to visible light is immediately painful. Fear and anxiety relating to the pain experienced during EPP photosensitivity reactions is often experienced by patients with EPP, resulting in their avoiding light life-long. EPP affects relationships, as patients are unable to fully engage with family, friends and colleagues. Increasing the amount of time that patients with EPP could spend outdoors would have significant health benefits.

Impact of new technology

Summary of evidence on comparative efficacy

The key evidence to support the marketing authorisation was CUV039, a phase III, multicentre, double-blind, randomised, placebo-controlled study of afamelanotide in patients with EPP. The study was conducted at seven porphyria centres in the United States (US). Inclusion criteria were adult patients (≥18 years old) with EPP (biochemically confirmed) who suffer from phototoxic reactions. The aim was to confirm safety and efficacy of afamelanotide subcutaneous implant. The primary objective was to identify whether afamelanotide can allow patients with EPP to expose themselves to sunlight without experiencing pain or phototoxic reactions.[2]

Patients were randomised equally to receive afamelanotide 16mg subcutaneous implant (released over 7 to 10 days) or placebo subcutaneous implant. This was administered on days 0, 60 and 120. The treatment phase lasted for six months and a safety follow-up visit occurred at 12 months.[2, 3]

The primary endpoint was the duration of direct exposure to sunlight between the hours of 10am and 6pm on days where the patient did not experience any pain related to phototoxicity, assessed over the six-month study period. Baseline data for exposure to sunlight prior to the intervention was not recorded. A Likert pain score of zero indicated no pain. Time spent outside was measured in 15-minute periods and recorded in the patient diary as separate entries for time spent in direct sunlight or in the shade.[2, 3] Intention to treat (ITT) population (defined as all treated patients who provided at least one post dose efficacy assessment) was the main population used for all efficacy analysis.[2]

The primary endpoint of total number of hours in direct sunlight on pain-free days (per patient) over the six-month study period was significantly increased in the afamelanotide group (n=46) compared with placebo (n=43), p=0.044. In the afamelanotide group, the mean was 115.6 hours (standard deviation 140.6) and the median was 69.4 hours (range 0–650.5). In the placebo

group, the mean was 60.6 hours (standard deviation 60.6) and median was 40.8 hours (range 0–224). Over the six month study, the mean difference for the duration of time spent in direct sunlight between 10am and 6pm on pain-free days for the two groups was 55.0 hours. The median difference was 28.6 hours. A key secondary outcome of mean daily exposure to direct sunlight between 10am and 6pm on pain free days showed no significant difference between afamelanotide and placebo (p=0.075) with medians of 25.9 and 18.1 minutes in the respective groups and means of 43.3 and 23.7 minutes.[2] There was a subgroup of 15 patients who were able to experience more than 60 minutes of sunlight each day; 12 of these were in the afamelanotide group, with six of these patients in the afamelanotide group able to experience more than 90 minutes each day.[2]

A number of other secondary efficacy outcomes were also reported, the majority of these did not identify any statistically significant differences between the afamelanotide and placebo groups, see table 1. No difference in the number of phototoxic episodes, which occurred at a very low frequency during the study, were observed between groups. There were also no statistically significant differences in the maximum and total pain severity scores (Likert scale) for phototoxic episodes.[2]

Table 1: CUV039 key secondary outcomes[2]

	Afamelanotide group (n=46)	**Placebo (n=43)**
The duration over the six-month study of sun exposure (hours in direct sunlight per patient) between 10am and 6pm on days when no pain or mild pain was experienced (Likert pain scores of 0 to 3)		
Mean	141.1 hours	74.6 hours
Median	80.0 hours	51.0 hours
Kruskal-wallis p value	p=0.053	
The duration over the six-month study of sun exposure (hours in direct sunlight per patient) between 10am and 6pm during the study regardless of pain score		
Mean	145 hours	81.8 hours
Median	83.5 hours	65.3 hours
Kruskal-wallis p value	p=0.066	
The duration over the six-month study of direct sunlight exposure between 10am and 3pm hours on days when no pain was experienced (Likert score of 0)		
Mean	71.2 hours	41.6 hours
Median	39.6 hours	31.8 hours
Kruskal-wallis p value	p=0.092	

Quality of life (QoL) was assessed by the Dermatology Life Quality Index (DLQI) which is not specific to EPP and the “purpose designed” EPP-QoL questionnaire.[2] Quality of life assessment score according to the DLQI did not result in any statistically significant or clinically relevant differences between the two groups although an improvement from baseline in both groups was observed.[2, 3] The EPP-QoL questionnaire designed by the submitting company specifically to assess QoL in patients with EPP (original and revised versions were used, scores cannot be compared with each other) identified significant differences between the treatment groups. The original scoring identified improvement from day 0 to day 180 (shown by decreasing scores) of 23 to -2.5 in the afamelanotide group and 24 to 5 in the placebo group (median values). The revised scoring identified improvement from day 0 to day 180 (shown by increasing scores) of 19 to 86 in the afamelanotide group and 22 to 69 in the placebo group (median values). Scores for the revised EPP-QoL questionnaire decreased at day 360 but were higher than initial scores

at day 0.[2] An end of study EPP questionnaire designed to assess differences in QoL was also completed as an exploratory endpoint. Answers to some questions were more positive in the afamelanotide group compared with the placebo group.[2]

Studies CUV029 and CUV030 were placebo-controlled studies of afamelanotide in patients with EPP. The results from these studies support a trend in efficacy favouring afamelanotide over placebo. However these studies were found to be non-compliant with Good Clinical Practice (GCP) standards following an inspection.[2]

A long-term observational study of 115 patients with EPP treated with afamelanotide for up to eight years was conducted in Italy and Switzerland. An improvement in QoL scores (using different EPP specific questionnaires) was observed.[5]

Summary of evidence on comparative safety

In the safety population, adverse events were reported by 94% (45/48) and 87% (39/45) of patients in the afamelanotide and placebo groups, respectively. These were generally mild or moderate. There were three serious adverse events reported in the afamelanotide group and two in the placebo group. The principal investigator did not consider that these were related to the study treatment.[3] The most frequently reported adverse events in the afamelanotide and placebo groups were headache (experienced by 40% and 29% of patients in the afamelanotide and placebo groups, respectively), nausea (19% and 18%), implant-site discolouration (19% and 0), back pain (12% and 13%) and nasopharyngitis (12% and 22%).[3]

The most common adverse event thought to be related to afamelanotide observed in a long-term observational study for up to eight years was nausea followed by headache. No major adverse effects thought to be related to afamelanotide were reported.[5]

A six-monthly full body skin examination is recommended to monitor all pigmentary lesions and other skin abnormalities as afamelanotide can cause darkening of pre-existing pigmentary lesions.[1]

Summary of clinical effectiveness issues

The pivotal study CUV039 identified that over the six month study period the total number of hours in direct sunlight between 10am and 6pm on pain-free days (per patient) was significantly higher in the afamelanotide group compared with the placebo group (median difference of 28.6 hours and mean difference of 55.0 hours, p=0.044).[2] The duration of time a patient spent in direct sunlight on pain-free days is a direct health outcome. The difference between the groups was statistically significant and, although small, may be considered beneficial. Baseline data for exposure to sunlight prior to the intervention was not recorded therefore the magnitude of the treatment benefit may be uncertain. Afamelanotide was given a marketing authorisation under exceptional circumstances due to the rarity of the indication, ethical considerations around obliging patients with EPP to expose themselves to sunlight and the lack of tools available to measure the impact of light on exposed skin in patients with EPP.[2] There is an ongoing non-interventional post-authorisation disease registry safety study (PASS) to produce data on the long-term safety and clinical effectiveness of afamelanotide 16mg in patients with EPP.[6]

CUV039 was a double-blind, placebo-controlled study however afamelanotide stimulates production of dark skin pigment therefore it would likely be noticeable which patients were in the active treatment group. It should be noted that no alternative method for concealment has been identified. The expert group convened by the European Medicines Agency (EMA) considered

that although patients would likely be aware of the treatment assignment they did not feel that it would translate into a change in their behaviour. They stated that beta-carotene has previously been evaluated in EPP patients and although it resulted in tanning, no treatment effect on patient behaviour was observed. Patient diaries were used to determine the primary endpoint which relied on accurate reporting and completion by the patients included in the study. It is also difficult to measure the total sunlight exposure that patients encountered.[2]

The clinical study report (CSR) was changed as there was ambiguity in the wording of the primary endpoint. Study protocol stated it as duration in hours but the ensuing calculation referred to mean daily duration. The primary endpoint of duration over the six month study was kept following statistical advice. However, for completeness and transparency mean daily duration was also calculated as a secondary outcome. It was noted in the EMA review that the handling of missing data in the analyses of these outcomes may have contributed to the difference in statistical significance observed between them. For the primary outcome two patients were initially analysed in the wrong group and statistical significance only occurred when these were reported correctly. Although no key secondary endpoints were statistically significant, the majority numerically favoured the afamelanotide group. The pivotal study only addressed phototoxic reactions caused by sunlight not bright artificial light.[2]

In relation to QoL data, the submitting company considered that as DLQI does not contain any questions that measure the impact of light on the skin no difference between the groups would be expected to be observed. The EPP-QoL questionnaires were more specific to patients with EPP however these were designed by the submitting company and have not been fully validated. In addition, there are limited QoL data.[2]

Long-term safety and efficacy data are limited. CUV039 was six months' duration which was mainly carried out in the summer months. The expert group convened by the EMA considered that an observational period limited to six months may make it challenging to demonstrate efficacy. This is due to the fact that patients with EPP have developed a learnt behaviour pattern from childhood and are often reluctant to expose themselves to sunlight due to the intense pain that it causes. The experts suggest that patients with EPP my require an extensive time period until they have confidence in the intervention and change their behaviour to allow exposure to sunlight.[2]

The pivotal study was conducted in US population.[2, 3] There are no data for use in patients with hepatic manifestations of EPP, the elderly (greater than 70 years of age) or use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment as these patients were excluded from the study.[2, 3] Clinical experts consulted by SMC state that UVB phototherapy may be used to prevent phototoxicity in patients with EPP. There are no available data comparing afamelanotide to UVB phototherapy.

Supporting studies CUV029 and CUV030 were not considered pivotal in the efficacy evaluation by the EMA due to critical GCP findings.[2]

Clinical experts consulted by SMC considered that afamelanotide is a therapeutic advancement due to the lack of alternative treatment options and they suggest that the place in therapy is as an alternative to UVB phototherapy. They considered that the introduction of this medicine may impact on the patient and service delivery as it is administered as a subcutaneous implant. Afamelanotide should only be prescribed by specialist physicians in recognised porphyria centres therefore patients would be required to attend these centres. The frequency of

administration is low (three implants are recommended per year, maximum of four) and the patient numbers will be small.

At the PACE meeting, it was noted that clinical studies may not have been able to capture the full benefit of afamelanotide in patients with EPP. The increased amount of time that patients treated with afamelanotide were able to spend in sunlight in clinical studies may equate to an even larger amount of time spent outdoors in the shade which also has a significant benefit to patients with EPP. The pivotal study was short term therefore there was little opportunity for patients to overcome their anxiety relating to phototoxicity reactions. Over the long term, patients' anxiety may reduce enough for them to increase their exposure to light even further.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of afamelanotide, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Patients with EPP are affected physically, mentally and socially by their condition where exposure to strong light causes painful burns, oedema and scarring. Painkillers often have little or no benefit and the severe pain of phototoxic reactions results in patients avoiding light which impacts on relationships with family and friends.

- There is a lack of effective treatment options and currently the condition is managed by avoiding light; wearing protective clothing; and use of unsightly thick sunscreens.

- With respect to evidence of benefit, the clinical study reported was short term so there was little opportunity for patients to overcome their anxiety relating to phototoxicity reactions. Over the long term, it was noted that anxiety may reduce enough for patients to increase their exposure to light even further.

- Increased time spent outdoors would allow patients to fully participate in family life and undertake routine activities. It was noted that some children of patients with EPP become isolated as activities that require supervision outdoors may not be possible.

- Afamelanotide is administered approximately three times a year (maximum of four) and this has a low impact on work and family responsibilities. The implant is very small, likened to the size of a grain of rice and administration was described as 'painless'.

- Many patients find it difficult to have a normal working life in view of their inability to cope with exposure to light. The potential to increase exposure with reduced photoxicity reactions may allow patients to have a greater range of potential careers, to become economically independent, to reduce sick days, and to have increased job security.

Additional Patient and Carer Involvement
We received a patient group submission from The British Porphyria Association, which is a registered charity. The British Porphyria Association has received 12.5% pharmaceutical company funding in the past two years, with none from the submitting company.

Representatives from The British Porphyria Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Value for money

The company submitted a cost-effectiveness analysis and a cost-utility analysis comparing afamelanotide with standard of care (SoC) in the management of phototoxicity in adult patients with EPP. SoC consisted of vitamin D plus calcium (assumed purchased over the counter), and was represented by the placebo arms of the afamelanotide clinical studies. SMC clinical experts mentioned current practice consisted typically of the use of UVB phototherapy therapy which has not been included as part of the SoC comparator.

SMC would wish to present details of the methods, data inputs and results upon which the SMC decision was based, but these cannot be presented as the company required these to be treated as confidential. Consequently none of this information can be presented here.

The economic analysis had numerous weaknesses, the most important of which are listed below:

- SMC had significant concerns about the company's choice of outcome measure used in the base case analysis.

- SMC identified weaknesses with the model used to analyse the decision-problem, and in particular, the implications of the simplified structure that was used.

- The EPP-QoL analysis based on the three afamelanotide clinical studies appears flawed. There is uncertainty over the robustness and validity of the questionnaire, for example some of the questions appear vague and there are no questions for example relating to anxiety or pain. In addition to the simplistic model structure using only day 120 QoL data, the classification of patients into mild, moderate and severe based on an apparent rule of thirds for the EPP-QoL scores appears to be arbitrary and too simplistic a base for mapping to a disability or utility weight. Also, data were derived from two clinical studies that were not considered pivotal in the efficacy evaluation by the EMA due to critical GCP findings, and hence the base case analysis should therefore only have been based on use of the CUV039 study. SMC also had other concerns regarding other aspects of the data used to estimate quality of life within the modelling.

- The clinical data were also limited by short term follow-up as a basis for a lifetime economic analysis with continuous treatment with afamelanotide and continual treatment benefits estimated. Due to the simple model structure, the ICER is not sensitive to the start age and time horizon, but the aggregate health benefits gained may be overestimated.

- The number of implant injections assumed each year is based on company forecasts rather than the clinical study data, and so is not aligned with treatment effect data used. The scenario analysis with 3 implant injections, which increased the ICERs, should be the base case as it aligns with study CUV039 dosing and is the number of doses recommended in the afamelanotide SPC.[1]

- SMC clinical experts indicated that UVB phototherapy and other photoprotection measures represent current treatment options, and hence could be considered relevant comparators. Some experts indicated that these interventions may have low effectiveness so it is unclear if SoC/placebo in the current economic analysis could still be considered representative of outcomes including use of UVB phototherapy, but the costs of SoC would be higher.

*Other data were also assessed but remain confidential.**

Impact beyond direct health benefits and on specialist services

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on patients and on service delivery as it is administered as a subcutaneous implant (likened to the size of a grain of rice). Afamelanotide should only be prescribed by specialist physicians in recognised porphyria centres therefore patients would be required to attend these centres. Patient numbers will be small.

The frequency of administration is low (three implants are recommended per year, maximum of four) which would have a low impact on work and family responsibilities for patients with EPP.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 43 patients eligible for treatment with afamelanotide in year 1 rising to 63 patients in year 5 to which confidential estimates of treatment uptake were applied.

*Other data were also assessed but remain confidential.**

Conclusion

The Committee also considered the benefits of afamelanotide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as afamelanotide is an ultra orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept afemelanotide for use in NHS Scotland.

Additional information: guidelines and protocols

No relevant guidelines were identified.

Additional information: comparators

There are no licensed comparators.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
afamelanotide	16mg subcutaneous implant every two months, three implants per year are recommended up to a maximum of four implants per year	£48,627 - £64,836

References

1. Clinuvel (UK) Limited. Afamelanotide (Scennesse®) Summary of product characteristics. Available at: www.ema.europa.eu.
2. European Medicines Agency. Assessment report: SCENESSE®. Procedure No. EMEA/H/C/002548/0000. 23 October 2014. www.ema.europa.eu
3. Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM*, et al.* Afamelanotide for Erythropoietic Protoporphyria. N Engl J Med. 2015;373(1):48-59. Epub 2015/07/02.
4. Holme SA, Anstey AV, Finlay AY, Elder GH, Badminton MN. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. Br J Dermatol. 2006;155(3):574-81. Epub 2006/08/17.
5. Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol. 2015;172(6):1601-12. Epub 2014/12/17.
6. CUV-PASS-002 protocol.
7. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A*, et al.* Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2129-43. Epub 2012/12/19.
8. Aygören-Pürsün E, Caballero T, Bygum A, Beusterien K, Hautamaki E, Sisic Z*, et al.* Health Status Utility Weights for Hereditary Angioedema Attacks and In Between Attacks. The Journal of Angioedema. 2013;1(1).
9. Grosse SD, Chaugule SS, Hay JW. Estimates of utility weights in hemophilia: implications for cost-utility analysis of clotting factor prophylaxis. Expert Rev Pharmacoecon Outcomes Res. 2015;15(2):267-83.

This assessment is based on data submitted by the applicant company up to and including 21 December 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their

clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.