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Clinician and Patient Involvement Group (CAPIG)
Summary of meeting held on 21 July 2017
Afamelanotide (SCENESSE®) 16 mg implant

Marketing authorisation holder

Clinuvel Pharmaceuticals Ltd

Licensed indication

Afamelanotide (SCENESSE®) for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

Company's proposed positioning (if any)

In line with the licensed indication.

1. Severity of the condition

EPP is a life-long genetic condition. Upon exposure to natural or artificial light, people with EPP experience severe and debilitating phototoxicity. This includes a tingling and burning sensation of the skin, which can develop into intense burning pain underneath the skin, dramatic swelling (oedema), wheals, redness and blisters. In severe episodes, 'crusting' can also take place, which can lead to thickening of the skin. An EPP reaction can occur after as little as a few minutes of light exposure; further exposure to light, heat, wind or pressure can become incapacitating. Many patients have nothing visibly wrong, despite the extreme discomfort and pain they are experiencing.

On average, people with EPP experience 3–10 severe EPP reactions per year and the resulting symptoms can last for many days. The intensity and painful burning of the skin is inescapable and renders all other activity impossible: the swelling of hands and limbs make them unusable, and the skin becomes so sensitive that any kind of contact on the affected area (such as wearing clothes) brings back the pain. Performing day-to-day tasks, like eating and drinking, can be painful. The overall pain makes it impossible to concentrate on anything other than trying to relieve and/or prevent exacerbation. Any additional light exposure during an ongoing episode is immediately and excruciatingly painful. People with EPP also experience chronic fatigue when recovering from an EPP reaction, particularly throughout the summer when light reactions are more likely.

Painkillers do not work against the pain experienced during an EPP reaction. The only way to avoid these episodes is to avoid natural, and sometimes artificial, light. This includes light emitted by energy saving light bulbs and phone screens – light bulbs that emit light at 'safe' wavelengths are no longer available in the UK. People with EPP are therefore extremely disabled by the condition and have to dramatically restrict all aspects of their lifestyle to avoid triggering painful episodes. Furthermore, people with EPP can become vitamin D deficient due to their reduced sun exposure and can develop osteoporosis. It can also cause liver damage due to an over-accumulation of photoporphyrin.

In addition to the physical effects, living with EPP has a psychological and social impact. Daily life is driven by the need to avoid light. If an episode is experienced away from shelter and shade, the stress of simply getting to a safe area is intense. When driving or walking, the choice is to either compromise safety by covering the face, or to deal with the pain caused by sun exposure. The pain felt during an episode leads to loss of sleep and severe irritability due to the unavoidable pain and consequent

incapability to work or perform other daily activities. Furthermore, the pain and associated swelling of a reaction can take over a week to subside (per episode). This can impact greatly on being able to socialise, making it difficult to establish and sustain friendships and relationships, develop careers, and sustain any earning potential. Family relationships are also greatly affected, leading to increased family tensions and a detrimental impact on family life. It can affect the decision on whether or not to have children in case the condition is passed on. Participation in 'normal' daily life is so restricted, it has drastic psychological effects throughout life, including isolation, depression and suicidal thoughts. People with EPP become terrified to leave their home. When they do, they are subjected to staring and comments due to the amount of clothing needed to protect themselves against the light.

Due to EPP being a rare 'invisible' condition, diagnosis is frequently delayed, sometimes for decades, with patients being recurrently dismissed by medical practitioners. There is widespread misunderstanding about EPP, which leads to the assumption that the condition is trivial or nonexistent. Patients experiencing an extreme EPP reaction have been admitted to hospital, but their condition has been misunderstood because there are no specialist EPP centres nearby. The condition is not generally considered a disability, so there is no help or support for people with EPP; for example, it is difficult to obtain government funding support for light filters at home or at work, or the use of a blue badge to reduce the time exposed to light when walking to and from the car. The lack of acknowledgment, understanding and empathy from others all add to the psychological, professional and social impact of the condition.

2. Unmet need

There are currently no effective or licensed treatments that can help people be less disabled by EPP. There are no NHS guidelines for the management of EPP and limited assistance for access to specialist physicians. Specialist clinicians are limited with what they can do for patients; current intervention is to listen to the patients, to advise on preventative measures, to monitor for vitamin D deficiency and liver damage, and to try to address psychological concerns.

Patients need a reliable, accessible and pain-free method of increasing levels of the pigment melanin, which is needed to extend time exposed to light without triggering phototoxic reactions. Unlicensed forms of alpha-MSH analogues are available online: it is a concern that if afamelanotide is not approved for use, desperate patients will start using these unregulated forms.

3. Added value of the medicine for the patient:
3a. How would this medicine be expected to add value to the patient's wellbeing and experience of care?

Afamelanotide has shown to improve the amount of time patients can expose themselves to light; those involved in the clinical trials and special access programmes reported incredible improvements in patients' lives. This enhances their ability to undertake normal activities required for day to day living. Patient experience with afamelanotide in the clinical trials made a significant difference by affording them longer exposure times and allowing them to lead a more 'normal' pain-free life that is not dictated by their condition. They were able to go outside wearing shorts, spend time in the sun, and enjoy a day at the pub or the park. An effective treatment would allow patients to reduce the pain that is suffered on a regular basis, reduce the psychological impact associated with EPP and its life-limiting impact, reduce loss of earnings from missed days at work, and enjoy the outdoors (such as spending time in the garden). Effective treatment from a younger age could completely change a person's life in terms of confidence, socialising and careers. The psychological effects of EPP should not be overlooked and a treatment that can increase the time spent in light to pursue

day-to-day activities should not be underestimated.

Quality of life data from the CUV039 trial was assessed using two different methods: the non-specific Dermatology Life Quality Index (DLQI) that is widely used in dermatology, and a disease-specific questionnaire EPP-QoL that was developed in the supporting trials. No differences were observed with the DLQI, however, EPP-QoL showed a significantly improved quality of life with afamelanotide compared to placebo. Patient improvement and improved quality of life could not be reflected in the clinical data, partly due to people with EPP not being willing to break learned behaviour and expose themselves to the light. However, both patients and clinicians reported an overwhelming positive benefit for patients treated with afamelanotide.

3b. How is this medicine better than current treatments?

Afamelanotide is an innovative treatment that has shown to make a significant difference to the lives of people with EPP. It is the first and only approved treatment: there are no other licensed therapies for EPP. There has been an overwhelming positive benefit observed during the 12 years of clinical development of afamelanotide, seen by both the clinicians and patients; however, this was not successfully captured by the clinical studies as effective tools to measure the impact of light exposure and treatment on people with EPP do not exist.

Current treatments like beta-carotene, sunscreens and titanium dioxide creams are not effective and people report little success in improving quality of life. Any benefit to taking beta-carotene is has not been proven, and many people stop taking it after a short period of time. Suncreens do not block the right wavelengths and in some cases, the ingredients of sunscreens can make the skin more sensitive, which can accelerate the onset of an EPP reaction. Current therapies therefore are not reliably effective and participating in work and day-to-day activities is still highly restricted.

Phototherapy does appear to extend the time people with EPP can be exposed to light without experiencing pain; however, evidence on efficacy is limited. Attending the regular hospital visits for treatment (three times a week for the first month) is impractical and can have a severe impact on work and earnings, whereas hospital visits with afamelanotide are less frequent (once every two months). Furthermore, phototherapy is not a widespread treatment and many UV light tubes used for other diseases are inappropriate for EPP as they give wavelengths that cause very painful skin reactions. Therefore, access to expertise and the right equipment (light tubes) is limited. Due to the repeated exposure to UV light, phototherapy can also increase the risk of cancer.

The main management of EPP is avoiding any exposure to light; this includes staying indoors, finding shade or wearing clothes that block the sunlight, e.g. gloves, facemasks, umbrellas. However, such measures are hot, uncomfortable, impractical and lead to psychological distress from isolation due to being perceived as outside of the social norm.

3c. Does this medicine have the potential to make a significant and substantial impact on health related benefits?

Afamelanotide is the only licensed treatment for people with EPP that activates synthesis of melanin in the skin, which appears to be the only viable means of extending the time skin can be exposed to light before a severe reaction occurs. Prolonged light exposure would increase participation in normal activities, including:

- Improving engagement in school or work
- Eliminating bullying
- Taking part in sports and other outdoor activities

- Working in a wider choice of careers
- Forming and maintaining friendships and relationships, including forming relationships at a younger age that will last
- Being able to travel, go on holidays and migrate to work abroad.

Patients who have received afamelanotide reported that it changed their life in a significantly positive direction and that they were able to do things that they never thought they would be able to do, such as playing outside with their children or visiting people. It is therefore likely to have a significant impact on their overall quality of life, including family, work and socialising. It also impacts emotionally and physically.

4. Added value of the medicine for the patient's family or carers

The patient organisation stated that the questionnaires used in the EPP trials may not capture the true impact of the benefits, including the wider values and benefits experienced by families. In some cases, a parent suffering from EPP places burden of responsibility on their children. Children would see the effects of light exposure on a parent with EPP and would be upset or scared to go outside, due to not wanting to cause their parent pain. The children feel responsibility to monitor the parent and remind them not to go outside or expose themselves to light. They also pick up the learned behaviour and think that going outside will also cause them pain. Removal of this burden opens up the social, educational and career potential of the child.

Family tensions can often run high as a result of the direct and indirect impact of EPP with a detrimental effect on family life. Family experiences are restricted; activities involving the family member with EPP are often limited, or families have to take part in activities without the family member. This can have a damaging effect on family relationships. An effective treatment has the potential to keep families together and also enhance the benefits of togetherness. People with EPP would be able to properly engage with family and take part in family events and activities. It would relieve family tension; shared roles would increase and relationship breakdowns would reduce. It would also reduce the time and financial burden of caring for people with EPP.

5. What is the most appropriate position for the medicine in the pathway of care for the condition? Does this differ from the company's proposed positioning?

There are currently no guidelines for the management of EPP. Clinicians suggest it would be offered as a first-line therapy to help patients be less disabled by their condition. There would need to be an agreed process and service in place to support the delivery of the treatment to patients: there is a post-authorisation safety study (PASS) protocol currently ongoing, which monitors safety and efficacy of afamelanotide in EPP. Patients would also benefit from more readily available psychological assistance.

There is a specialist centre in Wales (Cardiff) that will be well-placed to provide afamelanotide to people with EPP, as well as be a national reference centre for porphyrias.

6. Are there specific patient groups for whom the medicine is particularly beneficial? If so, please specify

Clinical expert opinion stated that there will be approximately 20 people with EPP eligible for treatment in Wales. Not all people with EPP would want implants, but following discussions with EPP patients, clinicians anticipate that most patients would request to try afamelanotide.

7. Are there any important considerations in relation to treatment delivery (e.g. how treatment should be monitored, how long it should be continued etc.)?

All patients are encouraged to enrol in a post-authorisation safety study (PASS) in line with EMA approval. This protocol provides the first ever uniform treatment guidelines for people with EPP, and ensures multi-disciplinary care in expert centres. If the treatment continues to deliver benefits without adverse side effects, there is no reason this should not lead to a reduction in the opportunity cost of administering the treatment.

8. Other considerations

Patients would also benefit from more readily available specialist psychological assistance to provide strategies for living with the effects of EPP.

9. Is there a key factor, or combination of factors, that would justify this medicine being available in NHS Wales?

- Afamelanotide is the first licensed treatment for the prevention of phototoxicity in adult patients with EPP. Current available treatments are not effective and do not improve any of the aspects of living with EPP.
- Most people with EPP need help with extending the amount of time they can spend in light. Any treatment that can increase the time spent exposed to light would improve patients' lives.
- There is currently a lack of equity in Europe, as afamelanotide is already available in some countries. Patients are aware of this inequity.
- Both patients and clinicians have expressed eagerness to start using afamelanotide, as until now no other treatment has been shown to improve the tolerance of EPP patients to light.

It should be noted that one expert involved in compiling this response declared a non-personal specific interest in relation to afamelanotide for the indication under consideration.