Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

5-aminolaevulinic acid (as hydrochloride), 78mg/g, gel (Ameluz®)

SMC No. (811/12)

Biofrontera Bioscience GmbH

05 October 2012 *(Issued 09 November 2012)*

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

5-aminolaevulinic acid (as hydrochloride) (Ameluz®) is accepted for use within NHS Scotland.

Indication under review: Treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2).

In a multi-centre, randomised, observer-blind, controlled phase III study, 5-aminolaevulinic acid gel met pre-specified non-inferiority criteria compared with an alternative topical agent in terms of complete clearance of actinic keratosis lesions, 12 weeks after the last of up to two sessions of photodynamic therapy. The treatment difference was sufficient to demonstrate superiority over the alternative topical agent.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2).

Dosing Information

The gel should only be administered under the supervision of a physician, a nurse or other healthcare professionals experienced in the use of photodynamic therapy.

The gel should cover the lesions and approximately 5mm of the surrounding area with a film of about 1mm thickness and applied to the entire lesion area using glove protected fingertips or a spatula. The gel can be administered to healthy skin around the lesions, whereas application near the eyes, nostrils, mouth, ears or mucosa should be avoided (keep a distance of 1cm). Direct contact of the gel with the eyes or mucous membrane should be avoided. An occlusive light-tight dressing is placed over the treatment site, after a drying time of 10 minutes. The dressing and remaining gel should be removed after three hours and the treatment area illuminated with a red light source. A narrow spectrum lamp is recommended to achieve higher clearance rates. A broader and continuous spectrum may be used if narrow-spectrum light sources are not tolerated. CE marked lamps should be used, and in accordance with their user manual.

One session of photodynamic therapy should be administered for single or multiple lesions. Actinic keratosis lesions should be evaluated three months after treatment. Non- or partially responding lesions should be re-treated in a second session.

Product availability date

1 November 2012

Summary of evidence on comparative efficacy

5-aminolaevulinic acid is a photosensitising agent intended for use in photodynamic therapy (PDT). It is a prodrug of protoporphyrin IX, a photoactive compound which accumulates within the cells of actinic keratosis (AK) lesions. Photoactivation by red light of suitable wavelength and energy triggers the creation of reactive oxygen species which leads to cell death. The nanoemulsion gel formulation both improves the stability of 5-aminolaevulinic acid and improves penetration into the AK cells within the epidermis.

Two phase III studies provide evidence for the use of 5-aminolaevulinic acid gel in PDT in the treatment of AK.[1,2]

In a multi-centre, randomised, controlled study, adults with four to eight mild to moderate biopsy-confirmed AK (classified as Olsen grade I or II) on the face and/or bald scalp were recruited. The lesions were required to be between 0.5cm and 1.5cm in diameter, and separated from adjacent lesions by at least 1cm. Patients were randomised 3:3:1 to 5-aminolaevulinic acid (78mg/g) gel, methyl aminolevulinate cream (160mg/g, Metvix®) or placebo (gel vehicle). The study treatment was applied to the lesions following curettage of any

crusts and preparation of the site with alcohol. A light-tight occlusive dressing was placed over the lesions after 10 minutes drying time, removed three hours later, and the area was illuminated with a red light source. Re-treatment with a second course of PDT was permitted 12 weeks after the first if lesions were still present. The treatment and illumination schedule corresponded to those specified in the marketing authorisation for methyl aminolevulinate cream. Due to the different formulations of the active treatments, the study was observer blinded with one investigator performing the PDT and another performing medical assessment pre- and post-treatment.[1]

The primary outcome measure was complete clearance of all lesions, as determined by clinical assessment, at 12 weeks after the last PDT course. The study had two co-primary endpoints and they were tested in a hierarchical manner; firstly, superiority of 5-aminolaevulinic acid gel to placebo, tested in the intention-to-treat (ITT) population, defined as all randomised patients who had received at least one treatment. Secondly, non-inferiority of 5-aminolaevulinic acid gel to methyl aminolevulinate cream was tested in the per-protocol population (ITT patients without any major protocol deviations), with a pre-defined non-inferiority margin of -15%.[1]

In the ITT population, superiority to placebo was demonstrated. In the per-protocol population, non-inferiority to methyl aminolevulinate was shown since the lower limit of the 97.5% confidence interval (CI) of the treatment difference was greater than the pre-specified margin of -15%. However, since the CI did not include zero, 5-aminolaevulinic acid gel was found to be superior to methyl aminolevulinate. The results of the primary analyses were supported when tested in the alternate sample population. The primary outcome results are presented in Table 1 below.[1]

		5-aminolaevulinic acid gel	**Methyl aminolevulinate cream**	**Placebo**
Intention to treat population	Number of patients	248	246	76
	Patient clearance rate, n (%)	194 (78%)	158 (64%)	13 (17%)
	5-aminolaevulinic acid treatment difference, % (CI)	-	14% (97.5% CI: 5.9 to ∞)*	**61%** **(95% CI: 51 to 71), p<0.0001**
Per protocol population	Number of patients	238	236	65
	Patient clearance rate, n (%)	189 (79%)	154 (65%)	13 (20%)
	5-aminolaevulinic acid treatment difference, % (CI)	-	**14%** **(97.5% CI: 6.0 to ∞)***	59% (95% CI: 48 to 70), p<0.0001

Table 1: Patient clearance rates after the last of up to two courses of PDT. [1] Results in bold type are the co-primary endpoints. * = one-sided test.

A relevant secondary endpoint of the study was the proportion of patients who had total clearance 12 weeks after the first session of PDT. The proportion of patients meeting this endpoint was 48% (95% CI: 42.0 to 54.8), 37% (95% CI: 30.9 to 43.4) and 3.9% (95% CI: 0.8 to 11.1) in the 5-aminolaevulinic acid, methyl aminolevulinate, and placebo groups, respectively. The difference between 5-aminolaevulinic acid gel and methyl aminolevulinate was not statistically significant.[1]

Patient complete clearance rates were compared across several sub-groups. The study was not powered to detect differences between these sub-groups; however, between-treatment comparisons of these sub-groups suggests that 5-aminolaevulinic acid was superior to methyl aminolevulinate when a narrow-spectrum light source was used, or in patients with moderate actinic keratosis (Olsen grade II), or with lesions located solely in the bald scalp.[1]

Patients who completed the study were followed up over 12 months to investigate lesion recurrence. Recurrence rates at 12 months were 42% (77/185) (95% CI: 34.4 to 49.1) for 5-aminolaevulinic acid gel and 45%, (69/154) (95% CI: 36.8 to 53.0) for methyl aminolevulinate cream. The probability of patients remaining completely cleared 12 months after the last PDT was estimated as 47% and 36% for 5-aminolaevulinic acid and methyl aminolevulinate respectively. For PDT using narrow-spectrum lamps, the estimated probabilities were 53% and 41% respectively.[3]

In the second, supportive, multi-centre, double-blind, placebo-controlled study, a similar population to the pivotal study was recruited and randomised to 5-aminolaevulinic acid gel and placebo and treated in up to two PDT sessions 12 weeks apart. The primary outcome was the same as in the pivotal study. In the full analysis set (all patients who received treatment and had at least one post-treatment assessment), the patient complete clearance rate for 5-aminolaevulinic acid gel was 66% (53/80) compared with 12% (5/40) for placebo, an absolute treatment difference of 54%, $p<0.0001$.[2] After 12 months of follow up, 64% (34/53) of responders in the 5-aminolaevulinic acid group remained completely clear.[3]

Summary of evidence on comparative safety

In the pivotal study, similar proportions of patients in the 5-aminolaevulinic acid gel group (96%, 239/248) and methyl aminolevulinate cream group (98%, 241/246) reported treatment emergent adverse events. In contrast, the rate was 72% (55/76) in the placebo group. There was a low rate of discontinuation due to adverse event: 5-aminolaevulinic acid (0.8%, 2/248), methyl aminolevulinate (0.8%, 2/246), and placebo (0%).[3]

The two most commonly reported adverse events were local skin reactions and discomfort during PDT. The incidence of local skin reactions with each treatment was: 5-aminolaevulinic acid gel 81% (200/248), methyl aminolevulinate 80% (197/246) and placebo 46% (35/76). The incidence of discomfort with each treatment was: 5-aminolaevulinic acid 89% (221/248), methyl aminolevulinate 93% (230/246) and placebo 41% (31/76). The local skin reactions tended to be mild to moderate in severity and self-limiting, resolving within a week of the PDT session. Use of narrow-spectrum light sources correlated with an increase in incidence and severity of adverse events reported.[1,3]

Summary of clinical effectiveness issues

Two phase III studies have shown that 5-aminolaevulinic acid gel is superior to placebo; one also showed superiority to methyl aminolevulinate cream in terms of complete clearance of AK lesions on the face and/or bald scalp, assessed 12 weeks after the last of up to two PDT sessions. The primary outcome measure in both studies, patient complete clearance, is a clinically relevant endpoint for patients with AK, as AK is associated with a risk of progression to squamous cell carcinoma. The rate of malignant transformation is less than 1 in 1,000 per year, and the risk has been estimated as 10% over 10 years in people with an average of 7.7 lesions. The studies were well conducted with little risk of bias identified.

Treatment strategies for AK include topical therapies such as application of emollients and sun-block. Medicines specifically licensed for the treatment of AK include: fluorouracil 5% cream, diclofenac 3% gel, imiquimod 5% cream, and fluororacil 0.5%/salicylic acid 10% cutaneous solution. The indications for each product vary by type (e.g. Olsen grade), number and surface area of lesion to be treated. Other treatment modalities include cryosurgery, curettage/excisional surgery, laser, chemical peel, dermabrasion, and PDT. SMC clinical experts have advised that photosensitising agents used in NHS Scotland for PDT include methyl aminolevulinate cream and unlicensed formulations of 5-aminolaevulinic acid.

While there is head-to-head data using a comparator relevant to NHS Scotland, methyl aminolevulinate cream, there is no comparative evidence against the other treatment modalities. Another limitation was the lack of data relating to treatment-related changes to quality of life.

5-aminolaevulinic acid gel offers clinicians a photosensitising agent that is licensed for moderate as well as mild AK lesions. The other licensed product available in the UK, methyl aminolevulinate cream, is indicated for thin/mild lesions only.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing 5-aminolaevulinic acid versus methyl aminolevulinate over a one year time horizon.

The clinical evidence was from the pivotal study comparing 5-aminolaevulinic acid with methyl aminolevulinate and placebo. 5-aminolaevulinic acid was superior to placebo and methyl aminolevulinate for the primary endpoint of complete lesion clearance 12 weeks after the last of two PDT sessions. A secondary endpoint of the study was the proportion of patients who achieved total clearance 12 weeks after the first session of PDT, with 5-aminolaevulinic acid found to be non-inferior to methyl aminolevulinate. Beyond the results of the study, no further analyses regarding patient outcomes were carried out for the economic evaluation.

5-aminolaevulinic acid and methyl aminolevulinate have the same treatment regimes. Therefore, only the costs of the medicines differed across the two comparator arms and these were the only items of resource use within the economic evaluation.

The results are reliant on the following key assumptions;

- The treatment regimes for 5-aminolaevulinic acid and methyl aminolevulinate are the same.

- The long term outcomes associated with 5-aminolaevulinic acid and methyl aminolevulinate treatment are the same.

The company estimated that the total annual cost per patient for 5-aminolaevulinic acid was £280 compared to methyl aminolevulinate at £324, demonstrating that 5-aminolaevulinic acid would be associated with a cost saving of £44 per patient per year. Sensitivity analyses showed that 5-aminolaevulinic acid is the preferred treatment regardless of the type of PDT lamp used.

The base case results included numerical differences in clearance rates which resulted in a lower proportion of patients in the 5-aminolaevulinic acid arm receiving a second treatment of PDT. SMC statistical advice confirmed that this is not appropriate as, in terms of the proportion of patients achieving total clearance 12 weeks after the first PDT, the results of the clinical study showed that 5-aminolaevulinic acid was non-inferior to methyl aminolevulinate. When the difference in clearance rate is removed, 5-aminolaevulinic acid remains cost-saving but the savings are reduced.

Given these results, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Skin Care Campaign Scotland (SCCS).

Additional information: guidelines and protocols

In 2008 the British Association of Dermatologists published as update of “Guidelines for topical photodynamic therapy”. This concluded that topical photodynamic therapy was an effective option for thin and moderate thickness actinic keratosis. Depending upon the protocol employed, there was evidence of superiority to cryotherapy, including for cosmetic outcome. There may be benefit from using this treatment for lesions on the extremities; however there was a lower clearance rate at six months compared with cryotherapy.

In 2007, the British Association of Dermatologists published “Guidelines for the management of actinic keratoses”. The guidelines concluded that there was insufficient comparative data to make a justified single recommendation on treatment choice, rather treatment should be individualised with the following factors considered: clinical presentation, the efficacy, morbidity, availability and cost of relevant treatments, the efficacy and patient choice. It was suggested that photodynamic therapy may be “best reserved” as an option for patients with multiple actinic keratoses that have inadequately responded to alternative treatments.

In February 2006 the National Institute for Health and Clinical Excellence published interventional procedure guidance (no. 155) on Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). This reported that there were no major safety concerns with the use of photodynamic therapy for non-melanoma skin tumours (including pre-malignant lesions such as actinic keratosis). The guideline found sufficient evidence to support the use of photodynamic therapy in actinic keratosis. This guidance has been endorsed by NHS Healthcare Improvement Scotland.

Additional information: comparators

Treatments for AK include topical therapies such as emollients and sun-block. Medicines specifically licensed for the treatment of AK include: fluorouracil 5% cream, diclofenac 3% gel, imiquimod 5% cream, and fluororacil 0.5%/salicylic acid 10% cutaneous solution. Methyl aminolevulinate cream is licensed for treatment of AK as part of PDT.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
5-aminolaevulinic acid gel	**Applied topically to lesions as part of photodynamic therapy. Can be repeated after 12 weeks if insufficient response.**	**184 to 368**
Methyl aminolevulinate cream	Applied topically to lesions as part of photodynamic therapy. Can be repeated after 12 weeks if insufficient response.	199 to 398
Imiquimod 5% cream	Applied to lesions three times a week for four weeks. Can be repeated after four week treatment-free period if lesions persist.	49 to 97
Diclofenac 3% gel	Applied topically to lesions twice daily for 60 to 90 days.	77
Fluorouracil 0.5% & salicylic acid 10% cutaneous solution	Applied to lesions once daily for up to 12 weeks.	77
Fluorouracil 5% cream	Applied topically to lesions once or twice daily for up to 28 days.	33

Doses are for general comparison and do not imply therapeutic equivalence. Costs based on treating surface area of 5x5cm. Costs from eVadis on 30 July 2012 except 5-aminolaevulinic acid (from company submission) and methyl aminolevulinate (from MIMS August 2012).

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 402 in year 1 rising to 567 in year 5, with an estimated uptake rate of 50% in year 1 and 100% in year 5. The gross impact on the medicines budget was estimated to be £54k in year 1 and £152k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be savings of £11k in year 1 and £30k in year 5.

References

The undernoted references were supplied with the submission.

1. Dirschka T, Radny P, Dominicus R, Mensing H et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. Br J Dermatol (2012); 166: 137-46.

2. Szeimies RM, Radny P, Sebastian M, Borrosch F et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. Br J Dermatol (2010); 163: 386-94.

3. European Medicines Agency. European Public Assessment Report – Ameluz. EMEA/H/C/002204. [online] Available from www.ema.europa.eu [Last updated January 2012].

This assessment is based on data submitted by the applicant company up to and including 13 August 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.