Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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5-aminolaevulinic acid (as hydrochloride) 78mg/g gel (Ameluz®)

SMC No. (1260/17)

Biofrontera Bioscience GmbH

07 July 2017

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 not recommended for use within NHS Scotland.

Indication under review: Treatment of superficial and / or nodular basal cell carcinoma (BCC) unsuitable for surgical treatment due to possible treatment-related morbidity and / or poor cosmetic outcome in adults.

In a phase III study of patients with BCC, up to two cycles of photodynamic therapy (PDT) with 5-aminolaevulinic acid gel was non-inferior to PDT with an alternative photosensitising agent for the primary endpoint, complete clearance, defined as clearance of all treated lesions, assessed visually at 12 weeks after the last PDT.

The submitting company did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Treatment of superficial and / or nodular basal cell carcinoma (BCC) unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.[1]

Dosing Information

For treatment of BCC, two sessions of photodynamic therapy are administered for one or multiple lesions with an interval of about one week between sessions. BCC lesions should be evaluated three months after last treatment. Treated lesions that have not completely resolved after three months should be retreated.[1]

5-aminolaevulinic acid should only be administered under the supervision of a physician, a nurse or other healthcare professional experienced in the use of photodynamic therapy.

Product availability date

27 January 2017

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 basal cell carcinoma (BCC) lesions. Photoactivation by red light of suitable wavelength and energy triggers the creation of reactive oxygen species which leads to cell death.[1]

The key evidence for 5-aminolaevulinic acid in the treatment of BCC is an ongoing, multinational, randomised, observer-blind, active-controlled phase III study. A five-year follow up is planned. Given the different formulations of the study treatments (gel and cream), the investigator conducting the PDT treatment was unblinded. A separate blinded investigator assessed efficacy and safety.[2, 3]

The study recruited adults with one to three primary BCC lesions located on the face / forehead, bald scalp, neck / trunk or extremities. The lesions were required to be biopsy-confirmed ≤2mm thickness, non-aggressive, primary BCC lesions (primary superficial, nodular, or mixed superficial / nodular). Lesion diameter was to be between 5mm and 2cm and total treatment area (including a 5mm to 1cm margin) was not to be larger than 10cm^2. Non-eligible lesions were to be surgically excised or treated with cryotherapy. Patients with a mixture of eligible and non-eligible lesions could be enrolled if the non-eligible lesion was at least 10cm apart from the eligible lesion(s).[2, 3]

Patients were randomised in a 1:1 ratio to either 5-aminolaevulinic acid 78mg/g gel (n=138) or methyl aminolevulinate 160mg/g cream (n=143).[2, 3] This treatment was applied as part of each PDT session. Each PDT cycle comprised two sessions of PDT (PDT-1 and PDT-2) delivered one week apart. At week 13 (12 weeks after PDT-2) patients were assessed for response. Patients with a complete response received no further treatment, however a second cycle of two sessions of PDT (PDT-3 and PDT-4) was delivered to patients who were either partial or non-responders.[3]

The primary outcome of the study was the overall patient complete response rate assessed 12 weeks after the last session of PDT. Overall complete response was defined as clearance of all treated lesions, assessed visually. The primary analysis was conducted in the per protocol population (all patients randomised and treated at least once with study treatment and who had no major protocol deviations) and tested non-inferiority of the treatments with a pre-specified margin of 15%. The primary outcome was achieved by 93% (113/121) of 5-aminolaevulinic acid patients and by 92% (101/110) of methyl aminolevulinate patients. The study demonstrated non-inferiority of 5-aminolaevulinic acid with methyl aminolevulinate; the treatment difference was 1.6% (97.5% one-sided confidence margin: -6.5%), p-value for non-inferiority test <0.0001. Supportive analysis in the full analysis set (n=281, intention to treat for all randomised patients treated at least once with study drug) also demonstrated non-inferiority; responder rates of 90% (124/138) and 85% (121/143), respectively, and treatment difference 5.2% (one-sided 97.5% confidence margin: -3.3%).[2, 3]

Patient complete response after the first cycle of PDT (12 weeks after PDT-2) was a secondary outcome and response rates were 58% (70/121) in the 5-aminolaevulinic acid group and 56% (62/110) in the methyl aminolevulinate group; treatment difference was 1.5% (95% confidence interval -12% to 15%). Similar efficacy between treatment groups was observed for the other secondary outcomes assessed 12 weeks after the last PDT: lesion complete response rate, change in lesion area, and overall cosmetic outcome. Subgroup analysis showed 89% (25/28) of nodular BCC lesions were cleared with 5-aminolaevulinic acid and 79% (22/28) with methyl aminolevulinate.[3]

Patient satisfaction of the overall cosmetic outcome was scored using a 5-point Likert-type scale. In the per protocol population, both treatment groups had a high proportion of patients rate their satisfaction as very good or good 12 weeks after their last PDT: 87% (104/120) and 85% (94/110) in the 5-aminolaevulinic acid and methyl aminolevulinate groups respectively. Less than 5% of patients in each group reported an unsatisfactory cosmetic outcome, 4.2% and 3.6% respectively.[3]

Of the 281 randomised patients in the full analysis set who enrolled in the main study, 242 entered the follow-up phase of the study; 88% (122/138) of 5-aminolaevulinic acid patients and 84% (120/143) of methyl aminolevulinate patients. In the full analysis set of patients who had complete clearance 12 weeks after the last PDT, BCC recurrence at six months was observed in 3.3% (4/122) of 5-aminolaevulinic acid patients and in 4.4% (5/114) of methyl aminolevulinate patients. In the full analysis set for follow-up, lesion recurrence in the 5-aminolaevulinic acid group was 2.7% and 6.9% at 6- and 12-months and in the methyl aminolevulinate group the respective lesion recurrence rates were 3.8% and 7.3%.[3]

Summary of evidence on comparative safety

All patients received at least one PDT session, 280/281 received PDT-2 to complete the first cycle. Taking into account discontinuation from the study and complete clearance following the first cycle of PDT, 40% of patients in the 5-aminolaevulinic acid group and 43% of patients in the methyl aminolevulinate group proceeded to receive a second cycle of PDT.[3]

All patients in the study reported at least one treatment-emergent adverse event (AE); the most common AE was application-site pain reported in 97% of 5-aminolaevulinic acid patients and in

all methyl aminolevulinate patients. Local application-site reactions were common: erythema (87% and 88% of patients respectively), pruritus (43% and 34%), oedema (30% and 36%) paraesthesia (29% and 27%), scab (25% and 29%), induration (23% and 19%), discharge (17% and 17%), exfoliation (16% and 8.4%) and erosion (13% and 6.3%). Application-site ulcers were reported in 2.2% and 2.8% of patients respectively.

AEs led to study discontinuation of five patients, one of whom was assigned to 5-aminolaevulinic acid. The frequency of severe treatment-emergent AEs was higher in the 5-aminolaevulinic acid group (39%) than the methyl aminolevulinate group (34%).[3]

When compared with the known safety profile of 5-aminolaevulinic acid when used for actinic keratosis additional adverse drug reactions have been added to the summary of product characteristics, namely: blurred vision, visual impairment, burning pain, inflammation and back pain. Post-marketing surveillance has picked up reports of transient memory loss and transient global amnesia associated with PDT with methyl aminolevulinate and 5-aminolaevulinic acid.[3]

Summary of clinical effectiveness issues

BCC is the most common cancer reported in Scotland; in 2015 there were approximately 8,500 people diagnosed with their first BCC. The true incidence is not known since only first lesions are registered for Scottish cancer statistics.[4] BCC is a slow-growing, locally invasive epidermal skin tumour which rarely metastasises. Local tissue invasion and destruction is the main morbidity and is particularly found on the head, neck and face. It predominantly affects Caucasians.[5]

Surgical excision is the mainstay of management, however non-surgical techniques are often considered for lesions classified to have low risk of recurrence. Non-excisional techniques include curettage and cautery, cryotherapy, laser ablation, topical immunotherapy with imiquimod, radiotherapy and PDT.[5] Recently an oral chemotherapy targeting the Hedgehog signalling pathway has been developed (vismodegib).[6] Vismodegib is not recommended for use in NHS Scotland by SMC, due to non-submission. 5-aminolaevulinic acid is the second photosensitising agent to be licensed in the UK for use in PDT for BCC. Methyl aminolevulinate cream is licensed for BCC,[7] and has been accepted for use in NHS Scotland for patients with superficial BCC lesions.

The observer-blind randomised, multicentre phase III study recruited adults with BCC lesions considered to be at “low-risk” of recurrence. The majority of these patients had only superficial BCC lesions, 42/231 (18%) had only nodular lesions. The study demonstrated that 5-aminolaevulinic acid gel was non-inferior to methyl aminolevulinate cream with respect to patient complete clearance when assessed three months after one or two cycles of PDT. The two treatments led to similar outcomes in terms of lesion clearance, efficacy after one cycle of PDT, cosmetic outcome and patient-reported satisfaction with treatment.[3] Patient complete clearance of BCC lesions is a direct health outcome; non-inferiority was demonstrated in both the per-protocol and full analysis set.

The EMA notes that the choice of non-inferiority margin was not justified from the perspective of clinically important differences in effect; however the one-sided 97.5% confidence margin in both analysis populations was small (-6.5% and -3.3%). This provides reassurance that a clinically important reduction in efficacy is unlikely if 5-aminolaevulinic acid gel is used instead of methyl aminolevulinate cream.

Due to the differing formulations of the photosensitising agents, the study was not double-blind. The investigator assessing treatment response was blinded to treatment; however patient reported outcomes may be open to bias.

The study is designed to follow up patients up to five years and is ongoing. Analysis of recurrence rates at landmarks at six and twelve months are available.[3] A review of historical studies of treatment of BCC found that only one third of recurrences presented in the first year; half of recurrences presented within two years, and 66% presented within three years.[5] Therefore longer-term outcomes are required to fully characterise the effectiveness of 5-aminolaevulinic acid.

Clinical experts consulted by SMC considered 5-aminolaevulinic acid PDT to be an alternative to methyl aminolevulinate PDT for the treatment of superficial BCC.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing 5-aminolaevulinic acid with methyl aminolevulinate cream (Metvix®) as part of PDT. The time horizon for the analysis was up to two cycles of treatment. A cycle of treatment was assumed to comprise two sessions of PDT given one week apart i.e. each patient could receive up to a total of four treatment sessions, with the second cycle of treatment (if required) occurring 3 months after the first cycle.

Clinical evidence to support the use of a cost-minimisation analysis came from the ongoing phase III study described above, which demonstrated non-inferiority between the treatment options in terms of clearance rates. Additionally, it was assumed that there would be no difference in adverse events between therapies.

Costs in the analysis related only to medicines acquisition costs. The costs of administration of PDT were not included on the basis that the method of administration would not differ between the treatments. For the company's base case analysis, it was assumed that one tube of 5-aminolaevulinic acid gel would be sufficient to treat a patients across all four administrations (if required) on the basis that the shelf life for the product is 12 weeks. For methyl aminolevulinate cream, it was assumed in the base case that two tubes would be required as the shelf life is only four weeks and thus would not permit the use of the same tube at the point of the second cycle of treatment.

The results of the company's base case analysis and relevant sensitivity analysis are shown in table 1 below:

	Scenario	Cost- 5-aminolaevulinic acid	Cost- methyl aminolevulinate cream	Difference per patient
1	Company base case	£184	£343	-£159
2	Sensitivity analysis- company base case but assuming 2 tubes of 5-aminolaevulinic acid required	£368	£343	£25
3	Sensitivity analysis- incorporating clearance rates and assuming 1 tube of 5-aminolaevulinic acid required	£184	£244	-£60
4	Sensitivity analysis- incorporating clearance rates and assuming 2 tubes of 5-aminolaevulinic acid required	£261	£244	£17

Table 1- Cost-minimisation analysis results

In the company's base case, the results showed that 5-aminolaevulinic acid was cost-minimising on the basis that only one tube of gel was required, compared to two tubes for methyl aminolevulinate cream. If two tubes of gel were required, the company provided sensitivity analysis to show that 5-aminolaevulinic acid was no longer cost-minimising (Table 1, Scenario 2).

A number of issues were noted with the analysis:

- Given the difference in the medicines acquisition costs between the two tubes of treatments, a key determinant of cost-effectiveness is the extent of requirement for a second tube of treatment for any second cycle of treatment. The company's base case results (table 1, scenario 1) did not use the data from the clinical study indicating the proportion of patients who achieved complete clearance at the first cycle of treatment, and who thus did not require a second cycle of treatment. It would have been more appropriate to have performed the base case analysis taking account of this information. The company subsequently provided this analysis and while 5-aminolaevulinic acid was still cost-minimising under the company's assumption of one tube being required, this reduced the cost saving per patient (table 1, scenario 3). The company also provided this analysis but including the assumption that a second tube of 5-aminolaevulinic acid would be required for the proportion of patients needing a second cycle of treatment. This resulted in the treatment no longer being cost-minimising (table 1, scenario 4).
- 5-aminolaevulinic acid gel has an in-use expiry of 12 weeks; it is therefore unlikely that the same tube could be used for two cycles of treatment which would take place over at minimum of a 13 week period. As noted in the results presented above, the ability to use the same tube of 5-aminolaevulinic acid gel for any repeat cycles was pivotal in achieving cost-minimisation. New Drugs Committee (NDC) was of the view that it would not be appropriate or feasible in clinical practice to assume that a patient could use the same tube of 5-aminolaevulinic acid for any second cycles of treatment that may be required. As such, this would result in a second tube being used and thus that 5-aminolaevulinic acid would not be cost-minimising (table 1, scenario 4). This was agreed as a more appropriate base case result for consideration.

- SMC experts indicated that methyl aminolevulinate cream is used in superficial BCC only therefore the case for use of 5-aminolaevulinic acid gel in nodular BCC has not been made.

Given these issues, the economic case has not been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Melanoma Action and Support Scotland (MASScot), which is a Scottish Charitable Incorporated Organisation (SCIO).

- MASScot has not received any pharmaceutical company funding in the past two years.

- Basal Cell Carcinomas (BCCs) occur most commonly on the face, head and neck and can be unsightly causing embarrassment. Once diagnosed the explanation that the lesion will be removed surgically can seriously upset some people. The potential for disfigurement also has to be explained and this too can cause real anxiety.

- For people with lesions unsuitable for surgical removal or where there is an unacceptable risk of scarring there are few treatment options. 5-aminolaevulinic acid gel may be a welcome alternative and may reduce the need for more expensive and frightening treatment at a later date.

Additional information: guidelines and protocols

NICE interventional procedure guidance, published in 2006 and endorsed by Healthcare Improvement Scotland, IPG 155, "Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions)" concluded that:

- Evidence of efficacy of this procedure for the treatment of basal cell carcinoma, Bowen's disease and actinic (solar) keratosis is adequate to support its use for these conditions, provided that the normal arrangements are in place for consent, audit and clinical governance.
- Current evidence suggests that there are no major safety concerns associated with photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions).[9]

The British Association of Dermatologists published its "Guidelines for the management of basal cell carcinoma" in 2008.[5] These are currently under review. Factors linked with poorer prognosis and higher-risk of recurrence include: increasing tumour size, site of lesions (lesions in the H-zone are at higher risk of recurrence), poorly defined clinical margins, histological subtype, histological features of aggression such as perineural and perivascular involvement, failure of previous treatment, and immunosuppression. Surgical excision is used to treat both low-risk and high-risk BCC, whereas other therapeutic approaches such as curettage, cryotherapy and PDT are generally used in low-risk BCC. The guideline recommended that PDT is a good treatment for primary superficial BCC, and it is a reasonable treatment for primary low-risk nodular BCC.

The European Dermatology Forum published its guidelines on topical photodynamic therapy in 2015.[10] PDT was recommended as a good treatment for superficial BCC and a fair treatment for

low-risk nodular BCC. It noted that since recurrence rates are greater than those associated with surgery that PDT should be considered for thin nodular lesions where surgical excision is relatively contraindicated. Patients choosing PDT over surgery, whether for cosmetic considerations, co-morbidities or past history should be aware that there is a higher risk of recurrence.

Additional information: comparators

Methyl aminolevulinate cream is used for PDT of BCC lesions in NHS Scotland.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
5-aminolaevulinic acid gel	**Applied topically to lesions as part of two photodynamic therapy sessions delivered one week apart.**	**184**
methyl aminolevulinate cream	Applied topically to lesions as part of two photodynamic therapy sessions delivered one week apart.	172

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS.co.uk on 01 May 2017. Costs calculated using the full cost of a single tube, assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 1,204 patients eligible for treatment with 5-aminolaevulinic acid hydrochloride gel in all years. The estimated uptake rate was 10% in all years (120 patients).

The gross impact on the medicines budget was estimated to be £22k in all years. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £19k in all years. These calculations assumed that only one tube of 5-aminolaevulinic acid gel would be required to cover all treatments.

References

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This assessment is based on data submitted by the applicant company up to and including 19 June 2017.

**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_statements/Policy_Statements

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.