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

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 3372

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).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
5-aminolaevulinic acid (Ameluz®) 78 mg/g gel

This assessment report is based on evidence submitted by Biofrontera[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	5-aminolaevulinic acid (Ameluz®) for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults[2].
Dosing	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. Two sessions of photodynamic therapy should be administered for one or multiple lesions with an interval of about one week between sessions. Basal cell carcinoma lesions shall be evaluated three months after last treatment. Treated lesions that have not completely resolved after three months shall be retreated. For further information on posology and administration, refer to the Summary of Product Characteristics[2].
Marketing authorisation date	27 January 2017 (licensed for treatment of actinic keratosis of mild to moderate severity on the face and scalp [Olsen grade 1 to 2] and of field cancerization in adults on 14 December 2011)[3].

2.0 DECISION CONTEXT

2.1 Background

Basal cell carcinoma (BCC) is a slow-growing, locally invasive, malignant epidermal skin tumour that predominantly affects fair-skinned individuals[3,4]. BCCs are generally innocuous with favourable prognosis and metastases are extremely rare[3,4]. However, BCC can cause substantial morbidity due to its location on the face, its tendency to relapse, its multiplicity and the possibility that it can invade and destroy local tissues[5]. Treatment usually aims to eradicate the tumour in a manner likely to result in an acceptable cosmetic outcome[4]; these therapies include surgical excision, radiotherapy and 5-fluorouracil, and photodynamic therapy (PDT)[3]. Surgical treatments are considered the most favourable therapy[4], but nonsurgical medical treatments such as PDT are advantageous with good cosmetic outcome and preservation of surrounding tissue[5,6].

BCCs are considered the most common skin cancer, forming an estimated 75% of non-melanoma skin cancers[7]. However, BCC incidence and prevalence figures are difficult to estimate due to inconsistent data collection[4,5]. In the UK, an estimated 53,000 new cases were reported in 2007, with incidence continuously rising[8]; Wales and South England had the highest recorded rates between 2004–2010[9]. Although no figures are available for North Wales or the Welsh population as a whole, in South Wales, incidence is estimated as 128 males and 105 females per 100,000 people (figures reported in 2012)[5].

WHO distinguishes forms of BCC according to different clinical characteristics, morphology and location[3]. Common subtypes include nodular BCC (nBCC) and superficial BCC (sBCC)[4]: primary nBCC, primary sBCC, or mixed sBCC and nBCC tend to be less aggressive with good to intermediate prognosis[3]. Approximately 10–30% of BCCs are diagnosed as sBCCs, and 60–80% of BCCs are considered nBCCs[3].

5-aminolaevulinic acid is a nanoemulsion-based gel initially licensed for the treatment of actinic keratosis with PDT[3,10]. Following application, 5-aminolaevulinic acid is metabolised to protoporphyrin IX, a photoactive compound, that accumulates in the cells of treated lesions[10]. Protoporphyrin IX is activated by illumination with a red light of suitable wavelength and energy[10]. In the presence of oxygen, this results in reactive oxygen species that damage cellular components and eventually destroy the target cells[10].

2.2 Comparators

The comparator included in the company submission is methyl aminolevulinate (Metvix®)[1].

2.3 Guidance and related advice

- European Dermatology Forum. Guidelines for the treatment of basal cell carcinoma (2012[5], update published 2014[11]).
- European Dermatology Forum. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma (2012)[6].
- British Association of Dermatologists (BAD). Guidelines for the management of basal cell carcinoma (2008)[4].
- National Institute for Health and Care Excellence (NICE). Improving outcomes for people with skin tumours including melanoma (2006, updated 2010)[12].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of 5-aminolaevulinic acid (Ameluz®) for the treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerization in adults[13].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes evidence from one pivotal phase III study, ALA-BCC-CT008, designed to evaluate the safety and efficacy of 5-aminolaevulinic acid in the treatment of non-aggressive BCC with PDT[1].

3.1 ALA-BCC-CT008

ALA-BCC-CT008 was a randomised, observer-blind, multinational phase III trial that compared the safety and efficacy of 5-aminolaevulinic acid versus methyl aminolevulinate in patients with non-aggressive BCC with PDT[3]. Patients were included in the study if they were ≥ 18 years of age with 1–3 primary BCC lesions in the face or forehead, including bald scalps, extremities and/or the neck or trunk. All lesions had to fulfil the criteria of non-aggressive BCCs according to the clinical judgement of the investigator (primary sBCC, primary nBCC, or mixed sBCC and nBCC, with a thickness ≤ 2 mm)[3]. Only eligible lesions with confirmation by biopsy taken at screening were included in the study. Eligible lesions had to have a diameter ranging between ≥ 0.5 cm and ≤ 2 cm, with a maximum treated area of approximately 10 cm^2. Target BCC lesions had to be located within 1–2 treatment areas. Patients with non-eligible lesions (confirmed by biopsy taken at screening) were included in the study if at least one lesion was eligible and was located at least 10 cm away from non-eligible lesions[3].

A total of 281 patients were recruited from 20 centres in Germany and 4 centres in the UK[3]. Patients were randomised 1:1 to receive either 5-aminolaevulinic acid (n = 138) or methyl aminolevulinate (n = 143). Baseline characteristics were comparable between the two groups. Each patient received two PDT treatments (PDT-1 and PDT-2) approximately one week apart. Patients were then assessed 12 weeks after PDT-2, and further study treatment plus observation was decided based on the patient response. Complete responders (patients with complete lesion clearance) had no further treatment, giving a total treatment and observation period of 13 weeks. Partial or non-responders received two further PDT treatments (i.e. a second cycle of the study medicine plus PDT), giving a total treatment and observation period of 26 weeks[3].

The primary outcome of the study was the overall patient complete response rate assessed at 12 weeks after the last PDT (two or four PDT sessions in total), in the per protocol population (n = 231)[3]. Secondary outcomes included overall patient complete response 12 weeks after PDT-2 (i.e. the first PDT cycle), overall lesion complete response 12 weeks after the last PDT, and cosmetic outcome 12 weeks after the last PDT. In the 5-aminolaevulinic acid arm, 93.4% of patients showed a complete response, compared to 91.8% of patients in the methyl aminolevulinate group. To determine non-inferiority, a one-sided 97.5% confidence interval (CI) for overall patient complete response between methyl aminolevulinate and 5-aminolaevulinic acid was calculated. If the 97.5% CI was above the designated non-inferiority margin of −15%, non-inferiority was claimed. As shown in Table 1, 5-aminolaevulinic acid demonstrated non-inferiority over methyl aminolevulinate based on these criteria (97.5% CI −6.5)[3].

Table 1. Primary and secondary outcomes of the ALA-BCC-CT008 trial[3].

	Methyl aminolevulinate	5-aminolaevulinic acid	Difference to 5-aminolaevulinic acid
Primary outcome: Overall patient complete response 12 weeks after the last PDT*			
n/N (%) 95% two-sided CI 97.5% one-sided CI p-value	101/110 (91.8) 84.6 to 96.0	113/121 (93.4) 87.0 to 96.9	1.6% −6.5 <0.0001†
Secondary outcome:			
Overall patient complete response rate 12 weeks after PDT-2 (PDT cycle 1)			
n/N (%) 95% two-sided CI	62/110 (56.4) 46.6 to 65.7	70/121 (57.9) 48.5 to 66.7	1.5% −11.7 to 14.6
Cosmetic outcome 12 weeks after last PDT* (Very good or good outcome)			
n/N (%) 95% two-sided CI	36/109 (33.0) 24.5 to 42.8	42/120 (35.0) 26.7 to 44.3	2.0% −10.8 to 14.6

PDT: photodynamic therapy; n: number; N: total number; CI: confidence interval
*2 or 4 PDT sessions in total
†p-value indicates non-inferiority

Of the 231 patients in the per protocol population, 178 (77.0%) had only sBCC, 42 (18.2%) had only nBCC and 11 (4.8%) patients had “Others”[3]. No definite conclusions regarding the relative efficacy of treatments could be drawn based on these subgroups due to the limited number of patients in some of the subgroup categories[3].

Of the 260 patients who completed the clinical aspect of the study, 242 (93.1%) entered a follow-up phase: 122 (88.4%) patients in the 5-aminolaevulinic acid arm and 117 (81.8%) in the methyl aminolevulinate arm[3]. Of the patients in the per protocol population who had a complete response 12 weeks after the last PDT, four patients in

the 5-aminolaevulinic acid arm (3.5%) and five patients in the methyl aminolevulinate arm (5.1%) had relapsed at the six month follow-up. Lesion recurrence at six months was low in both treatment groups; 2.9% in the 5-aminlevulenic acid group versus 4.3% in the methyl aminolevulinate group. By the 12 month follow-up, lesion recurrence rates had increased slightly, to 6.7% and 8.2%, respectively[3].

3.2 Comparative safety

Patients were included in the safety analysis of the ALA-BCC-CT008 trial if they had received the first session of PDT (PDT-1): 138 patients in the 5-aminolaevulinic acid arm and 143 patients in the methyl aminolevulinate arm[3]. All patients in both treatment groups reported at least one treatment-emergent adverse event (TEAE) possibly related to the study treatment. Pain at the site of treatment application was the most common individual TEAE in both groups, reported in 134 (97.1%) of patients in the 5-aminolaevulinic acid group and 143 (100.0%) of patients in the methyl aminolevulinate group. The most common TEAEs rated as skin reactions at the application site include erythema, oedema, scabs, induration, discharge, exfoliation and erosion. The frequency of severe TEAEs was slightly higher with 5-aminolaevulinic acid (39.1%) compared to methyl aminolevulinate (33.6%). No treatment-related serious TEAEs or deaths were reported[3].

Of the 281 patients in the safety population, 270 (97.1%) entered the six month follow-up period: 134 patients (97.1%) in the 5-aminolaevulinic acid arm and 136 patients (95.1%) in the methyl aminolevulinate arm[3]. At least one post-treatment adverse event was reported in 31 patients in the 5-aminolaevulinic acid arm and 28 patients in the methyl aminolevulinate arm. Three adverse events were considered possibly related to treatment in the 5-aminolaevulinic acid arm (recurrent BCC, solar lentigo and lichenoid keratosis), versus one adverse event in the methyl aminolevulinate group (recurrent BCC). No treatment-related serious TEAEs were reported in the six month follow-up[3].

3.3 AWTTC critique

- The primary analyses of the ALA-BCC-CT008 trial was based on the per protocol population, rather than an intent-to-treat population (referred to as the full analysis set in this study). However, ancillary analyses of the full analysis set demonstrated similar results to the per protocol population; the Committee for Medicinal Products for Human Use (CHMP) considered this acceptable and no major issues were raised with the conduct of the study[3].
- The non-inferiority margin of 15% was derived from an analysis of previous studies, but no evidence was provided that the margin can be regarded as clinically relevant, as per the EMA Guideline on the choice of the non-inferiority margin[14]. As the difference between methyl aminolevulinate and 5-aminolaevulinic acid was small, CHMP did not think this posed a major issue.
- Evidence of clinical effectiveness (efficacy and safety) was based on one pivotal phase III trial and follow-up data at 6 and 12 months. The company submission highlights that ALA-BCC-CT008 includes a follow-up period of five years, so additional longer-term data will become available, but no publication date is planned at this time[1]. The company also states that a Quality of life (QoL) study is ongoing, but no QoL data has been included with the submission, and no publication of these data is planned[1].
- ALA-BCC-CT008 was carried out as an observer-blind study, rather than double-blind. 5-aminolaevulinic acid has a different consistency to methyl aminolevulinate[3], and therefore using a double-blind approach was not possible. Instead, the investigator assessing the efficacy outcomes was kept blind, while a second investigator (or delegated person) performed the PDT treatment, alongside all safety evaluations, at the PDT sessions[3]. The follow-up period is not observer-blind[3].

- The SPC for 5-aminolaevulinic acid states that lesions should be reassessed after three months of the final treatment, at which point any previously treated BCC lesions that have not resolved should be retreated[2]. In their submission, the company highlights that 5-aminolaevulinic acid can be stored for up to 12 weeks once opened[1]. Therefore, the same tube may be used for the second cycle of treatment. Methyl aminolevulinate has a shorter shelf-life of four weeks, so cannot be used for a second treatment cycle[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a cost-minimisation analysis (CMA) of 5-aminolaevulinic acid compared to methyl aminolevulinate for cutaneous application in combination with PDT, for the second-line treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

A simple cost calculation with an NHS perspective is used to assess the cost-effectiveness of 5-aminolaevulinic acid compared to methyl aminolevulinate over two treatment cycles (two PDT treatments in cycle 1 and two PDT treatments in cycle 2). Based on evidence from the pivotal study ALA-BCC-CT008[3], efficacy and adverse events are assumed equal. The company reports no significant differences in the safety of 5-aminolaevulinic acid and methyl aminolevulinate. Health-related QoL (HRQoL), survival, adherence and patient preference are assumed equal.

It is assumed that there is no difference in resource use between the comparators as it is a direct substitution of one topical photosensitising agent for another and the clinical process of PDT administration is identical. Medicine acquisition costs are therefore the only costs considered in the calculation. It is assumed in the base case that one tube of 5-aminolaevulinic acid will be used for cycle 1 and cycle 2 because of its 12-week in-use stability. In contrast, two tubes of methyl aminolevulinate will be required because it can only be used for four weeks after opening.

The company presents two scenarios to assess parameter uncertainty. The first scenario assumes two tubes for all second cycle 5-aminolaevulinic acid and methyl aminolevulinate treatments. The other scenario uses different lesion complete response rates as observed in study ALA-BCC-CT008. This scenario has not been considered as it violates the CMA premise of equal efficacy. Instead AWTTC have calculated scenarios considering the cycle 1 complete response rates. While the company assumes that all patients will require a second cycle, AWTTC believe that only people without complete clearance in cycle 1 (42.1% in the 5-aminolaevulinic acid group and 43.6% in the methyl aminolevulinate group) would continue to cycle 2 based on the results from study ALA-BCC-CT008.

4.1.2 Results

The results of the company's base case suggest that treatment with 5-aminolaevulinic acid costs £170 for two treatment cycles compared to £343 for methyl aminolevulinate, with an incremental cost of £173 per patient (Table 2).

Table 2. Results of the base case analysis

Scenario	Costs	5-aminolaevulinic acid	Methyl aminolevulinate	Difference	Plausibility
Base case					
5-aminolaevulinic acid versus methyl aminolevulinate	Medicine acquisition costs	£170.00	£343.00	−£173.00	
	Total costs	£170.00	£343.00	−£173.00	
Scenario analysis:					
Scenario 1: A new tube of 5-aminolaevulinic acid is required for the second cycle	Medicine acquisition costs	£340.00	£343.00	−£3.00	This scenario is plausible as some people may require a second tube. However, no data are available to verify how many people will require a second tube
	Total costs	£340.00	£343.00	−£3.00	
Scenario 2: Only people without complete clearance in cycle 1 require a second cycle of treatment. People requiring cycle 2 either reuse the same tube of 5-aminolaevulinic acid or use a second tube of methyl aminolevulinate	Medicine acquisition costs	£170.00	£246.27	−£76.27	This scenario is plausible as only people whose lesions did not clear in cycle 1 would require a second cycle (43.6% in comparator group)
	Total costs	£170.00	£246.27	−£76.27	
Scenario 3: Only people without complete clearance in cycle 1 require a second cycle of treatment. Two tubes of either 5-aminolaevulinic acid or methyl aminolevulinate are assumed for people receiving both cycles	Medicine acquisition costs	£241.57	£246.27	−£4.70	This scenario is plausible as only people whose lesions did not clear in cycle 1 would require a second cycle (42.1% in 5-aminolaevulinic acid group, 43.6% in comparator group)
	Total costs	£241.57	£246.27	−£4.70	

Table 2 also summarises the scenarios provided by the company and calculated by AWTTC in order to address uncertainty around the key input parameters of the CMA. Three scenario analyses were tested using different numbers of tubes. The incremental costs of 5-aminolaevulinic acid range from −£3 to −£76 per patient.

4.1.3 AWTTC critique

The reliability of the CMA presented is dependent on the extent to which 5-aminolaevulinic acid is considered to be therapeutically equivalent to methyl aminolevulinate. The phase III trial ALA-BCC-CT008 evaluating efficacy and safety found 5-aminolaevulinic acid to be statistically non-inferior to methyl aminolevulinate in adult patients. Outcomes with 5-aminolaevulinic acid were improved across all clearance and recurrence rates.

Strengths of the economic analysis:

- The only comparator used in the CMA is methyl aminolevulinate, which appears appropriate. The company states that previous use of alternative unlicensed 5-aminolaevulinic acid formulations should have ceased in Wales following MHRA guidance. Furthermore, surgery as first line treatment of BCC was not considered as a direct comparator because available PDT treatments are used second-line after surgery or if patients are unsuitable for surgery.

Limitations of the economic analysis:

- The company assumes that the only difference between the two comparators is in the drug acquisition cost. However, based on the information provided, it is uncertain whether this would be the case in practice. Furthermore, the calculation assumes that all patients receiving 5-aminolaevulinic acid will use the same tube for cycles 1 and 2. It is uncertain how realistic this assumption is as no evidence was provided by the company to support it. The cost savings achieved with 5-aminolaevulinic acid could therefore be overestimated.
- The calculation assumes that all patients require a second treatment cycle after 12 weeks. Considering the complete clearance rate of around 57% after the first cycle, this assumption appears unreasonable because less than half of the people would continue to cycle two. The calculations could therefore overestimate the savings produced by 5-aminolaevulinic acid. Calculations undertaken by AWTTC suggest a cost saving of £76 if only 43.6% of people receiving methyl aminolevulinate are assumed to continue with cycle 2 and only one tube of 5-aminolaevulinic acid gel is assumed for both treatment cycles. Considering two tubes for both treatments and applying the respective rate of cycle 2 uptake to each treatment arm, results in reduced cost savings of £4.70 per patient.
- For the purpose of the CMA, the company assumes adverse events, QoL and clinical efficacy between 5-aminolaevulinic acid and methyl aminolevulinate to be equivalent. However, the CMA approach in this case is inappropriate and is unlikely to accurately reflect the cost-effectiveness of 5-aminolaevulinic acid for several reasons:
    - According to the pivotal study, 93.4% of patients in the 5-aminolaevulinic acid arm were complete responders 12 weeks after the last PDT, compared to 91.8% in the methyl aminolevulinate group. While this was a significant non-inferiority with respect to patient complete clearance rate ($p < 0.0001$), and both treatments demonstrated comparable rates of adverse events (100% for both), the trial was not designed to assess equivalence of treatment options.
    - The submission includes data that demonstrates advantages of 5-aminolaevulinic acid over methyl aminolevulinate regarding lesion clearance rate, lesion recurrence rate and cosmetic outcome (excluding

patients without skin quality problems at baseline). The CMA could therefore underestimate the cost-effectiveness of 5-aminolaevulinic acid.
    - The submission also includes data that demonstrates disadvantages of 5-aminolaevulinic acid over methyl aminolevulinate; for example, lesion complete response rate for people with sBCC was lower in the 5-aminolaevulinic acid group compared to the methyl aminolevulinate group. A CMA could therefore overestimate the cost-effectiveness of 5-aminolaevulinic acid.
    - No data on HRQoL (e.g. survival, adherence or patient preference) are presented. Although the HRQoL equivalence assumption appears reasonable, it cannot be verified due to the lack of data.
- The base case CMA assumes that only one tube of 5-aminolaevulinic acid is required for all four PDT treatments (two treatments in cycle 1 and two treatments in cycle 2). However, the company states that no data are available to verify this assumption which could introduce bias and underestimate the cost of 5-aminolaevulinic acid.
- While the CMA assumes equivalence regarding HRQoL, survival, adherence and patient preference, the company do not provide evidence to support this assumption.
- In summary, the CMA conducted is inappropriate because of the differences in clinical outcomes. Also, costs are not based on actual usage data. The real cost is therefore uncertain. However, it can be expected that overall treatment costs will not differ substantially between 5-aminolaevulinic acid and methyl aminolevulinate.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The incidence of non-melanoma skin cancer in Wales in year 1 is estimated to be 2,888 people based on an incidence of 128 male and 105 female per 100,000 population in South Wales[5] applied to the Welsh population[15] and the assumption that 80% of non-melanoma skin cancer cases are BCC[16]. An annual incidence increase of 3.4% is applied[17] resulting in 2,997 cases in year 5. A condition-specific mortality rate of 0.01% is considered[18]. The company assumes that 25% of people with BCC will be unsuitable for surgery, resulting in 722 people treated with PDT in year 1 increasing to 749 in year 5. 5-aminolaevulinic acid is thought to replace 4% of the market share of methyl aminolevulinate upon introduction to the market increasing to 7.5% in year 3 and remaining stable thereafter. This gives a number of 29 people treated with 5aminolaevulinic acid in year 1 and 56 in year 5. It is assumed that all patients require two cycles of treatment (two PDT treatments in cycle 1 and two PDT treatments in cycle 2). People treated with 5-aminolaevulinic acid are thought to need one tube only at a cost £170 per patient. The 43.6% of people treated with methyl aminolevulinate cream who require a second cycle are assumed to use two tubes at a cost of £343 per patient. All other costs are assumed equal. The company presents a scenario analysis that calculates the budget impact if two tubes of 5-aminolaevulinic acid are assumed for the 42.1% of people who require a second treatment cycle at a cost of £170 per tube.

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 3. The introduction of 5-aminolaevulinic acid is estimated to result in cost savings of £2,212 in year one increasing to £4,271 per year after year 3. The total budget impact over five years would be expected to be in the region of −£18,457.

Table 3. Company-reported costs associated with use of 5-aminolaevulinic acid

	Year 1 2017	Year 2 2018	Year 3 2019	Year 4 2020	Year 5 2021
Number of eligible patients (all licensed indications)	2,888	2,987	2,990	2,993	2,997
Sub-population of eligible patients (indication under consideration)	722	747	747	748	749
Uptake of new medicine (%)	4	6	7.5	7.5	7.5
Number of patients receiving new medicine allowing for discontinuations	29	45	56	56	56
Net medicine acquisition costs	−£2,212	−£3,432	−£4,271	−£4,271	−£4,271
Medication costs	£4,930	£7,650	£9,520	£9,520	£9,520
Savings from displaced medicines	£7,142	£11,082	£13,791	£13,791	£13,791
Net costs	−£2,212	−£3,432	−£4,271	−£4,271	−£4,271

The scenario analysis provided by the company shows that the cost savings would be reduced to £136 in year 1 and £263 from year 3 onwards if two tubes of 5-aminolaevulinic acid are assumed for the 42.1% of people who require a second treatment cycle, with an estimated total budget impact over five years of −£1,137.

5.1.3 AWTTC critique

- The data sources and calculations provided by the company for the budget impact calculation are poorly described, and limited sensitivity analyses are undertaken. Furthermore, the company keeps contradicting itself and data entered in the models at different times do not match. Therefore, the accuracy of the numbers used to calculate the budget impact, especially the uptake rates, are highly uncertain.
- The company assumes that 25% of BCC cases are unsuitable for surgery. However, this figure is based on clinical opinion only and cannot be verified.
- The company assumes that of the 2,888 BCC cases in Wales, 722 will be ineligible for surgery. However, it then assumes that of these 722 people, 85% will receive surgery. The company argues that it double-counted surgery because dermatologists will often treat unsuitable people with surgery as many do not own the required red light source needed for PDT (wavelength of 570 nm to 670 nm). While this statement appears reasonable, it cannot be verified and it is uncertain how realistic this assumption is.
- The company states that additional cost savings will be achieved because of higher treatment efficacy and lower treatment failure rate of 5-aminolaevulinic acid compared to methyl aminolevulinate. However, this was not considered in the budget impact calculations, which might therefore underestimate the potential cost savings.
- Uptake rates are estimates and data sources were not available for review. Any changes to the uptake rate will affect the budget impact of 5-aminolaevulinic acid. The company assumes that market share will remain constant after year 3. This assumption is based on the company's experience that there will be no uptake of additional red light lamps in the UK. Therefore, it is unlikely that

the number of available lamps, and thus the number of people treated, will change over the next five years. However, this cannot be verified and could underestimate the number of people treated with PDT.

5.2 Comparative unit costs

Medicine acquisition costs of 5-aminolaevulinic acid and its main comparator are described in Table 4. To date, no other treatment options are licensed in the UK in combination with PDT for the second-line treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

Table 4. Examples of acquisition costs of second-line treatment of superficial and/or nodular basal cell carcinoma

Regimens	Example doses	Approximate costs per cycle
5-aminolaevulinic acid 78 mg/g gel (Ameluz®) 2 g tube	Apply layer (1 mm thickness) to lesions for two PDT sessions approximately 1 week apart. Review at three months and retreat if no or partial response.	£170.00 (£170.00 per tube)
Methyl aminolevulinate 160 mg/g cream (Metvix®) 2 g tube	Apply layer (1 mm thickness) to lesions for two PDT sessions approximately 1 week apart. Review at three months and retreat if no or partial response.	£171.50 (£171.50 per tube)
Costs and doses from Monthly Index of Medical Specialities (MIMS)[19].		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, 5-aminolaevulinic acid hydrochloride (Ameluz®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

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

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