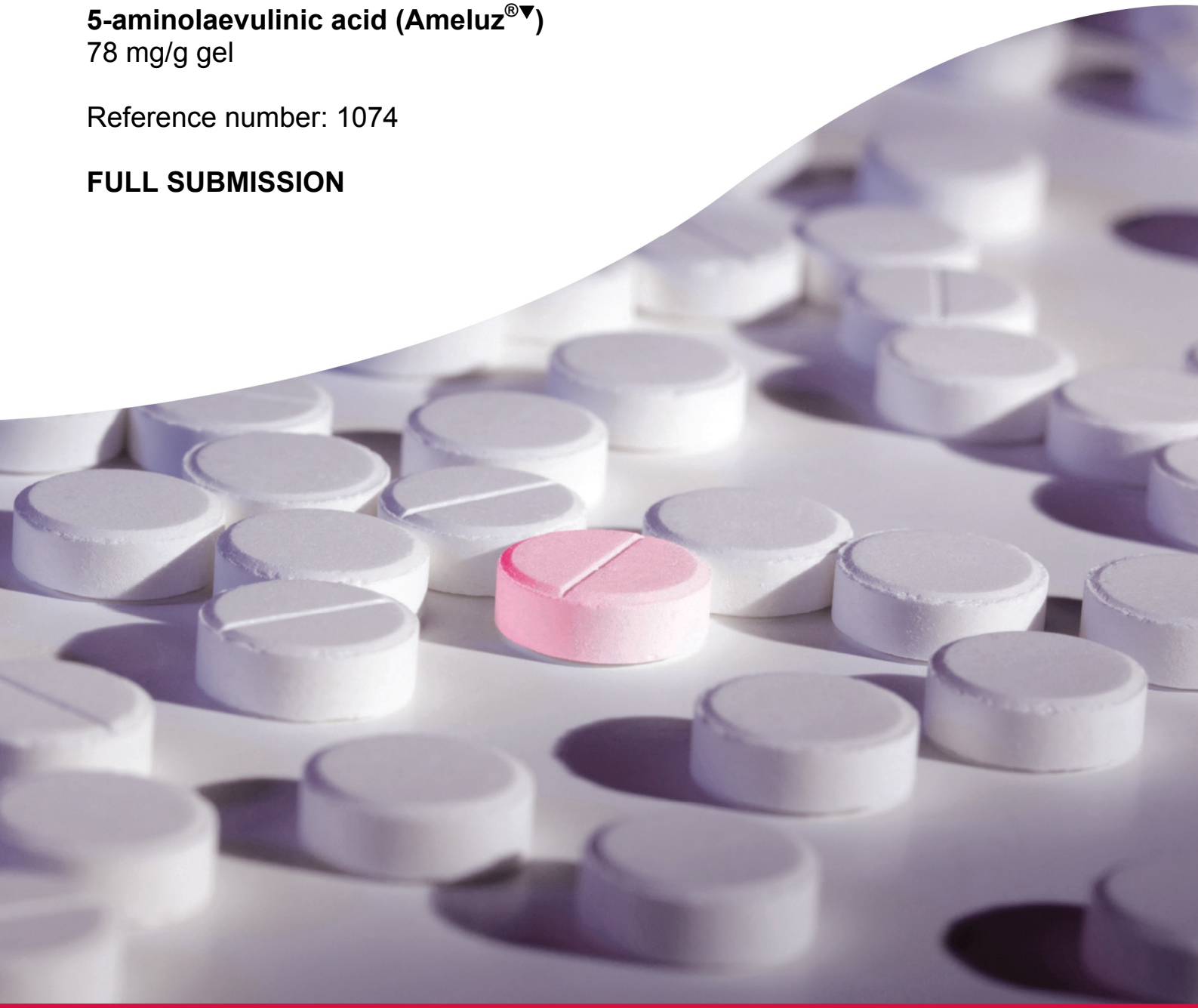
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 1074

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. 5-aminolaevulinic acid (Ameluz®▼) 78 mg/g gel. Reference number: 1074. September 2013.

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

This assessment report is based on evidence submitted by Spirit Healthcare Ltd on 13 May 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	5-aminolaevulinic acid (Ameluz®▼) for the treatment of actinic keratosis of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2).
Dosing	5-aminolaevulinic acid should only be administered under the supervision of a physician, a nurse or other healthcare professionals experienced in the use of photodynamic therapy. 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. The gel should cover the lesions and approximately 5 mm of the surrounding area with a film of about 1 mm thickness. The entire treatment area will be illuminated with a red light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm^2 or a broader and continuous spectrum in the range between 570 and 670 nm with a light dose between 75 and 200 J/cm^2. Refer to the Summary of Product Characteristics (SPC) for further information regarding administration[2].
Marketing authorisation date	14 December 2011[1]
UK launch date	01 November 2012[1]

2.0 DECISION CONTEXT

2.1 Background

Actinic keratoses (AKs) are skin lesions considered to be precursors to squamous cell carcinoma (SCC) and most result from chronic exposure to ultraviolet radiation[3,4]. They present as dry, rough, yellow-brown scaly plaques which may become thickened and horny[5]. AKs occur most commonly on areas of increased sun exposure (for example the face, scalp, hands and forearms), and occur more frequently in individuals with fairer skin types. Prevalence of AKs is higher in men than women, and a study conducted in South Wales estimated the prevalence of AK in individuals aged 60 or over to be 23%[6,7].

The risk of progression of an AK lesion to malignancy is low and lesions may undergo spontaneous regression without treatment; rates of spontaneous regression over one year have been reported as 15–25%[3]. Most individuals present with multiple lesions, and the risk of malignant transformation of at least one lesion over a ten-year period has been estimated as 10%[3]. In addition to preventing the progression of AK lesions to SCC, treatment may also aim to provide relief of symptoms or disfigurement resulting

from the presence of lesions[3]. Treatment strategies include palliative treatment with an emollient, active topical treatment (options available in the UK include fluorouracil cream [Efudix®][8], imiquimod 5% cream [Aldara®][9], fluorouracil and salicylic acid solution [Actikerall®][10] and 3% diclofenac gel [Solaraze®][11]), surgical excision, cryotherapy or photodynamic therapy (PDT)[3]. 5-aminolaevulinic acid is a novel nanogel formulation, which is used in combination with PDT[1]. This nanogel formulation increases the stability of the active ingredient and improves its penetration into the epidermis[1]. Following topical application, 5-aminolaevulinic acid is metabolised to the photoactive component protoporphyrin IX. Protoporphyrin IX accumulates intracellularly in the treated AK lesions and is activated by illumination with red light. In the presence of oxygen, reactive oxygen species are formed causing the damage of cellular components; this eventually leads to cell death[2].

2.2 Comparators

The comparator included in the company submission was methyl aminolevulinate cream (Metvix®).

2.3 Guidance and related advice

- Primary Care Dermatology Society. Clinical guidance: actinic keratoses (2013)[5].
- Primary Care Dermatology Society. Actinic (solar) keratosis primary care treatment pathway (2012)[12].
- European Dermatology Forum. Guideline on actinic keratoses (2011)[13].
- British Association of Dermatologists. Guidelines for topical photodynamic therapy: update (2008)[14].
- British Association of Dermatologists. Guidelines for the management of actinic keratoses (2007)[3].
- National Institute for Health and Care Excellence (NICE). Interventional Procedure Guidance 155. Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions) (2006)[15].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of:

- Fluorouracil/salicylic acid (Actikerall®) is recommended as an option for use within NHS Wales for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent adult patients (2012)[16].
- Ingenol mebutate (Picato®▼) is recommended as an option for use within NHS Wales for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults (2013)[17].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of two pivotal phase III studies, ALA-AK-CT002 and ALA-AK-CT003, which assess the efficacy and safety of 5-aminolaevulinic acid in patients with mild to moderate AK of the face and scalp. A 12-month follow-up study of ALA-AK-CT002 was also included. Study ALA-AK-CT003 will not be discussed further, as it does not inform the comparison of 5-aminolaevulinic acid with an active comparator.

3.1 Comparative Efficacy

3.1.1 Study ALA-AK-CT002

This was a randomised, multicentre, observer-blind, placebo-controlled phase III trial, which evaluated the efficacy and safety of 5-aminolaevulinic acid versus methyl aminolevulinate in adult patients diagnosed with four to eight mild to moderate AK

lesions (Olsen grade 1 to 2, see Glossary) on the face and/or bald scalp[4,18]. The diameter of each AK lesion was to be not less than 0.5 cm and not greater than 1.5 cm and adjacent AK lesions had to show a distance of more than 1.0 cm to one another. Patients (n = 571) were randomised 3:3:1 to receive 5-aminolaevulinic acid 78 mg/g gel (n = 248), methyl aminolevulinate 160 mg/g gel (n = 247) or placebo (n = 76). The lesions were thoroughly prepared by removing scabs/crusts and cleaning with alcohol, before one tube containing 2 g of treatment was dispensed for one PDT session. The gel was allowed to dry for approximately ten minutes before applying an occlusive, light-tight dressing over the lesions. After an incubation time of approximately three hours, the occlusion was removed and the remnant gel wiped off with 0.9% sodium chloride solution. The target area was then illuminated with a suitable red light source for 8–15 minutes[4,18].

The primary endpoint was complete response (defined as a subject in whom all treated lesions were cleared), which was assessed at 12 weeks after the last PDT. In cases of remaining lesions, a second treatment was permitted 12 weeks after the first. The results demonstrated superiority of 5-aminolaevulinic acid over placebo ($p < 0.0001$) and noninferiority of 5-aminolaevulinic acid to methyl aminolevulinate. This was shown in both the intention-to-treat (ITT) and per protocol (PP) populations (refer to Table 1 for the primary endpoint results). These results were supported by the main secondary endpoint: the lesion complete response (defined as the number of treated lesions that were cleared) measured at 12 weeks after the last PDT[4,18].

Differences in results were achieved when different irradiation sources were used. For complete response rates, the rates were significantly higher in patients who were irradiated with narrow-spectrum light sources (84.8% 5-aminolaevulinic acid versus 67.5% methyl aminolevulinate and 12.8% placebo) than with broad spectrum light sources (71.5% 5-aminolaevulinic acid versus 61.3% methyl aminolevulinate and 21.6% placebo)[4,18].

It should be noted that both treatments were more effective when AK lesions were located on the face/forehead (81.9% 5-aminolaevulinic acid versus 77.5% methyl aminolevulinate) than the bald scalp (70.1% 5-aminolaevulinic acid versus 39.7% methyl aminolevulinate)[1,18].

Table 1. Results of the primary and main secondary efficacy endpoints[4,18].

	Number (%) of subjects			Difference to 5-aminolaevulinic acid	
	5-aminolaevulinic acid	**Methyl aminolevulinate**	**Placebo**	**Methyl aminolevulinate**	**Placebo**
Primary endpoint: Subjects with total AK lesion clearance 12 weeks after last PDT					
ITT population	194/248 (78.2)	158/246 (64.2)	13/76 (17.1)	14.0% (97.5% CI: 5.9;∞)	61.1% (95% CI: 51.2, 71.0) $p < 0.0001$
PP population	189/238 (79.4)	154/236 (65.3)	13/65 (20.0)	14.2% (97.5% CI: 6.0;∞)	59.4% (95% CI: 48.4, 70.4) $p < 0.0001$
Main secondary endpoint: Total AK lesion clearance 12 weeks after last PDT					
ITT population	1,359/1,504 (90.4)	1,295/1,557 (83.2)	182/490 (37.1)	7.2%	53.2%
CI: confidence interval, ITT: intention to treat; PDT: photodynamic therapy; PP: per protocol					

3.1.2 Follow up study of ALA-AK-CT002

This 12-month follow-up study enrolled 549 patients who had completed study ALA-AK-CT002, and was designed to assess the long-term efficacy with regards to recurrences of AK lesions and safety. After 12 months, recurrence rates were 41.6% for 5-aminolaevulinic acid and 44.8% for methyl aminolevulinate[4]. The occurrence of new lesions was found to be lowest in the 5-aminolaevulinic acid group (41.8%), followed by the methyl aminolevulinate group (48.7%) and placebo (56.1%)[1].

3.2 Comparative safety

Safety evidence is presented from the pivotal phase III study ALA-AK-CT002. Treatment-emergent adverse events (TEAEs), related to the study medicine, were observed in 95.2% of patients receiving 5-aminolaevulinic acid, 97.6% receiving methyl aminolevulinate group and 65.8% receiving placebo. The majority of related TEAEs were application site reactions associated with PDT (94.8% animolevulinic acid versus 96.7% methyl aminolevulinate and 64.5% placebo). The most common application site reactions reported by 5-aminolaevulinic acid patients were irritation (88.3% versus 90.2% and 32.9%), erythema (79.8% versus 80.9% and 40.8%) and pain (70.6% versus 72.8% and 25.0%). Patients who were irradiated with the narrow spectrum light sources were associated with a more intense and higher number of TEAEs[1,4].

In the follow-up study of ALA-AK-CT002, nonmelanoma skin cancers in the treatment area were reported in 1.3% of patients in the 5-aminolaevulinic group versus 0.8% of patients in the methyl aminolevulinate group and 4.5% of patients in the placebo group. The majority of these patients (14/20) were noncomplete responders or had a history of skin diseases including AK for several years (18/20). No serious medicine-related TEAEs were reported during the study duration[1,4,19].

3.3 AWTTC critique

- Evidence of efficacy and safety was presented from two pivotal phase III trials; both of which had a follow-up period of 12 months[1,4]. The company state that no longer-term data, beyond 12 months, are available.
- 5-aminolaevulinic acid is licensed for the treatment of mild to moderate AK[2]; it should be noted that the comparator methyl aminolevulinate is licensed for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other therapies are considered less appropriate[20].
- The company reports that 5-aminolaevulinic acid and methyl aminolevulinate PDT will be positioned as second line treatments following failure of topical preparations in Welsh practice[1].
- Although study ALA-AK-CT002 was designed to demonstrate superiority to placebo and noninferiority to methyl aminolevulinate, superiority of 5-aminolaevulinic acid over methyl aminolevulinate was additionally proven (97.5% CI 6.0–∞)[18].
- In study ALA-AK-CT002, the type of irradiation source used in PDT was found to have an effect on complete response rates and the intensity of TEAEs; narrow-spectrum light sources demonstrated an increased effect on both when compared to broad-spectrum light sources[1,4]. The company highlight that in the UK, including Wales, most clinicians use narrow angle (Light Emitting Diode [LED]) lamps to illuminate lesions[1].
- In study ALA-AK-CT002, 5-aminolaevulinic acid demonstrated a beneficial effect on the treatment of the bald scalp compared to the comparator treatment, methyl aminolevulinate (patient complete response rate: 70.1% versus 39.7%)[18].
- The SPC for 5-aminolaevulinic acid states that lesions should be reassessed after three months at which point any residual lesions may be retreated[2]. In their submission, the company highlighted that 5-aminolaevulinic acid may be refrigerated and suitably stored in a pharmacy for up to 12 weeks; therefore, the same tube may then be used for a second treatment[1]. The comparator

treatment, methyl aminolevulinate has a one week expiry after first opening and cannot be used for a second treatment[20].

- The company suggest that PDT may have advantages over surgical procedures, as PDT removes visible AK lesions without scar formation or lasting hypopigmentation. Additionally, treatment failures due to poor patient compliance are negligible as PDT is performed by a healthcare professional[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence submitted by the company

4.1.1 Context

The company submission described a cost minimisation analysis (CMA) of 5-aminolaevulinic acid 78 mg/g gel in its licensed indication for the treatment of actinic keratosis of mild to moderate intensity on the face or scalp (Olsen grade 1 to 2), in combination with PDT[1].

The CMA approach assumes equivalent efficacy and safety for 5-aminolaevulinic acid and its comparator, methyl aminolevulinate 160 mg/g cream. This assumption is based on the results of a noninferiority phase III randomised controlled trial (RCT; ALA-AK-CT002) in which 5-aminolaevulinic acid was compared to methyl aminolevulinate, as an active control, and to placebo. The results proved noninferiority, and superiority of 5-aminolaevulinic acid in relation to the primary endpoint of achieving complete clearance (79.4% vs. 65.3%; $p < 0.05$, PP population). Subgroup analysis of patients in whom narrow angle LED lamps were used, reported to be representative of Welsh practice, showed similar results and was used in scenario analysis in the CMA[18].

The CMA is undertaken from the perspective of NHS Wales. Only drug acquisition costs have been included[21]. In response to comments from AWTTC, the company provided additional analysis including the costs of storage and labelling of partially used 5-aminolaevulinic acid tubes. In the base case analysis, the efficacy of both medicines was set at the level observed for methyl aminolevulinate in the PP population analysis[18] and the proportion of patients requiring a second photodynamic therapy was calculated accordingly. It was assumed that the same tube of 5-aminolaevulinic acid would be used for these patients, based on the difference in in-use shelf-life of both medicines (12-week shelf-life of an in-use 5-aminolaevulinic acid tube[2] compared with one-week for methyl aminolevulinate[20]). Efficacy estimates and number of tubes needed for a second photodynamic therapy were varied in scenario analyses.

4.1.2 Results of the company's analyses

The results of the base case analysis are presented in Table 2. These suggest that 5-aminolaevulinic acid is cost saving when compared with methyl aminolevulinate.

Table 2. Base case analysis results.

Base case comparison	Total costs per course of treatment			Plausibility
	5-aminolaevulinic acid	Methyl aminolevulinate	Difference	
Medicine costs	£184	£322.98	**−£138.98**	Estimated saving represents best case scenario
Total cost	£184	£322.98	**−£138.98**	Re-dosing issue? (Assumes that none of the patients requiring a second PDT will require a new tube of 5-aminolaevulinic acid)

Scenario analyses exploring the impact of varying the assumption relating to the need for re-dosing and the efficacy estimate (percentage of responders at first PDT) are also presented (see Table 3). These showed that 5-aminolaevulinic acid remained cost saving compared to methyl aminolevulinate in all scenarios, with a minimum saving of £21.96 per treatment course when using the highest efficacy estimate (53.6%, the efficacy of 5-aminolaevulinic acid in the LED sub-group).

Table 3. Scenario analyses results.

Scenarios	Total cost per course of treatment			Plausibility
	5-aminolaevulinic acid	Methyl aminolevulinate	Difference	
Lowest efficacy scenario: Efficacy equal to methyl aminolevulinate efficacy in the PP population analysis (37.7% responders after first PDT) and:				Using the lowest efficacy estimate may over-estimate the proportion of patients requiring second PDT and, hence, increases the costs associated with using methyl aminolevulinate
- tubes of 5-aminolaevulinic acid required for second PDT = 0.5	£241.32	£322.98	**−£81.66**	Re-dosing issue? Assumes 50% of patients require a second tube
- tubes of 5-aminolaevulinic acid required for second PDT = 1	£298.63	£322.98	**−£24.35**	Assumes all patients require a second tube
Highest efficacy scenario: Efficacy equal to 5-aminolaevulinic acid efficacy in the PP population analysis (53.6% responders after first PDT) and:				
- tubes of 5-aminolaevulinic acid required for second PDT = 0	£184.00	£291.34	**−£107.34**	Re-dosing issue?
- tubes of 5-aminolaevulinic acid required for second PDT = 0.5	£226.69	£291.34	**−£64.65**	Re-dosing issue?
- tubes of 5-aminolaevulinic acid required for second PDT = 1	£269.38	£291.34	**−£21.96**	Most conservative estimate of cost saving

4.1.3 AWTTC critique of the economic evidence

The reliability of the company's CMA is dependent on the extent to which 5-aminolaevulinic acid is considered to be therapeutically equivalent in terms of efficacy, safety and patient preference, to its comparator, methyl aminolevulinate. Noninferiority has been demonstrated at 12 weeks in the head-to-head ALA-AK-CT002 trial and is suggested at 12 months. There are no longer term data beyond 12 months. There is also a suggestion of superiority; however, the ALA-AK-CT002 trial was not specifically designed for demonstrating superiority or equivalence. Additionally, it was assumed that there is no difference in resource use and that the only difference between the two comparators is in the drug acquisition cost, though it is uncertain whether this would be the case in practice.

Strengths of the economic evidence include:

- Direct comparative evidence is available from a pivotal phase III RCT (ALA-AK-CT002) that compared 5-aminolaevulinic acid with methyl aminolevulinate[18].

Limitations of the economic evidence include:

- In the ALA-AK-CT002 trial, enrolled patients received either 5-aminolaevulinic acid or methyl aminolevulinate[18]. The company report that 5-aminolaevulinic acid and methyl aminolevulinate PDT will be positioned as second line treatments following failure of active topical preparations in Welsh practice[1]. In the absence of data from the pivotal trial regarding the proportion of patients receiving PDT as second line treatment, it is not clear whether the efficacy demonstrated in the trial can be generalised in practice for Wales.
- The company suggests that 5-aminolaevulinic acid is superior to methyl aminolevulinate and that the use of CMA is a conservative approach[1]. However the use of CMA requires an assumption of equivalence across all domains of outcome including safety, tolerability and patient preference. Long-term efficacy and safety data are not available to support this assumption of equivalence between 5-aminolaevulinic acid and methyl aminolevulinate beyond 12 months. CMAs implicitly assume indefinite equivalence in outcomes, though the company has restricted the time horizon as that there are no longer term data beyond 12 months.
- In the company analysis, it is assumed that all patients treated with 5-aminolaevulinic acid who may require a second PDT would be identified and treated within the 12 week in-use shelf-life of 5-aminolaevulinic acid[1]. This is only plausible if both the evaluation of the lesion and administration of the second PDT take place at exactly three months after treatment (the minimum time specified for re-evaluation in the 5-aminolaevulinic acid SPC[2]). It is not clear if this would be feasible in real practice and hence longer durations between the two applications may be seen in practice. This would necessitate the use of a new tube of 5-aminolaevulinic acid for the second PDT application and eliminate the cost advantage resulting from reduced drug wastage compared to methyl aminolevulinate. Furthermore, the costs of pharmacy time involved in the labelling, storing and subsequent disposal of 5-aminolaevulinic acid tubes have not been taken into account in the calculations. However, the company provided further analysis to estimate these costs which showed that they were negligible.
- The two efficacy estimates used in the scenario analysis to calculate the proportion of patients requiring re-dosing are both different from the estimate reported in the trial (59.8% of patients required a second treatment[18]). Nevertheless, the different estimates will only impact the size of the saving made and not whether 5-aminolaevulinic acid is cost saving.
- An analysis based on the ITT population has not been presented, though this may arguably be less conservative than the per protocol analysis of non-inferiority trials.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of 5-aminolaevulinic acid within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates that around 500 patients are treated in Wales with PDT and around 40% of them access PDT for actinic keratosis of the face and scalp[1]. These estimates are based on communication with Welsh consultant dermatologists. Hence, it is estimated that around 200 AK patients will access PDT in Wales. The company assumed that this annual number of patients is constant in the five years 2013–2017 inclusive[1].

The company estimates that 25% of these 200 patients would have access to 5-aminolaevulinic acid in year one, rising to 50% in years two to five. The company reports that the yearly cost per patient is £184 minimum (one tube)/£368 maximum (two tubes). However, the company anticipates that it is unlikely that many patients will require a second tube.

5.1.2 Results

Based on the reported numbers, the company anticipates an overall net cost savings from switching from methyl aminolevulinate to 5-aminolaevulinic acid. The results are summarised in Table 4 below.

Table 4. Company-reported costs associated with the use of 5-aminolaevulinic acid (Ameluz®▼) for actinic keratosis in Wales.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	200	200	200	200	200
Uptake (%)	25%	50%	50%	50%	50%
Treated patients	50	100	100	100	100
Net costs for all Welsh patients (negative values indicate savings)					
Medication	-£6,950	-£13,900	-£13,900	-£13,900	-£13,900
Other costs	None reported	None reported	None reported	None reported	None reported
Overall net cost	-£6,950	-£13,900	-£13,900	-£13,900	-£13,900

5.1.3 AWTTC critique of the budget impact analysis

- Given the reported lack of data on the prevalence of mild and moderate AK of face and scalp, the company has relied on the opinion of Welsh consultants to estimate the number of patients who would have access to PDT treatment and who would be eligible for treatment with 5-aminolaevulinic acid in Wales. These data have not been verified. Constant patient numbers are also assumed over the five-years. This is based on an assumption of limited provision of PDT. Hence, the estimated patient numbers are subject to uncertainty.
- The cost estimates are derived from the company's CMA; therefore, the limitations and uncertainties associated with the costs assumed in the CMA also apply to the budget impact analysis.
- Overall, the analysis is subject to uncertainty, particularly in relation to the number of eligible patients. Although 5-aminolaevulinic acid is cheaper and offers saving in drug acquisition cost under the assumption of equivalence, it is not clear whether the magnitude of the estimated saving reported by the company would be realised in practice.

5.2 Table of comparative unit costs

Examples of acquisition costs for 5-aminolaevulinic acid and other agents licensed for the treatment of actinic keratosis are shown in Table 5.

Table 5. Examples of acquisition costs for actinic keratosis treatments.

Drug	Example dose*	Example cost per treatment course**
Ameluz®▼ (5-aminolaevulinic acid) Gel, 78 mg/g in 2 g tube	Apply thin layer (approx. 1 mm thick) to lesion and 5 mm surrounding skin using a spatula. Review at three months; retreat if no or partial response	**£184–£368**
Metvix® (methyl aminolevulinate) Cream, 160 mg/g in 2 g tube	Apply thin layer (approx. 1 mm thick) to lesion and 5–10mm surrounding skin using a spatula. Repeat if necessary after three months	**£199–£398**
Solaraze® (Diclofenac Sodium) Gel, 3%, 50 and 100 g tube	Apply thinly twice daily for 60–90 days; max. 8 g daily	**£229.80–£344.70*** **
Efudix® (Fluorouracil) Cream, 5% in 40 g tube	Apply thinly to the affected area once or twice daily; maximum area of skin treated at one time, 500 cm^2 (e.g. 23 cm × 23 cm); usual duration of initial therapy, three to four weeks	**£114.66*** **
Actikerall® (fluorouracil 0.5%, salicylic acid 10%) Cutaneous solution, 25 ml	Low or moderately thick hyperkeratotic actinic keratosis, apply to affected area once daily for up to 12 weeks; maximum area of skin treated at one time, 25 cm^2	**£38.30*** **
Aldara® (Imiquimod) Sachets, 5%	Apply to lesion three times a week at night for four weeks; assess response after a four week treatment-free interval; repeat four-week course if lesions persist; maximum two courses	**£48.39–£96.78**
Zyclara® (Imiquimod) Sachets, 3.75%	Apply to lesion on face or balding scalp at bedtime for two weeks (maximum two sachets daily); repeat course after a two-week treatment-free interval; assess response eight weeks after second course	**£56.50–£226**
Picato® (Ingenol mebutate) Cream, 150 and 500 micrograms/g tubes	Face or scalp: apply contents of one 150 microgram/g tube to affected area over 25cm^2 once daily for three days	**£65**

*Based on BNF and MIMS dosing instructions[21,22].
**Costs are based on current BNF and MIMS list prices as of 26 May 2013[21,22].
*** Costs based on 25cm^2 surface area.
This table does not imply therapeutic equivalence of drugs or the stated doses.
See relevant SPCs for full dosing details[2,8–11,20,23–25].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company do not anticipate that 5-aminolaevulinic acid (Ameluz®▼) will be supplied by a home healthcare provider.

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 Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 21 May 2013.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Olsen grade

This is a scale of AK intensity, which was described in 1991 by Olsen and colleagues[26]. See Table 6.

Table 6. The Olsen scale of AK intensity.

Grade		Clinical description of intensity grading
0	None	No AK lesion present, neither visible nor palpable
I	Mild	Flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, with AK felt better than seen
II	Moderate	Pink to reddish papules and erythematous plaques either hyperkeratotic surface, moderately thick AK that are easily seen and felt
III	Severe	Very thick and/or obvious AK

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