EXTERNAL ASSESSMENT CENTRE REPORT

Title: Ambulight photodynamic therapy

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Declared interests of the authors

None.

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None

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Abbreviations

5-ALA	5-aminolaevulinic acid
AK	actinic keratosis
BCC	basal cell carcinoma
BPD-MA	benzoporphyrin derivative monoacid ring A
CE	Conformité Européenne
CSGSTIM	Cancer Service Guidance - Skin Tumours including Melanoma
EAC	External Assessment Centre
FWHM	full width at half maximum
GP	general practitioner
GPwSI	general practitioner with a special interest
h	hour
HES	hospital episode statistics
IFU	instructions for use / information for use
LED	light emitting diode
MAL	methyl aminolaevulinate
nBCC	nodular basal cell carcinoma
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMSC	non-melanoma skin cancer
NRS	numerical rating score
PDT	photodynamic therapy
PpIX	protoporphyrin IX
PSSRU	Personal Social Services Research Unit
sBCC	superficial basal cell carcinoma
SCC	squamous cell carcinoma
VAS	visual analogue scale

Note on use of page numbers

Page numbers provided in parentheses in this assessment report refer to the manufacturer's submission document, unless otherwise stated. Page numbers in parentheses prefixed with 'A' refer to page numbers in the appendix provided by the manufacturer "Ambicare Health - Review of clinical data for NICE".

1 SUMMARY

1.1 Scope of the submission

This report assesses the submission to NICE by the manufacturer (Ambicare Health) for use of the Ambulight PDT device in the treatment of non-melanoma skin cancer. Specifically the submission considers Ambulight PDT for the treatment of single lesions (less than 2.4 cm in diameter) of superficial basal cell carcinoma, actinic keratosis or Bowen's disease, which is in line with the scope issued by NICE for the appraisal. This report includes an assessment of both the clinical effectiveness and the cost implications, based on evidence submitted by the manufacturer.

1.2 Summary of submitted clinical effectiveness evidence

The submission presented evidence for treatment efficacy by examining the effects of differences between treatment protocols for the Ambulight PDT with those for conventional PDT. In addition, the results from one study which used the Ambulight PDT were included in the analysis. For adverse effects, and in particular pain during treatment, the submission presented evidence from studies with conventional PDT which considered the effect of reduced irradiance on pain. In addition, the results from two pilot studies with the Ambulight PDT device which considered pain as an outcome were included in the submission. A total of 28 papers, including 18 clinical trials, two animal trials, one laboratory study, two papers reporting clinical experience, two case studies and three review articles or guidelines were included in the submission.

No randomised trials which directly assessed either treatment efficacy or adverse effects of treatment with the Ambulight PDT were presented. Direct evidence for tumour clearance and reduced pain during treatment with the Ambulight device was limited to two non-randomised studies (one unpublished) with 12 and 16 patients respectively.

Treatment protocol with the Ambulight PDT requires that the cream remains on the lesion site during the 3 h illumination period. No randomised trials were

presented which considered the effect of extending cream application time during illumination. One randomised study was included which reported that reduced application time (1 h versus 3 h) was associated with a small reduction in clearance rate. The remaining six studies were either of non-randomised design or were not designed specifically to measure the effect of increased cream application time. There were no reported adverse effects from prolonged contact between the cream and skin and no reports of reduced treatment efficacy from studies with application times longer than 3 h.

The Ambulight uses reduced irradiance which is intended, amongst other things, to reduce pain during treatment. One randomised study was presented which compared the effect of irradiance using conventional PDT lamps with daylight and found no significant differences in the treatment effect. Five other non-randomised studies or animal studies found that reduced irradiance was at least as effective as higher irradiance.

For reduced pain, one randomised study was presented which compared the pain (using a numerical scale) using conventional PDT with pain during treatment with daylight. Illumination with LED, at conventional irradiance, was found to be significantly more painful than daylight. Three other studies, which were not randomised, or not specifically designed to measure the effect of irradiance on pain, also reported a reduction in pain at lower irradiances.

From the clinical evidence submitted, the EAC concludes it unlikely that reduced irradiance or prolonged cream application time associated with therapy using the Ambulight will result in reduced tumour clearance or increased recurrence rate compared with conventional PDT. There is evidence that reduced irradiance is associated with reduced pain. The concept and principles of the Ambulight device are, therefore, sound but there is insufficient direct evidence available, at present, to be confident of its efficacy for the treatment of each tumour type.

1.3 Summary of submitted economic evidence

The searches conducted by the manufacturer identified ten relevant papers which reported costs of items associated with delivery of PDT. To populate

the cost model, the manufacturer used results from these studies, NHS reference costs, unit costs for health and social care, a NICE economic evaluation and estimates of staff time provided by a clinical expert.

Estimates of the cost associated with two treatments per patient of NMSC lesions were provided through the calculation of resource costs in four clinical scenarios for delivery of treatment. All scenarios involved treatment provision by a GP with special interest. The comparator, as defined in the scope, was conventional PDT in secondary care with a static lamp.

The manufacturer calculated the maximum cost saving per patient for each of the four scenarios as: £141 (GPwSI in own practice); £136 (GPwSI in specialist centre); £147 (GPwSI in secondary care) and £195 (GPwSI nurse hybrid model).

From the economic evidence submitted and from calculations from the EAC, the EAC concludes that use of the Ambulight in primary care has the potential to reduce the cost of treatment by between £92 and £195 per patient episode compared with PDT in secondary care, provided that treatment is delivered in an appropriate setting.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The clinical effectiveness evidence focused on the areas in which the treatment protocol with Ambulight PDT differed from conventional PDT and identified studies which considered the effects of each difference. This is an appropriate approach which recognises that there is limited direct evidence for the efficacy of treatment using the Ambulight PDT. All included studies were relevant to the decision problem and were consistent with the outcome measures identified in the scope.

The cost analysis used an appropriate comparator (conventional PDT) for which item costs were available from published studies and from reference costs. The device is intended for use in primary care and the choice of

scenarios and cost items appears sensible. The cost analysis was adequate in addressing the decision problem.

1.4.2 Weaknesses

The search strategies for the identification of studies relating to cream application time, reduced irradiance and adverse effects were not sensitive. The EAC cannot be confident whether all relevant studies have been identified.

1.4.3 Areas of uncertainty

The EAC cannot be confident about the identification of studies from the literature searches for clinical effectiveness that were conducted. There is uncertainty over whether there are studies which were not included but which are relevant to the differences between the Ambulight and conventional PDT protocols.

Only one, non-randomised, study is available on tumour response and recurrence rates with PDT treatment using the Ambulight PDT. Twelve patients were included (eight with Bowen's Disease and four with superficial basal cell carcinoma) with lesion diameters of less than 2.0 cm. Clearance rates at 12 months were less than typically achieved with conventional PDT. Failures at the treatment margins were reported in four cases. There is uncertainty over the effectiveness of the Ambulight PDT near the margins of the treatment site.

1.5 Key issues

The evidence base presented in the submission, in the form of randomised trials, for the direct efficacy of the Ambulight PDT, and for the effect of differences between the Ambulight PDT and conventional PDT is small. No evidence was presented to contraindicate the use of the Ambulight in the specified population; it has been CE marked and light dose and wavelength have been shown to be consistent with conventional PDT light sources. A larger study would enable clearance rates to be established with greater confidence.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The submission describes photodynamic therapy (PDT) as effective treatment for forms of non-melanoma skin cancer (NMSC); specifically superficial basal cell carcinomas (sBCCs), actinic keratoses (AKs) and Bowen's disease (also known as squamous cell carcinoma *in situ*) (9). It is noted that PDT cannot be used to treat squamous cell carcinomas (SCCs) (9).

All of these forms of NMSC are associated with genetic factors and exposure to sunlight. The submission describes damage mechanisms and reasons for treatment of basal cell carcinomas (BCCs) (9).

Relevant information is provided in relation to the expected annual incidence of NMSC in the UK (100,000) and the number of patients (24,000) assumed to be eligible for treatment with the Ambulight, based on statistics provided to the manufacturer by Dundee Ninewells Hospital and other PDT clinics.

Due to inaccuracy in reporting methods it is not possible to determine the numbers of PDT treatments in the UK each year (see section 7.3).

The EAC consulted two clinical experts for their views of the predicted population by the manufacturer for treatment with the Ambulight. The first clinician explained that the estimation of 24,000 patients was based on the assumption that 40% of the 60,000 new cases per year of sBCC in the UK would be of suitable size and location for treatment with the Ambulight. In their clinic over 350 PDT treatments are performed per year and there are around 100 centres in the UK that provide PDT (email correspondence 28/09/2010). The EAC considers this as the upper limit for market size. The second clinician confirmed that the estimate of 100,000 new cases of NMSC was by Cancer Research UK. This clinician expressed the view that the projected number of cases for which the Ambulight could be used was too high, as from their experience only a small proportion of patients require PDT (email correspondence 26/09/2010 and 27/09/2010).

Alternative treatments to PDT for NMSC include topical chemotherapy, curettage, surgical excision, cryotherapy and radiotherapy [1]. Some patients receive no treatment. There are a number of patient-specific factors that influence the clinician's choice of treatment including general fitness, coexisting serious medical conditions and the use of antiplatelet or anticoagulant medication [2]. In addition to these, treatment selection can be influenced by patient choice, local availability of specialised services, together with the experience and preference of the specialist clinician [2].

2.2 Critique of overview of current service provision

The scope describes several treatment options currently used for NMSC, including PDT. The submission was concerned with the service provision of PDT, as defined by the final scope of work issued by NICE to the manufacturer.

The submission described the procedures for conventional PDT delivered in secondary care (the comparator) and for the Ambulight in primary care (11-12). The manufacturer presented four issues relating to current clinical practice (12): limited access to services, pain and inconvenience, overhead of secondary care delivery and burden of PDT treatment on patients' lives. No evidence was provided to assess the extent of these barriers to treatment.

The manufacturer states that PDT should be offered to patients with suitable lesions as a treatment option. This is supported by NICE interventional procedure guidance [1].

The Ambulight has the potential for use in both the primary and secondary care settings and the manufacturer claims that the primary care setting offers greatest benefits to healthcare providers and patients (13). In correspondence, the manufacturer noted that conventional PDT is available in selected primary care clinics and that the Ambulight has been trialled in primary care.

3 Critique of definition of decision problem

3.1 Patient population

Patients with single lesion NMSC or dysplasia (*ie* sBCC, AK or Bowen's disease) of a diameter less than 2.4 cm were outlined as being relevant in the scope issued by NICE. The submission focuses on a patient population with sBCC, AK or Bowen's disease. The maximum treatable lesion size is limited by the extent of the Ambulight's illuminated patch. One study was reported in which the Ambulight was used in the treatment of 12 patients with sBCC and Bowen's disease, with maximum pre-treatment lesion size of 2.0 cm (A19-A23) [3].

The scope outlined that treatment using the Ambulight may be appropriate in patient subgroups, including patients with different NMSC lesion types, multiple lesions, smaller lesions and different body sizes. Subgroup analysis was not undertaken as part of the submission.

3.2 Intervention

The intervention considered in the submission is PDT using the Ambulight with either Metvix or 5-aminolaevulinic acid (5-ALA) photosensitizing pharmaceutical.

The submission states that the "Ambulight PDT device delivers the light dose required to activate a separate pharmaceutical, thereby allowing PDT to be delivered in an ambulatory fashion for the treatment of NMSC" (5).

The Ambulight is CE marked for use in the treatment of sBCC, Bowen's disease and AK in combination with a photosensitising cream such as methyl aminolaevulinate (generic name for Metvix) or 5-aminolaevulinic acid (5-ALA) (6). It is a class IIa medical device for which regulatory approval was granted in September 2009 (5).

3.3 Comparator

The comparator identified by NICE's scope was conventional hospital-based PDT with the use of Metvix and 5-ALA. In the evidence for clinical

effectiveness, studies with either ALA or Metvix were included and reviewed. In the cost-analysis, conventional PDT with Metvix was considered.

3.4 Outcomes

The outcomes specified in the scope were tumour response rates (*eg* recurrence rates, need for re-treatment or additional treatment), pain during treatment, quality of life parameters, device failure and other complications or adverse effects. In the submission the clinical outcomes considered were tumour response rates, pain during treatment and other complications or adverse effects. These outcomes were agreed with NICE prior to submission.

3.5 Cost analysis

The scope specified that a cost analysis for the Ambulight PDT with Metvix should be compared with conventional PDT with Metvix. The cost analysis was to take account of: initial delivery costs, including equipment, pharmaceuticals and staff costs during set up and monitoring, hospital and clinic care, staff training; long-term disease management; adverse events including repeat or additional treatments and a sensitivity analysis of the effect of using 5-ALA instead of Metvix. The submission presented a comparison of the resource costs of conventional PDT with Metvix with Ambulight PDT with Metvix in different clinical settings. Costs for two PDT treatments were included both for conventional PDT and for the Ambulight. Costs associated with long-term disease management or adverse effects were not studied and there was no sensitivity analysis for using 5-ALA.

3.6 Other relevant factors

None identified

3.7 Equality and diversity issues

No equality and diversity issues were identified to be addressed in the submission.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description and critique of the manufacturer's identification and selection of studies.

The Ambulight is a wearable, ambulatory light source for PDT which does not require the patient to remain in clinic whilst receiving treatment. The Ambulight has a much lower irradiance than conventional light sources, which is intended to reduce pain during treatment. Consequences of the ambulatory technique are that the photo-sensitizer cream remains on the skin for the duration of the treatment and that the prepared lesion is illuminated via transparent Tegaderm tape.

The manufacturer presented literature searches and technical performance assessments for each of the four outcome measures defined in the scope. A critique of the selection of outcome measures is given in section 4.1.4.

Treatment efficacy

The manufacturer's consideration of treatment efficacy focuses on the product and not on the evidence for the effectiveness of the photosensitizing pharmaceutical. The submission provides direct evidence for efficacy with the Ambulight and considers the effect of technical differences and variations from the instructions for use (IFU) which have the potential to alter efficacy. These are discussed in the following sections.

Direct evidence

The manufacturer presented one unpublished study (A19-A23), since published [3], which considered tumour response after treatment with ALA and illumination with the Ambulight. No searches were submitted which specifically identified the Ambulight as the source of illumination. It is anticipated that the manufacturer of the Ambulight will be aware of the relevant studies which investigate its use, although we cannot say for with certainty whether all of these have been included.

Pharmaceutical application time

The manufacturer presented a literature search intended to demonstrate the safety and efficacy of extended cream application time. The search strategy included the Cochrane Library, EMBASE and Medline.

The search terms are minimal (A27), do not include any synonyms (*eg* American names for pharmaceuticals) or subject indexing terms and were limited to the period 1996 to 2009. When replicating the manufacturer's search strategy, the EAC found only one of the cited papers in the results. The strategy is not sensitive and risks missing relevant studies. With regards to limits, studies of the effective use of PDT in the treatment of NMSC have been reported since 1990 [4]. Possible additional search approaches are presented in section 4.1.2 of this report.

Reduced irradiance

The manufacturer presented a literature search to examine the evidence relating to safety and efficacy at reduced irradiance (A24). The search strategy included EMBASE and Medline. The Cochrane library was not searched.

The search terms are minimal (A26), do not include any synonyms or subject indexing terms and were limited to the period 1996 to 2009. The strategy is not sensitive and risks missing relevant studies. The strategy used in the submission (A26) combined each group of terms with an AND operator, *ie* (therapy or drug terms) AND (light source terms) AND (irradiance terms). This makes the search too specific and only one of the papers cited as relevant in the submission was found by this strategy. A more sensitive approach is to combine the light source terms and irradiance terms using an OR operator, *ie* (therapy or drug terms) AND ((light source terms) OR (irradiance terms)) ensuring the inclusion of all cited papers in the results. Possible additional search approaches are presented in section 4.1.2 of this report.

Differences of light sources

The manufacturer presented optical output spectra for the Ambulight light emitting plaster and for an LED-based lamp used in conventional PDT (Aktilite CL128). Results were not taken from a published source and appear to be the manufacturer's own measurements (A11,A12). Provided that there was appropriate measurement traceability, this is acceptable.

Light transmission through Tegaderm.

The manufacturer reported that this has been measured (A18), but did not provide results and did not cite any published evidence.

Light transmission through Metvix

The manufacturer reported that this has been measured (A18), but did not provide results and did not cite any published evidence.

Lesion not cleaned with saline

The manufacturer deals separately with the possible effects of illumination via a layer of photo-sensitizer cream (by measurement) and of delivering and illuminating the pharmaceutical beyond 3 h (by literature review).

Adverse effects

The Ambulight PDT device is a light source for activating the photochemical reaction of a photosensitive drug in contact with the skin. The light wavelength and irradiance are not considered hazardous (A8) in this tissue. The manufacturer considered pain during treatment and other complications or adverse effects of PDT.

The manufacturer presented an unpublished clinical study (A23-A24) where pain experienced during treatment was recorded when PDT was performed with the Ambulight and other light sources. No searches were submitted which specifically identified adverse effects experienced when PDT was delivered with the Ambulight. It is anticipated that the manufacturer will be aware of the relevant studies which investigate adverse effects with the Ambulight, although we cannot say with certainty whether all of these have been included.

The manufacturer presented a literature search to identify the adverse effects of PDT. The search strategy included the Cochrane Library, EMBASE and Medline.

The search terms are minimal (A25) and do not include any synonyms or subject indexing. When replicating the manufacturer's search strategy, the EAC found none of the cited papers in the results. This shows that the strategy is not sensitive and risks missing relevant studies. Research into searching adverse effects indicates that it is complex and a variety of search approaches should be used [5]. Search terms should include specific adverse effects of PDT, indexing terms and adverse effect subheadings linked to PDT, and synonyms for adverse effects such as side effects and adverse events. Possible additional search approaches are presented in section 4.1.2 of this report.

Use of inclusion/exclusion criteria in the selection of studies

The inclusion criteria used for the selection of studies was not stated in the submission but was supplied by the manufacturer when requested by the EAC. The criteria were that only studies relating to Metvix or skin cancer were included. This was not consistent with the decision problem as 5-ALA, though not licensed for use in the UK, is also used as a photo-sensitizer cream for PDT in the treatment of NMSC (6).

There were no other specific exclusion criteria.

The submission refers to the literature review as being systematic (A1). However, it did not fully follow systematic methodology. In particular the number of reviewers who screened the studies and applied the eligibility criteria was not stated explicitly, but appears to be one (A25). Thus it is unclear whether the review process was subject to reviewer error or bias.

In total, 28 papers were cited in the reviews of irradiance, cream application time and adverse effects; 18 clinical trials, one animal trial, two laboratory studies, two papers reporting clinical experience, two case studies and three review articles. The clinical trials were:

- Braathen *et al* 2009 (A27,A28) (Short incubation with methyl aminolevulinate for photodynamic therapy in actinic keratoses.)
- Korshøj *et al* 2009 (A9) (Frequency of sensitization to methyl aminolaevulinate after photodynamic therapy.)
- Wiegell *et al* 2009 (A9) (Cold water and pauses in illumination reduces pain during photodynamic therapy: a randomized clinical study.)
- Wiegell *et al* 2009 (A27) (Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial.)
- Wiegell *et al* 2008 (A9) (Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses: a randomized, controlled, single-blinded trial.)
- Berroeta *et al* 2007 (A28) (A randomised study of minimal curettage followed by topical photodynamic therapy compared with surgical excision for low-risk nodular basal cell carcinoma.)
- Ibbotson *et al* 2006 (A27) (Characteristics of 5-aminolaevulinic acid-induced protoporphyrin IX fluorescence in human skin in vivo.)
- Sandberg *et al* 2006 (A9) (Important factors for pain during photodynamic therapy for actinic keratosis.)
- Pagliaro *et al* 2004 (A9) (Cold air analgesia in photodynamic therapy of basal cell carcinomas and Bowen's disease: an effective addition to treatment: a pilot study.)
- Piacquadio *et al* 2004 (A28) (Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials.)

- Choudry *et al* 2003 (A9) (The effect of an iron chelating agent on protoporphyrin IX levels and phototoxicity in topical 5-aminolaevulinic acid photodynamic therapy.)
- Smith *et al* 2003 (A28) (Short incubation PDT versus 5-FU in treating actinic keratoses.)
- Grapengiesser *et al* 2002 (A9) (Pain caused by photodynamic therapy of skin cancer.)
- Monfrecola *et al* 2002 (A9) (Hyperpigmentation induced by topical 5-aminolaevulinic acid plus visible light.)
- Dijkstra *et al* 2001 (A28) (Photodynamic therapy with violet light and topical δ-aminolaevulinic acid in the treatment of actinic keratosis, Bowen's disease and basal cell carcinoma.)
- Langmack *et al* 2001 (A9,A26) (Topical photodynamic therapy at low fluence rate- theory and practice.)
- Morton *et al* 2001 (A9) (Photodynamic therapy for large and multiple patches of Bowen's disease and basal cell carcinoma.)

In addition, one published study using the Ambulight was included:

- Attili *et al* 2009 (A19-A23) (An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode source in the treatment of nonmelanoma skin cancer).

4.1.2 Table of identified studies. What studies were included in the submission and what were excluded. Include details of any relevant studies that were not included in the submission.

Treatment efficacy

Direct evidence

The manufacturer presented one unpublished study in the submission (A19-A23), which has since been published [3], relating specifically to the efficacy of the Ambulight. Twelve patients with Bowen's disease or sBCC were treated with PDT using a prototype of the Ambulight. Patients were followed for 12 months to assess tumour response.

Pharmaceutical application time

Seven papers were identified as being relevant to assessing the effect of altering the application time of the photo-sensitizer cream (A27-A28), comprising five clinical trials (Dijkstra *et al* 2001 [6], Smith *et al* 2003 [7], Piacquadio *et al* 2004 [8], Ibbotson *et al* 2006 [9] and Braathen *et al* 2009 [10]), one case study (Yang *et al* 2003 [11]) and one letter (Berroeta *et al* 2007 [12]). Of the five clinical trials only two, Ibbotson *et al* [9] and Braathen *et al* [10], were specifically designed to assess the effect of pre-irradiation cream application time. Braathen *et al* [10] compared the effect of pre-irradiation application times of 1 h with 3 h in a randomized, but not blinded, multi centre study of 112 patients with AK. Ibbotson *et al* [9] studied the effect of application time on protoporphyrin IX fluorescence in 21 healthy volunteers, with ALA applied to separate sites for 1, 2, 3, 4, 5 and 6 h for each subject.

Details of the studies relating to the effect of cream application time that were excluded from the submission, or the reasons behind the exclusion, were not provided in the submission document.

Reduced irradiance

Seven papers were identified as being relevant to demonstrating the efficacy of reduced irradiance (A26-A27), comprising one review (Veenhuzin and Stewart 1995 [13]), two laboratory-based studies (Foster *et al* 1993 [14] and Ilinuma *et al* 1999 [15]), one animal trial (Robinson *et al* 1998 [16]) and three

clinical trials (Langmack *et al* 2001 [17], Wiegell *et al* 2008 [18] and Wiegell *et al* 2009 [19]). Two clinical trials [18, 19] used randomisation of patients, with Wiegell *et al* 2008 using single blinding.

The clinical trials evaluated the efficacy and safety of low irradiance by monitoring tumour response during follow up and pain experienced during treatment. Langmack *et al* [17] studied 22 patients treated with an LED light source. Patients were followed for 6-8 months. Wiegell *et al* 2008 [18] studied 29 patients, each with two treatment areas, one irradiated with daylight and the other with a red LED light. Patients were followed for 3 months.

In the submission, the manufacturer stated that Wiegell *et al* 2009 [19] studied the use of sunlight to irradiate the site (A27). On reviewing the study, we found that this paper considered the effect of cooling the treatment site on pain and did not consider the efficacy of low irradiance. The EAC identified another study by Wiegell *et al* [20], published in 2009, which used sunlight to irradiate the treatment site and we assume that the manufacturer intended to cite this paper.

Details of the studies relating to efficacy of reduced irradiance that were excluded from the submission, or the reasons behind the exclusion, were not provided in the submission document.

Adverse effects

Fourteen papers were cited in identifying the potential adverse effects of PDT (A8-A10), comprising ten clinical trials (Langmack *et al* 2001 [17], Morton *et al* 2001 [21], Grapengiesser *et al* 2002 [22], Monfrecola *et al* 2002 [23], Choudry *et al* 2003 [24], Pagliaro *et al* 2004 [25], Sandberg *et al* 2006 [26], Wiegell *et al* 2008 [18], Korshøj *et al* 2009 [27] and Wiegell *et al* 2009 [19]), one case study (Guarneri and Vaccaro 2009 [28]), one review article (Lehmann 2007 [29]), one guideline (Morton *et al* 2008 [30]) and one paper describing clinical experience (Ibbotson *et al* 2004 [31]).

Five of the clinical trials were designed to assess the adverse effects of PDT (Grapengiesser *et al* [22], Monfrecola *et al* [23], Sandberg *et al* [26], Korshøj

et al [27] and Wiegell *et al* 2008 [18]). Grapengiesser *et al* [22] investigated pain during PDT in 60 patients with a range of skin cancers. Monfrecola *et al* [23] investigated hyperpigmentation in five healthy volunteers. Sandberg *et al* [26] investigated pain during PDT in 91 patients with AK. Korshøj *et al* [27] investigated sensitization to methyl aminolaevlinate (Metvix) in 20 patients who had previously been treated with Metvix and 60 previously unexposed subjects. Wiegell *et al* [18] considered the effect of low irradiance on pain during PDT in 29 patients with AK.

Three of the clinical trials (Langmack *et al* [17], Morton *et al* [21] and Choudry *et al* [24]) reported adverse effects as part of studies into the effectiveness of PDT under different conditions.

The remaining clinical trials, Pagliaro *et al* [25] and Wiegell *et al* 2009 [19], reported studies where cold air, cold water or pauses in illumination were used to relieve pain during treatment.

In addition to the studies identified by the literature search, the manufacturer presented two unpublished studies, one of which has since been published [3], considering pain during treatment. The first study was a pilot study of 12 patients with Bowen's disease or sBCC treated with a prototype of the Ambulight. Pain experienced during treatment was recorded using a ten point numerical rating score (NRS) (A19-A23). The pain scores were compared with data from 50 patients who received conventional PDT. The second study included 16 patients with forms of NMSC and comparing pain during treatment with the Ambulight with other PDT treatments and treatments for NMSC (A24).

Details of the studies relating adverse effects that were excluded from the submission, or the reasons behind the exclusion, were not provided in the submission document.

Details of any relevant studies that were not included in the submission

Treatment efficacy

The approach taken for the search strategies is at risk of missing potentially relevant studies. Additional search strategies put forward by the EAC for identification of clinical studies relating to pharmaceutical application time and reduced irradiance are given in the following sections.

Pharmaceutical application time

The search strategy for pharmaceutical application time could include:

#1 Photochemotherapy [mh] OR "photodynamic therapy" [title, abstract] OR "aminolaevulinic acid" [title, abstract] OR aminolevulinic acid [mh] OR metvix OR metvixia OR "methyl aminolaevulinate" [title, abstract] OR "methyl aminolevulinate" [title, abstract] OR "methyl 5-aminoleavulinate" [title, abstract] OR "methyl aminolevulinate" [title, abstract]

#2 Application [title, abstract] OR time [title, abstract] OR administration [title, abstract] OR time factors [mh] OR incubation [title, abstract]

#3 Topical [title, abstract]

We combined the search terms #1, #2 and #3 as (#1 AND #2) OR (#1 AND #3) and ran the search in Medline identifying 5132 titles. The search strategy in the submission found 21 titles in Medline (A27), indicating that there may have been relevant studies that were not included in the submission. Two reviewers from the EAC reviewed a representative sample (year of publication 2009, 368 titles) of the 5132 titles, and found 6 papers that may be relevant (three clinical trials, one animal trial, one modelling paper and one letter) including the following which the EAC would consider relevant.

- Lesar *et al* 2009 [32] (A time course investigation of the fluorescence induced by topical application of 5-aminolevulinic acid and methyl aminolevulinate on normal human skin.)
- Hauschild *et al* 2009 [33] (Effective photodynamic therapy of actinic keratoses in the head and face with a novel, self-adhesive 5-aminolaevulinic acid patch.)

Reduced irradiance

The search strategy for reduced irradiance could be expanded to:

(photochemotherapy [mh] OR “photodynamic therapy” [title, abstract])
AND
((irradiance [title, abstract] OR “fluence rate” [title, abstract] OR “dose rate” [title, abstract] OR dose [title, abstract] OR fluence [title, abstract])
OR
(“light source” [title, abstract] OR “light emitting diode” [title, abstract] OR LED [title, abstract] OR laser [title, abstract] OR incoherent [title, abstract] OR daylight [title, abstract] OR illumination [title, abstract]))

When we ran this search in Medline we identified 4539 titles. The search strategy in the submission found 175 titles in Medline (A26), indicating that there may have been relevant studies that were not included in the submission. Two reviewers from the EAC reviewed a representative sample (year of publication 2009, 286 titles) of the 4539 titles, and found 11 papers that may be relevant: one clinical trial (the Wiegell *et al* study which was mis-cited in the submission (A27)), one animal trial, six review articles, two modelling papers and one letter. In addition, our search identified the publication of the pilot study for the prototype of the Ambulight, published since the submission (A19).

Adverse effects

The search strategy for adverse effect of PDT when used with Metvix or ALA could be expanded to:

(photochemotherapy [mh] OR “photodynamic therapy” [title, abstract] OR aminolevulinic acid [mh] OR “aminolaevulinic acid” [title, abstract] OR metvix [title, abstract] OR metvixia [title, abstract] OR “methyl aminolaevulinate” [title, abstract] OR “methyl aminolevulinate” [title, abstract] OR “methyl 5-aminolevulinate” [title, abstract] OR “methyl 5-aminolaevulinate” [title, abstract])
AND
(photochemotherapy [adverse effects] OR aminolevulinic acid [adverse effects] OR “adverse effects” [title, abstract] OR “side effects” [title, abstract]

OR “adverse events [title, abstract] OR erythema [mh] OR pigment* [title, abstract] OR pustular [title, abstract])

When we ran this search in Medline we identified 2334 titles. The number of titles identified by the strategy in the submission (A25) was not reported and there may have been relevant studies that were not included in the submission. Two reviewers from the EAC reviewed a representative sample (year of publication 2009, 171 titles) of the 2334 titles, and found 21 papers that may be relevant (16 clinical trials, one case study and four review articles) including the following which the EAC would consider relevant.

- Caekelbergh *et al* 2009 [34] (Photodynamic therapy using methyl aminolevulinate in the management of primary superficial basal cell carcinoma: clinical and health economic outcomes)
- Halldin *et al* 2009 [35] (Nerve blocks enables adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp)
- Hauschild *et al* 2009 [36] (Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results for two randomized controlled phase III studies)
- Hauschild *et al* 2009 [33] (Effective photodynamic therapy of actinic keratoses on the head and face with a novel, self-adhesive 5-aminolaevulinic acid patch)
- Serra-Guillen *et al* 2009 [37] (Comparative study between cold air analgesia and supraorbital and supratrochlear nerve block for the management of pain during photodynamic therapy for actinic keratoses of the frontotemporal zone)
- Steinbauer *et al* 2009 [38] (Phototoxic reactions in healthy volunteers following photodynamic therapy with methylaminolevulinate cream or with cream containing 5-aminolevulinic acid: a phase II, randomized study)
- Steinbauer *et al* 2009 [39] (Topical photodynamic therapy with porphyrin precursors—assessment of treatment-associated pain in a retrospective study)

- Wiegell *et al* 2009 [20] (Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial)

4.1.3 Description and critique of manufacturers approach to validity assessment and details of the quality assessment of studies.

The manufacturer used a clinical expert to assess the quality of the literature included in the review. They identified the strength of the evidence to support the use of the Ambulight and rated its quality. The criteria defined for the strength of recommendations and quality of evidence were reasonable, given the nature of the evidence.

4.1.4 Description and critique of manufacturers outcome selection

The scope issued by NICE specified the outcome measures as tumour response rate (including recurrence rates or need for re-treatment or additional treatment); pain during treatment; quality of life parameters; device failure; other complications or adverse events. The manufacturer's approach to each of these outcome measures is described in the following sections.

Tumour response rate

The manufacturer claimed not to explicitly include tumour response rate as an outcome measure (17,18), giving the rationale that efficacy of the treatment is dependent on the pharmaceutical and not on the light that activates the drug.

This was supported by evidence [1, 30]. For the population defined in the scope, treatment efficacy with conventional PDT is already known [1, 30] and it is reasonable to expect similar efficacy with the Ambulight provided that differences between the Ambulight and conventional PDT light sources and between the Ambulight protocol and the IFU of the pharmaceutical are shown to have no significant effect.

In relation to treatment efficacy, the manufacturer presented evidence for the effect of the following differences between the Ambulight and conventional light sources, and between the Ambulight protocol and the IFU of the pharmaceutical.

- Pharmaceutical application time
- Reduced irradiance
- Differences in light source
- Light transmission through Tegaderm
- Light transmission through Metvix
- Lesion not cleaned with saline

In addition, tumour response rate for the Ambulight was one of the outcome measures of the pilot study provided by the manufacturer.

Elsewhere within this report we discuss the manufacturer's evidence relating to this outcome measure under the heading “Treatment efficacy”.

Pain during treatment
The manufacturer included pain within their study of adverse effects and as one of the outcome measures in the pilot trial. Within this report we discuss the manufacturer's evidence relating to this outcome measure under the heading "Adverse effects".

Quality of life parameters
By agreement with NICE prior to the submission, the manufacturer did not explicitly address this outcome measure.

Device failure
By agreement with NICE prior to the submission, the manufacturer did not explicitly address this outcome measure.

Other complications or adverse events
The manufacturer included other complications or adverse events within their study of adverse effects. Within this report we discuss the manufacturer's evidence relating to this outcome measure under the heading "Adverse effects".

4.1.5 Describe and critique the statistical approach used

No statistical approach was used in the submission.

4.1.6 Summary statement about the review of clinical effectiveness

The studies included in the submission were relevant to the decision problem in terms of patient population and interventions. The review highlighted areas where the Ambulight differs from conventional PDT, considering whether these changes alter the overall effectiveness of the treatment. The EAC considers this approach is appropriate, since few studies have been undertaken using the device.

The EAC considers that the manufacturer's search strategies were not sensitive and may have missed relevant studies. Studies were also included by the manufacturer that were outwith their stated search criteria.

The validity assessment of the included studies was adequate, although it was limited to one reviewer. The clinical outcomes selected for the assessment of the Ambulight relate to those outlined in the NICE scope and no statistical methods were undertaken.

4.2 Summary of submitted evidence

4.2.1 Summary of results

Results from the included trials and from technical performance measurements were presented for treatment efficacy - by comparison of the Ambulight protocol with conventional PDT and from pilot studies with the Ambulight - and for adverse effects, including pain during treatment.

Treatment efficacy

Direct evidence

The pilot study using a prototype of the Ambulight considered tumour response. The 12 patients enrolled in the study had a histological diagnosis of Bowen's disease or sBCC. The median lesion size was 1.1 cm (range 0.6-1.9 cm). At six months, nine of the 12 patients had a complete response, with two relapsing at the 12 months follow up. In the patients where treatment was unsuccessful, the lesion size was >1.5 cm. Clearance rates were at the lower end of the range expected with conventional PDT [30].

Cream application time

The submission included two studies which were specifically designed to assess the effect of pre-irradiation cream application time.

Braathen *et al* [10] compared the effect of pre-irradiation application times of 1 h with 3 h in a randomized, but not blinded, multi centre study of 112 patients with AK. Complete response rates were similar in both groups, with the 3 h application group receiving greater benefit (87-96%) compared with the 1h group (74-86%) for a 160 mg/g methyl aminolevulinate (MAL) dose; it was not reported whether the difference was significant. The 1h group had a slightly higher recurrence rate at 3 months (19%) compared with the 3 h group (17%). It was not reported whether the difference was significant. For recurrence rate, the effect of the difference in application time was small compared with the effect of reduced MAL dose.

Ibbotson *et al* [9] studied the effect of application time on protoporphyrin IX fluorescence in 21 healthy volunteers, with ALA applied to separate sites for 1, 2, 3, 4, 5 and 6 h for each subject. Considerable inter and intra-subject variability in time to peak fluorescence was reported. For inter-subject variability in time, 40% of subjects had reached peak fluorescence within 7 h, 15% by 8h and the remaining 45% by 12-24 h. For intra-subject variability in time, 80% of subjects reached peak fluorescence within 8 h and only 10% reached peak fluorescence at 24 h. However, there were no significant differences observed in the degree of fluorescence achieved. The study found that within subjects, the time to peak fluorescence depended upon the ALA application time, suggestive of a strategy for optimal application and irradiance time. But the study was too small, and the inter-subject variability too large, to provide clear recommendations.

The submission cited five further studies [6-8, 11, 12] to illustrate the range of application time used in practice (1 h to 18 h) and concludes that it has little effect on therapeutic efficacy. However, these studies included different tumour types and different pharmaceuticals and none was specifically designed to measure the effect of application time. From these studies it cannot be concluded with certainty that application time has no effect on

efficacy, although the findings are consistent with Braathen *et al* [10] and Ibbotson *et al* [9] that the effects are likely to be small.

Reduced irradiance

The submission included three clinical trials, two of which were designed to assess the effect of irradiance.

Wiegell *et al* 2008 [18] compared two PDT treatment areas, one irradiated by red LED light and the other irradiated with daylight, in 29 patients with AK. At 3 months, no significant differences were found between the percentage reduction in AK lesions in treatments, with a reduction of 79% in the daylight area compared with 71% in the LED area. The mean effective light dose of daylight was 43.2 J/cm^2 (range 11.7-65.9 J/cm^2) compared with 37 J/cm^2 for LED light. Daylight treatment was significantly less painful than LED light with a maximum score of 2.0 for daylight compared to 6.7 for LED light. In this study PDT using daylight was found to be as effective as conventional PDT using LED light.

Langmack *et al* [17] studied 22 patients with sBCC in a non-randomised trial considering the effectiveness of a low irradiance of 7 mW/cm^2. In the 22 patients, the tumour response rate was 84% after 12 months. This response was comparable to other PDT studies using higher irradiances.

Wiegell *et al* 2009 [20] measured the range of effective light doses for daylight, but did not investigate the effect of the light dose on tumour response.

The submission cited three further studies (an animal trial [16] and two laboratory-based studies [14, 15]) and a review article [13], which considered the effect of irradiance at a cellular level. The conclusion of these studies was that tumour cell damage increased with a decrease in irradiance. It was also noted that in healthy tissue, a decrease in irradiance increased photobleaching and PDT-induced damage.

Comparison of light sources

The manufacturer provided output spectra for the LEDs used in the Ambulight and for an LED light approved for use with conventional PDT (Aktilite CL128). There were no significant differences between measurements of peak wavelengths or FWHM (640 nm (FWHM 25 nm) vs. 635 nm (FWHM 18 nm)).

Transmission through Tegaderm

The manufacturer reported (A18) that they had measured the light absorption by Tegaderm and found it not to have a significant effect. No results (*eg* an absorption spectrum) were provided to support this conclusion.

Transmission through Metvix

The manufacturer reported (A18) that they had measured the light absorption by a layer of Metvix and found it not to have a significant effect. No results (*eg* an absorption spectrum) were provided to support this conclusion.

Non-removal of cream by saline

The EAC accepts that the application of saline does not itself have any effect and that the effect of not removing the cream prior to illumination was taken into account in the previous point.

Adverse effects

The submission included five studies which were specifically designed to assess adverse effects of PDT.

Grapengiesser *et al* [22] investigated pain during PDT in 60 patients with different types of skin cancer using a visual analogue scale (VAS) graduated from 0 (no pain) to 10 (unbearable pain). There was a significant difference between lesion types with respect to VAS. The mean VAS value was 5.3 for AK lesions, 3.5 for BCC lesions and 3.6 for Bowen's Disease. There was also a significant difference between lesion locations with respect to VAS. The mean VAS value for lesion located on the head was 5.3, for the torso it was 3.4 and for the extremities 3.0. In 23 patients, lesions were examined by fluorescence imaging and no significant correlation was found between VAS and measured fluorescence intensity.

Monfrecola *et al* [23] investigated hyperpigmentation by applying different concentrations of ALA as test patches on the forearms of five healthy volunteers and irradiating the site. All subjects complained of a mild burning sensation during irradiation and an erythematous response with pruritus and oedema appeared in all subjects just after the session for 24 h. In the 48 h after treatment, variable hyperpigmentary response occurred lasting 1-2 weeks depending on skin type.

Sandberg *et al* [26] investigated pain during treatment of AK using a VAS in 91 patients from ten centres. Size, redness, scaling and induration of lesion were also recorded. Pain during PDT was found to have a large variation. The mean VAS was 4.6. Of the patients, 21% had severe pain (VAS 7-10) and 31% had low or no pain (VAS 0-3). Redness of AK lesions was found to be significantly related to pain, the reduction in AK area and the cure rate. Patients with the largest reduction in AK area seemed to experience more pain.

Korshøj *et al* [27] investigated sensitization to Metvix in patients who had previously been treated five times or more with Metvix and previously unexposed subjects. Of the 20 patients previously treated, seven were sensitized to Metvix, giving a sensitization risk of 35%. In the 60 previously unexposed subjects, only one became sensitized after a single exposure.

Wiegell *et al* [18] compared the pain during treatment in 29 patients on a numerical scale (0-10) for irradiation with daylight and with conventional PDT. The mean pain score for daylight was 2.0 (SD ± 1.9) compared with 6.7 (SD ± 2.2) for conventional PDT ($P < 0.0001$).

In addition, the study by Morton *et al* [21], whose primary focus was not adverse effects, measured pain during PDT. During the treatment of 40 large patches of Bowen's disease, patients rated pain on a VAS (0-10). Pain was absent in 14 lesions, mild (VAS 0-3) in 12, moderate (VAS 3-7) in 6 and severe (VAS 7-10) in 8, although local anaesthesia was requested in three cases. Morton *et al* [21] also noted the adverse effect of localised hair loss.

Other studies which noted adverse effects included pain and temporary pigmentation change, were Langmack *et al* [17] and Choudry *et al* [24].

The studies relating to the use of the Ambulight and its prototype reported lower pain scores than experienced with conventional PDT. In the pilot study, the pain score was ≤2 using the NRS (median score = 1; range 0-2) for all the 12 patients and none required pain relief during treatment. These scores were compared with those of 50 patients who had received conventional PDT. The conventional PDT cohort had a median score of 6 (range 1-10). Eleven of the 50 required local analgesia and all required cool air treatment (A22). From the clinical data recorded at Dundee Ninewells Hospital, the NRS for the Ambulight ranged from 0 to 8 compared with conventional PDT which ranged from 2 to 10 (A24).

4.2.2 Critique of submitted evidence syntheses

The submission did not include any evidence syntheses.

5 ASSESSMENT OF COST ANALYSIS

5.1 Overview of manufacturer's economic assessment

5.1.1 Methods

This section assesses the cost analysis submitted by the manufacturer regarding the use of the Ambulight PDT.

The manufacturer's submission to NICE included:

- A description of the literature search that was undertaken to identify cost and cost effectiveness studies in relation to PDT for the treatment of forms of NMSC.
- An Excel file containing:
  - A summary of the relevant studies identified by the literature search (table B1)
  - Estimated delivery costs of conventional PDT and the Ambulight in different clinical scenarios
  - List of costs (table B3)
  - List of sources for costs
- Email correspondence revising costs:
  - Cost of the cream revised from £126.71 to £177.57
  - In GPwSI accounting model E, GP costs were reduced from £300 to £30

Identification of studies

The searches for cost-effectiveness studies were executed in EMBASE, EconLIT, NHS EED and Medline using the terms (photodynamic AND cost) and (photodynamic AND economic) (30). The searches were limited to the period 1996 to 2010. The four databases returned 1586 titles.

One reviewer assessed the publications and excluded all articles that did not consider PDT of the skin (30). Ten studies were cited in the submission (table B1) as being relevant: Aguliar *et al* 2010 [40], Caekelbergh *et al* 2009 [34], Downs 2009 [41], Muston *et al* 2009 [42], Annemans *et al* 2008 [43], Gold 2008 [44], Caekelbergh *et al* 2006 [45], Clayton *et al* 2006 [46], Ramrakha-Jones and Herd 2003 [47] and Morton *et al* 2002 [4]. Data from these studies were used in the model as well as data from the 2008-2009 National Schedule of Reference Costs for NHS Trusts [48], 2009 PSSRU Unit Costs for Health and Social Care [49] and NICE CSGSTIM Economic Evaluation [50].

Details of the excluded studies were not included in the submission.

Model structure

The manufacturer provided a linear assessment of resource costs for the Ambulight in four clinical scenarios and compared them with the resource costs of conventional PDT, the outcome being a calculated overall value for the resources in each setting, and the difference in cost between the Ambulight and conventional PDT.

The four clinical scenarios considered for the Ambulight were:

- GPwSI operating in their own practice
- GPwSI operating in a specialist centre
- GPwSI operating in secondary care
- GPwSI nurse hybrid service model

The first three scenarios are based on the service models defined in NICE's CSGSTIM economic evaluation [50]. The GPwSI nurse hybrid service model considers the treatment of patients with PDT in their own home by a nurse, after diagnosis by a GPwSI.

The resource costs were defined with the aid of a clinical expert (36). For conventional PDT the resource costs consisted of a cost for:

- an ambulance to and from hospital
- lesion assessment by a clinician

- room hire for preparing and illuminating the lesion
- a nurse informing the patient about the procedure and after care
- lesion debridement by a nurse
- cream application by a nurse
- the photosensitizing cream
- consumables
- PDT lamp
- anaesthesia

For the Ambulight in the three GPwSI specific scenarios, the resource costs consisted of a cost for:

- an ambulance to and from the clinic
- GP and overheads
- the photosensitizing cream
- consumables
- the Ambulight

For the GPwSI nurse hybrid service model, the resource costs consisted of a cost for:

- transport for the nurse
- the nurse
- the photosensitizing cream
- the Ambulight

This was not an economic analysis model *per se* and no consideration was given to cost factors relating to failure to treat NMSC or the effects of disease recurrence. As the manufacturer presented a comparison of resource costs in different settings, time horizon, half cycle correction and discounting were not applicable (table B2).

Assumptions

The manufacturer assumed that patients were already diagnosed with a form of NMSC and that they would all receive two PDT treatments.

Resources and costs

The costs included in the calculations were from the studies identified by the literature review, NHS reference costs [48], unit costs for health and social care [49] and NICE's CSGSTIM economic evaluation [50]. Table B3 of the submission lists the resource costs used in the calculations. Where costs were associated with time spent by nurses or GPs to complete a specific task, the time was estimated by a clinical expert (36).

Time horizon

No time horizon was defined as the manufacturer calculated the fixed resource costs to compare the total resource cost of conventional PDT with total resource cost of Ambulight PDT when used in four different scenarios.

Sensitivity analysis

A sensitivity analysis as described in the scope issued by NICE was not included in the submission. For three of the clinical scenarios proposed for the use of Ambulight a range of costs were given.

5.1.2 Results

Results were presented in terms of the expected resource cost for delivering two treatments of PDT to a patient with conventional PDT or the Ambulight. For each clinical scenario, the total resource cost and itemised costs, including technology, clinician and/or nurse costs, pharmaceuticals, overheads, consumables and patient transport, were reported. A full description of the results presented by the manufacturer are provided in section 5.3.

5.1.3 Model validation

The manufacturer estimated the cost elements of a PDT clinic and time for nurses and GPs on the basis of advice from a clinical expert (36). No other validation was presented.

5.2 Critique of approach used

The manufacturer presented calculations for resource costs to the NHS of the Ambulight in different clinical settings and compared the total resource cost for each of these with the total resource cost of conventional PDT (32).

Details of different aspects of the approach taken by the manufacturer are provided below.

Comparator

The manufacturer compared the use in the treatment of NMSC of the Ambulight for PDT in primary care with conventional PDT using a static lamp in secondary care (33 and table B9). This is consistent with the scope and consistent with the approach applied to the presentation of clinical evidence which compared the efficacy of the device with conventional PDT light sources.

The manufacturers did not compare the costs of using Ambulight with those for no treatment, or for other forms of treatment. This was agreed with NICE prior to the submission.

Inputs

The cost elements of a PDT clinic and the staff times required for each phase of the treatment were estimated by one clinical expert (36) and may not be representative of clinical practice in other centres.

The use of national cost data means that the cost inputs are applicable to the UK.

Resources and costs

The EAC confirmed that the costs supplied by the manufacturer were for two PDT treatments. GP and overhead costs were per patient and not per treatment. The manufacturer had assumed that the per patient related cost included two treatments of PDT. The EAC considered this to be reasonable after reviewing the supporting evidence [50].

The time taken for a nurse to prepare the skin lesion and place the Ambulight in the GPwSI nurse hybrid service model was assumed to be a total of 0.6 hours for two treatments. The EAC notes that in conventional PDT the nurse takes a total of 1.4 hours for two treatments to explain the procedure, debride the lesion and apply the cream (from resources for conventional PDT, with a clinical expert advising on times (36)). These tasks do not vary significantly between the Ambulight and conventional PDT, so the EAC were unable to determine the cause of the claimed reduction in time. Following correspondence with the EAC, the manufacturer explained the decrease in time due to the ease of using the Ambulight compared with existing lamps and the average size of lesions.

The average selling price of the Ambulight was stated in the submission as £200, with the price range being £180-£250 (7). In the models the Ambulight cost defined by the manufacturer was £166 and following correspondence with the EAC the manufacturer stated that this was a volume price. The EAC suggests that it would have been more appropriate to use the average selling price in the calculations.

Literature search

The literature search was sensitive, but contained a significant number of duplicates in the results as the manufacturer searched Medline twice, (EMBASE searched EMBASE and Medline). The EAC replicated these and found 1035 distinct papers, including all the papers cited by the manufacturer.

Analysis

The analysis evaluated the cost variance with the Ambulight in different clinical scenarios compared with conventional PDT. The costs included the technology, clinician and/or nurse costs, pharmaceuticals, overheads, consumables and patient transport. A sensitivity analysis as defined in NICE's scope was not performed, but variations in GP and overhead costs were presented for three of the Ambulight clinical scenarios: GPwSI operating in their own practice, GPwSI operating in a specialist centre and GPwSI operating in secondary care.

5.3 Results included in manufacturer's submission

The results of the calculations were presented in the Excel file accompanying the submission. For conventional PDT and the four clinical scenarios using the Ambulight, the total cost per patient was calculated, assuming that each patient received two treatments of PDT.

The total cost per patient for conventional PDT was £799.77 (table 1).

Table 1. Costs for conventional PDT

Cost Description	Cost
Ambulance to Hospital/Clinic	£58.00
Lesion Assessment (clinician)	£35.20
Room Hire - Lesion Preparation	£100.00
Communication/Education of Patient (Nurse)	£27.00
Lesion Debridement (Nurse)	£27.00
Cream Application (Nurse)	£9.00
Cream	£177.57
Illumination of Lesion (Nurse)	£45.00
Room Hire - Lesion Illumination	£100.00
Consumables (Curette, Gloves, Dressings)	£10.00
Lamp Cost	£53.00
Anaesthesia (inc. Doctor form filling time)	£100.00
Ambulance Home	£58.00
Total	£799.77

GPwSI operating in their own practice

The total cost per patient for using the Ambulight in the clinical setting of a GPwSI operating in their own practice ranged from £658.61 to £1,335.57. The accounting models reflect the different GP and overhead costs presented in NICE's economic impact analysis for skin tumours [50] used as the source for these resource costs. Table 2 shows itemised costs for the two accounting models presented for this clinical scenario.

Table 2. Costs for GPwSI operating in their own practice

Cost Description	Accounting model A	Accounting model B
Ambulance to Hospital/Clinic	£58.00	£58.00
GP costs	£100.00	£23.04 (*inc. overheads*)
Overheads	£600.00	
Cream	£177.57	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00
Lamp Cost	£332.00	£332.00
Ambulance Home	£58.00	£58.00
Total	£1,335.57	£658.61

GPwSI operating in a specialist centre

The total cost per patient for using the Ambulight in the clinical setting of a GPwSI operating a specialist centre ranged from £663.30 to £1,105.57. The accounting models reflect the different GP and overhead costs presented in NICE's economic impact analysis for skin tumours [50] used as the source for these resource costs. Table 3 shows the itemised costs for the four accounting models presented for this clinical scenario.

Table 3. Costs for GPwSI operating in a specialist centre

	Accounting model			
Cost Description	**A**	**B**	**C**	**D**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00
GP costs and Overheads	£470.00	£123.67	£43.41	£27.73
Cream	£177.57	£177.57	£177.57	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00
Total	£1,105.57	£759.24	£678.98	£663.30

GPwSI operating in secondary care

The total cost per patient for using the Ambulight in the clinical setting of a GPwSI operating in secondary care ranged from £652.42 to £678.42. The accounting models reflect the different GP and overhead costs presented in NICE's economic impact analysis for skin tumours [50] used as the source for these resource costs. Table 4 shows the itemised costs for the two accounting models presented for this clinical scenario.

Table 4. Costs for GPwSI operating in secondary care

Cost Description	**Accounting model E**	**Accounting model F**
Ambulance to Hospital/Clinic	£58.00	£58.00
GP costs and overheads	£42.85	£16.85
Cream	£177.57	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00
Lamp Cost	£332.00	£332.00
Ambulance Home	£58.00	£58.00
Total	£678.42	£652.42

GPwSI Nurse hybrid service model

The total cost per patient for using the Ambulight in the clinical setting of a Nurse delivering treatment in the patient's home (GPwSI Nurse hybrid service model) was £604.57. Table 5 shows the itemised costs.

Table 5. Costs for GPwSI Nurse hybrid service model

Cost Description		Cost
Transport for Nurse		£58.00
Nurse Costs		£27.00
Cream		£177.57
Consumables (Curette, Gloves, Dressings)		£10.00
Lamp Cost		£332.00
	Total	£604.57

Comparisons

The cost differences between using conventional PDT and the different clinical scenarios for using the Ambulight ranged from a saving of £195.20 to a cost increase of £535.80. Table 6 shows the cost difference between conventional PDT (comparator) and each of the manufacturer's cost models.

Table 6. Cost differences for each cost model

Model	Cost	Comparator	Cost difference (model – comparator)
GPwSI operating in their own practice - Accounting model A	£1,335.57	£799.77	£535.80
GPwSI operating in their own practice - Accounting model B	£658.61	£799.77	-£141.16
GPwSI operating in a specialist centre - Accounting model A	£1,105.57	£799.77	£305.80
GPwSI operating in a specialist centre - Accounting model B	£759.24	£799.77	-£40.53
GPwSI operating in a specialist centre - Accounting model C	£678.98	£799.77	-£120.79
GPwSI operating in a specialist centre - Accounting model D	£663.30	£799.77	-£136.47
GPwSI operating in secondary care - Accounting model E	£678.42	£799.77	-£121.35
GPwSI operating in secondary care - Accounting model F	£652.42	£799.77	-£147.35
GPwSI Nurse hybrid service model	£604.57	£799.77	-£195.20

5.4 Comment on validity of results presented with reference to methodology used

In some settings, the Ambulight might provide a cost saving per treatment. The validity of costings is subject to the accuracy of the cost assumptions for conventional PDT and the clinical scenarios. The EAC attempted to confirm all the costs defined in models and identified potential differences, described in the following sections.

Cream cost

The manufacturer calculated the mean cost for Metvix (£177.57) from values reported by Aguliar *et al* [40] (€113, two treatments), Downs [41] (£128 for treating BCC, £163 for treating Bowen's disease and £65 for treating AK, all single treatments) and Caekelbergh *et al* [45] (€182.77 for treating AK, €182.32 for treating nBCC and €129.83 for treating sBCC, the number of treatments were not specified). The manufacturer did not state the exchange rate which they used. For the latter study [45] the manufacturer assumed a cost for two treatments, but this was not specifically stated by the authors. If the cost was for a single PDT treatment, then the mean cost from the three studies [40, 41, 45] is £234.91, using an exchange rate of €1 = £0.85.

Lesion assessment by a clinician in conventional PDT

The clinician cost was derived from the hourly rates published in the PSSRU unit costs [49]. The EAC were unable to establish how the manufacturer had derived the costs, but using the same approach as the manufacturer had used for the nursing cost, we determined the cost for the clinician should be £33.40 compared with £35.20 based on the per patient-related hourly rate including qualifications.

Lamp costs in conventional PDT

The cost for the lamp was an average cost calculated from the costs presented by Morton *et al* [4] and Clayton *et al* [46]. The manufacturer assumed that these costs were for two PDT treatments, but the EAC found them to be for a single PDT treatment. Therefore, the lamp costs for conventional PDT should have been £106 compared with £53.

Anaesthesia cost in conventional PDT

The manufacturer cited no source for this cost (£100) and on reviewing the evidence cited for the consumable costs (Morton *et al* [4]), the EAC found that they included the cost of anaesthesia, so this cost does not need to be included separately in this calculation.

Lamp costs for the clinical scenarios using the Ambulight

The manufacturer used a price for the Ambulight that was appropriate for volume pricing (£166). This was significantly lower than the stated average selling price of £200 (7).

Consumable costs included in accounting model A of GPwSI operating in their own practice

The manufacturer included the estimated consumable cost in this calculation. However, when the EAC reviewed the evidence for the GP and overheads cited for this model, it found that the cost of consumables was included in the overhead costs and therefore, not required separately in this calculation.

Consumable costs included in accounting model E of GPwSI operating in secondary care

The manufacturer included the estimated consumable cost in this calculation. However, when the EAC reviewed the evidence for the GP and overheads cited for this model, it found that the cost of consumables was included in the overhead costs and therefore, not required separately in this calculation.

Nurse costs in GPwSI Nurse hybrid service model

The manufacturer calculated nurse costs on a time of 0.6 hours (£27.00). As already discussed, the EAC are unclear how the nurse time is reduced by over 50% when using the Ambulight, so have used the times taken to inform the patient, debride the lesion and apply the cream in conventional PDT, totalling 1.4 hours for two treatments, as the basis for the nurse time. Using the PSSRU unit costs [49], the nurse costs would increase to £76.50.

EAC cost calculations

Tables 7 to 11 show the total and itemised costs per patient for conventional PDT and the four clinical scenarios using the Ambulight, with the EAC cost estimates.

Table 7. EAC costs for conventional PDT

Cost Description	Cost
Ambulance to Hospital/Clinic	£58.00
Lesion Assessment (clinician)	£33.40
Room Hire - Lesion Preparation	£100.00
Communication/Education of Patient (Nurse)	£27.00
Lesion Debridement (Nurse)	£27.00
Cream Application (Nurse)	£9.00
Cream	£234.91
Illumination of Lesion (Nurse)	£45.00
Room Hire - Lesion Illumination	£100.00
Consumables (Curette, Gloves, Dressings)	£10.00
Lamp Cost	£106.00
Ambulance Home	£58.00
Total	£808.31

Table 8. EAC costs for GPwSI operating in their own practice

Cost Description	Accounting model A	Accounting model B
Ambulance to Hospital/Clinic	£58.00	£58.00
GP costs	£100.00	£23.04 (*inc. overheads*)
Overheads	£600.00	
Cream	£234.91	£234.91
Consumables (Curette, Gloves, Dressings)	£0.00	£10.00
Lamp Cost	£332.00	£332.00
Ambulance Home	£58.00	£58.00
Total	£1,382.91	£715.95

Table 9. EAC costs for GPwSI operating in a specialist centre

	Accounting model			
Cost Description	**A**	**B**	**C**	**D**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00
GP costs and Overheads	£470.00	£123.67	£43.41	£27.73
Cream	£234.91	£234.91	£234.91	£234.91
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00
Total	£1,230.91	£884.58	£804.32	£788.64

Table 10. EAC costs for GPwSI operating in secondary care

Cost Description	Accounting model E	Accounting model F
Ambulance to Hospital/Clinic	£58.00	£58.00
GP costs and overheads	£42.85	£16.85
Cream	£234.91	£234.91
Consumables (Curette, Gloves, Dressings)	£0.00	£10.00
Lamp Cost	£332.00	£332.00
Ambulance Home	£58.00	£58.00
Total	£793.76	£777.76

Table 11. EAC costs for GPwSI Nurse hybrid service model

Cost Description		Cost
Transport for Nurse		£58.00
Nurse Costs		£76.50
Cream		£234.91
Consumables (Curette, Gloves, Dressings)		£10.00
Lamp Cost		£332.00
	Total	£779.41

Table 12 shows cost difference for clinical scenarios compared with conventional PDT using the EAC's cost estimates. The EAC costs result in the cost difference ranging from a saving of £92.36 to a cost increase of £574.60, compared with a range of -£195.20 to £535.80 using the manufacturer's costs. Using the EAC's item costs, the scenario offering the maximum potential saving is a GPwSI operating in their own practice.

Table 12. EAC cost differences for each cost model

Model	Cost	Comparator	Cost difference (model – comparator)
GPwSI operating in their own practice - Accounting model A	£1,382.91	£808.31	£574.60
GPwSI operating in their own practice - Accounting model B	£715.95	£808.31	-£92.36
GPwSI operating in a specialist centre - Accounting model A	£1,230.91	£808.31	£422.60
GPwSI operating in a specialist centre - Accounting model B	£884.58	£808.31	-£76.27
GPwSI operating in a specialist centre - Accounting model C	£804.32	£808.31	-£3.99
GPwSI operating in a specialist centre - Accounting model D	£788.64	£808.31	-£19.67
GPwSI operating in secondary care - Accounting model E	£793.76	£808.31	-£14.55
GPwSI operating in secondary care - Accounting model F	£777.76	£808.31	-£30.55
GPwSI Nurse hybrid service model	£779.41	£808.31	-£28.90

5.5 Summary of uncertainties and issues

In general, the EAC considered the manufacturer's submission in relation to the cost impact of the Ambulight to be adequate in addressing the decision problem. The main issues raised by the EAC are summarised below.

Resource and costs

There were differences between item costs estimated by the manufacturer and by the EAC. The maximum cost saving was £195.20 for the manufacturer's estimates and £92.36 for the EAC estimates.

Sensitivity analysis

In the scope issued by NICE the manufacturer was asked to perform a sensitivity analysis that considered variation in the Metvix cream costs, variation in the device costs and cost of using 5-ALA. The manufacturer did not consider these cost variations.

6 Additional work undertaken by the External Assessment Centre

Additional work undertaken by the EAC comprised:

- Additional literature searches in order to investigate the completeness of the manufacturer's literature searches that were used in identifying clinical data. Details of these are provided in section 4.1.2.
- Recalculation and revision of the resource costs after reviewing the evidence originally cited for the cost analysis. Detail of this is provided in section 5.4.
- Completion of the sensitivity analysis of the manufacturer costs, see below.

Sensitivity analysis

The scope issued by NICE required a sensitivity analysis including:

- Variance in Metvix cream costs
- Range in price of PDT devices
- Cost of using 5-ALA

From the studies cited by the manufacturer, the maximum Metvix cream cost was £326.00 (for two treatments) [41] and the minimum Metvix cream cost was £95.53 (for two treatments) [40].

The range of the lamp costs for conventional PDT was £27.00 to £80.00 [4]. The EAC used the same assumptions as the manufacturer for the lamp costs of conventional PDT, *ie* the cost was for two PDT treatments.

For the purpose of the varying cost of the Ambulight, the average selling price of £200 (7) was used (*ie.* for two treatments the cost would be £400).

The cost of 5-ALA was defined in four studies [4, 44, 46, 47] and was £46.67 for two PDT treatments.

All other costs were as stated by the manufacturer in their calculations.

Tables 13 to 22 present the sensitivity analysis for the resource costs for conventional PDT and the four scenarios using the Ambulight. This was a univariate sensitivity analysis which examined the effect of four independent variations to the manufacturer's cost estimates for nine cases (four scenarios each with various accounting models). The four variants were: maximum Metvix cream cost, minimum Metvix cream cost, therapy with 5-ALA and average sales price of Ambulight.

Table 23 summarises the ranges of resource costs for each scenario and the comparator.

In each case, the cost differences with respect to the manufacturer's estimates for each of the four variants were £148.43 (maximum Metvix cost), -£82.04 (minimum Metvix cost), -£130.90 (5-ALA) and £68 (Ambulight sale price). The sensitivity analysis shows that the greatest effects on the resource costs is that of the cream costs, in particular which of Metvix or 5-ALA is used or the price of Metvix.

Table 13. Sensitivity analysis for conventional PDT in secondary care

		Sensitivity analysis of manufacturer's costs				
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Maximum device cost**	**Minimum device cost**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00	£58.00
Lesion Assessment (clinician)	£35.20	£35.20	£35.20	£35.20	£35.20	£35.20
Room Hire - Lesion Preparation	£100.00	£100.00	£100.00	£100.00	£100.00	£100.00
Communication/Education of Patient (Nurse)	£27.00	£27.00	£27.00	£27.00	£27.00	£27.00
Lesion Debridement (Nurse)	£27.00	£27.00	£27.00	£27.00	£27.00	£27.00
Cream Application (Nurse)	£9.00	£9.00	£9.00	£9.00	£9.00	£9.00
Cream	£177.57	£326.00	£95.53	£46.67	£177.57	£177.57
Illumination of Lesion (Nurse)	£45.00	£45.00	£45.00	£45.00	£45.00	£45.00
Room Hire - Lesion Illumination	£100.00	£100.00	£100.00	£100.00	£100.00	£100.00
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£53.00	£53.00	£53.00	£53.00	£80.00	£27.00
Anaesthesia (inc. Doctor form filling time)	£100.00	£100.00	£100.00	£100.00	£100.00	£100.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£799.77	£948.20	£717.73	£668.87	£826.77	£773.77

Table 14. Sensitivity analysis for GPwSI operating in their own practice – accounting model A

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs	£100.00	£100.00	£100.00	£100.00	£100.00
Overheads	£600.00	£600.00	£600.00	£600.00	£600.00
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£1,335.57	£1,484.00	£1,253.53	£1,204.67	£1,403.57

Table 15. Sensitivity analysis for GPwSI operating in their own practice – accounting model B

Cost Description	Manufacturer's cost	Sensitivity analysis of manufacturer's costs: Maximum Metvix cream cost	Minimum Metvix cream cost	Using 5-ALA	Average selling price of Ambulight
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£23.04	£23.04	£23.04	£23.04	£23.04
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£658.61	£807.04	£576.57	£527.71	£726.61

Table 16. Sensitivity analysis for GPwSI operating in a specialist centre – accounting model A

Cost Description	Manufacturer's cost	Sensitivity analysis of manufacturer's costs: Maximum Metvix cream cost	Minimum Metvix cream cost	Using 5-ALA	Average selling price of Ambulight
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£470.00	£470.00	£470.00	£470.00	£470.00
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£1,105.57	£1,254.00	£1,023.53	£974.67	£1,173.57

Table 17. Sensitivity analysis for GPwSI operating in a specialist centre – accounting model B

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£123.67	£123.67	£123.67	£123.67	£123.67
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£759.24	£907.67	£677.20	£628.34	£827.24

Table 18. Sensitivity analysis for GPwSI operating in a specialist centre – accounting model C

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£43.41	£43.41	£43.41	£43.41	£43.41
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£678.98	£827.41	£596.94	£548.08	£803.41

Table 19. Sensitivity analysis for GPwSI operating in a specialist centre – accounting model D

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£27.73	£27.73	£27.73	£27.73	£27.73
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£663.30	£811.73	£581.26	£532.40	£731.30

Table 20. Sensitivity analysis for GPwSI operating in secondary care – accounting model E

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£42.85	£42.85	£42.85	£42.85	£42.85
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£678.42	£826.85	£596.38	£547.52	£746.42

Table 21. Sensitivity analysis for GPwSI operating in secondary care – accounting model F

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£16.85	£16.85	£16.85	£16.85	£16.85
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Ambulance Home	£58.00	£58.00	£58.00	£58.00	£58.00
Total	£652.42	£800.85	£570.38	£521.52	£720.42

Table 22. Sensitivity analysis for GPwSI Nurse hybrid service model

		Sensitivity analysis of manufacturer's costs			
Cost Description	**Manufacturer's cost**	**Maximum Metvix cream cost**	**Minimum Metvix cream cost**	**Using 5-ALA**	**Average selling price of Ambulight**
Ambulance to Hospital/Clinic	£58.00	£58.00	£58.00	£58.00	£58.00
GP costs and overheads	£27.00	£27.00	£27.00	£27.00	£27.00
Cream	£177.57	£326.00	£95.53	£46.67	£177.57
Consumables (Curette, Gloves, Dressings)	£10.00	£10.00	£10.00	£10.00	£10.00
Lamp Cost	£332.00	£332.00	£332.00	£332.00	£400.00
Total	£604.57	£753.00	£522.53	£473.67	£672.57

Table 23. The range of resources cost for each model from the sensitivity analysis

Model	Cost range
Comparator – conventional PDT	£668.87 - £948.20
GPwSI operating in their own practice – Accounting model A	£1,204.67 - £1,484.00
GPwSI operating in their own practice – Accounting model B	£527.71 - £807.04
GPwSI operating in a specialist centre – Accounting model A	£974.67 - £1,254.00
GPwSI operating in a specialist centre – Accounting model B	£628.34 - £907.67
GPwSI operating in a specialist centre – Accounting model C	£548.08 - £827.41
GPwSI operating in a specialist centre – Accounting model D	£532.40 - £811.73
GPwSI operating in secondary care – Accounting model E	£547.52 - £826.85
GPwSI operating in secondary care – Accounting model F	£521.52 - £800.85
GPwSI Nurse hybrid model	£473.67 - £753.00

7 Discussion

7.1 Summary of clinical effectiveness issues

Three separate literature searches were presented for the effect of cream application time, the effect of reduced irradiance and for adverse effects, including pain during treatment. In all three cases the search strategy was not sensitive and the EAC cannot be confident that all relevant studies were identified.

All studies included in the submission were relevant to the decision problem in terms of patient population and outcomes, but most were not found when the EAC repeated the searches using the terms stated in the submission. Validity assessments of the included studies were limited to one reviewer.

There were 18 studies of human subjects reviewed in the submission, including 16 clinical trials designed to investigate particular aspects of PDT and two trials (one unpublished) which considered the treatment efficacy and pain reduction associated with using the Ambulight device as a PDT light source. Recognising that, to date, few studies have been undertaken with the Ambulight as a light source, the submission considered factors in which the Ambulight differs from conventional PDT light sources and presented technical performance results and evidence from published studies to assess whether the differences alter the effectiveness of treatment. The EAC considers that this approach is appropriate.

For treatment efficacy, evidence was presented for the effect of cream application time and the effect of reduced irradiance with conventional PDT, and for the tumour clearance rates with the Ambulight light source. None of the presented studies specifically compared clearance rates for 3 h versus 6 h application times; one found slightly reduced clearance with 1 h versus 3 h application, but none reported reduced clearance for times exceeding 3 h. Two studies (29 and 22 patients) reported no reduction in clearance when comparing conventional PDT with lower irradiance PDT. This was supported by animal studies which suggested an increased effectiveness with reduced irradiance. One study of 12 patients used the Ambulight as a light source for

treating BD (8 cases) and sBCC (4 cases) lesions reported initial clearance (3 months) in 10 cases (83%) and sustained clearance (12 months) in 7 cases (58%). Margin failure was reported as the main reason for not achieving clearance. These rates are at the lower end of the range reported for conventional PDT [30], but the study was too small to be confident of overall efficacy.

For pain during treatment, evidence was presented to show that reduced irradiance was associated with reduced pain. Only two studies have been designed to assess the effect of reduced irradiance on pain. One (29 patients) reported a significant reduction in pain when using sunlight compared with conventional PDT and the other (16 patients, 39 lesions, unpublished) reported similar results when comparing the Ambulight score with conventional PDT at the same centre.

7.2 Summary of cost issues

For the comparison of the Ambulight treatment with conventional PDT, the resource cost calculations represented real clinical practice and the EAC considered it to be a justifiable approach.

The literature searches used to determine costs were sensitive, although as with clinical effectiveness, there are relatively few studies available for analysis. The manufacturer presented itemized costs for conventional PDT and calculated the difference in cost per patient for four clinical scenarios, all led by a GP. The maximum cost saving was calculated as £195 for the GP-nurse hybrid service model.

The EAC estimated different itemized costs, based on an alternative interpretation of the published evidence. The maximum saving was calculated as £92 per patient, based on a GP with special interest operating in their own practice.

A sensitivity analysis by the EAC identified the key drivers of the results to be the cost of the pharmaceutical and the cost of the device (conventional PDT lamp or the Ambulight).

7.3 Implications for guidance and research

The currently available direct evidence for the efficacy of the Ambulight as a light source is limited to one published trial with 12 subjects with two tumour types. It would be warranted to study a larger population to assess clearance rates for the three tumour types separately at 3 months and 12 months and compare with published rates for conventional PDT. The manufacturer states that three investigations are currently in progress including at least 100 patients (7).

A study at a later date to analyse how the Ambulight compares with other treatments for NMSC would be useful to identify further patient benefits and cost savings.

As part of a larger study of the Ambulight, a cost-consequence economic analysis may be appropriate. However, if the clinical outcomes of the Ambulight are similar to conventional PDT, as suggested by the clinical evidence provided in the submission, an economic analysis that considers benefit may be more applicable (*eg* cost-effectiveness analysis).

There are several clinical codes which have been used to identify treatment of NMSC with PDT. Further work is needed to establish the sensitivity and specificity of coding practices with respect to clinical practice.

The submission does not consider patient compliance for treatment with the Ambulight. However, both conventional and ambulatory PDT involve periods without supervision. Therefore similar risks of non-compliance exist with both treatment methods. Evidence of improved compliance or at least equal compliance to conventional PDT is an important consideration as approximately 80% of NMSCs occur in people aged 60 years and over [51] and this should be investigated in a comparative trial when larger patient numbers are being treated with the Ambulight.

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