Ambicare Health – Review of Clinical Data for NICE

Ambicare Health Limited is a Medical Device Development Company who have developed Ambulight PDT. The Ambulight PDT is a light emitting plaster that consists of two parts; a small light emitting adhesive 'plaster', and a battery pack that is worn about the person. The device is intended to be used with a pharmaceutical to treat Non-Melanoma Skin Cancer (NMSC) via a combination therapy known as Photodynamic Therapy (PDT).

This document is intended to provide an overview of the relevant clinical data relating to the Ambulight device. As such this report is divided up into four sections;

1) An introduction to PDT in general, and how the Ambulight sits in the field. This section provides the rationale that Ambicare have taken in the compilation of relevant clinical data.
2) A systematic comparison of the technical performance between the Ambulight and an existing PDT light source. This is followed by a systematic comparison between the Instructions for Use (IFU) of the pharmaceutical and the IFU of the Ambulight. This section concludes by highlighting what clinical data should be analysed in this review.
3) A presentation of the clinical data generated to date by Ambicare. As this is a new device there is limited clinical data presenting use of the device, however post marketing surveillance data continues to be collected. The clinical data that exists is presented in this section.
4) A systematic review of the literature, including methods and conclusions.

1. Introduction to PDT

The incidence of pre-malignant and malignant skin disease is growing rapidly and now affects 20% of the UK population, 40% of the American, and 75% of the Australian populations during their lifetimes. Existing treatments for pre-malignant skin disease are typically invasive or highly unpleasant and can lead to secondary problems such as infections and scarring. They are also resource intensive and ultimately show poor cost benefit performance.

Photodynamic therapy (PDT), has over the last 15 years become a standard therapy being indicated in up to 20% of skin cancers. PDT is a combination therapy including use of a light sensitive pharmaceutical in tandem with a light source. The pharmaceutical typically comes in the form of a cream (ALA or Metvix®) that is topically applied for three hours to lesions on the skin. The pharmaceutical will not be supplied by Ambicare Health.

The PDT process consists of three main steps;

1. The pharmaceutical is topically applied to the lesion and the area surrounding the skin cancer.
2. The pharmaceutical is left on the skin for a period of three hours. During this time the drug is absorbed into the skin and converted enzymatically into a light sensitive downstream metabolite predominantly within the tumour.
3. Red light is shone onto this treatment area; the light penetrates the skin and activates the photosensitiser in an oxygen dependent process. This reaction occurs with a level of selectivity within the tumour leaving surrounding healthy tissue relatively untouched.

The different steps involved in PDT are shown graphically in **Figure 1** below.

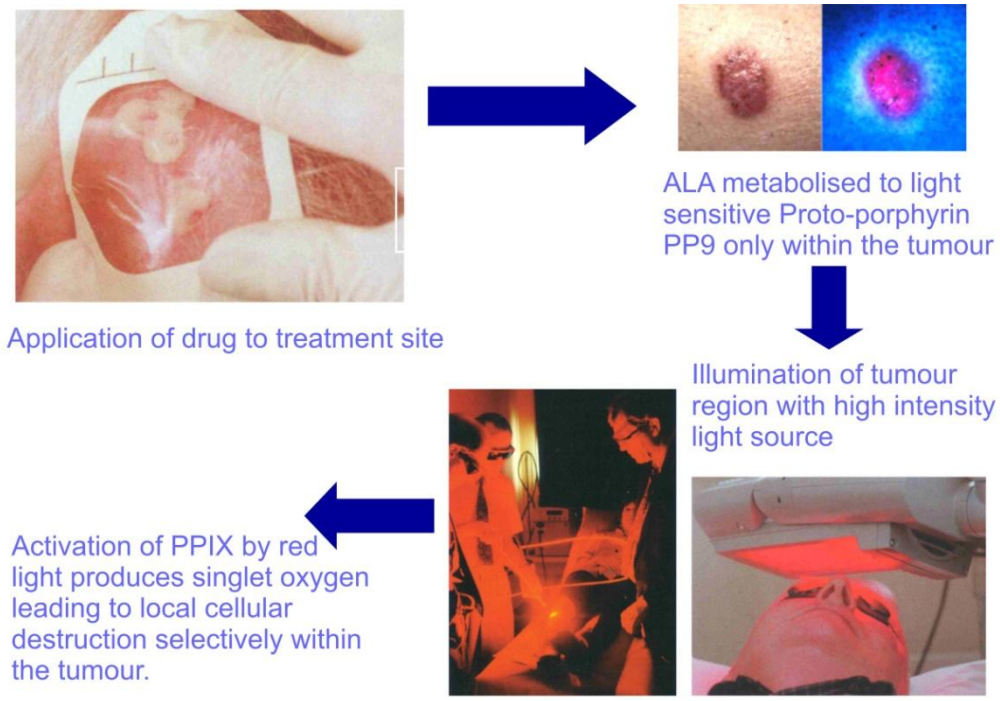

Figure 1 Illustration of the different steps involved in the application of Photodynamic Therapy (PDT).

The Instructions for Use (IFU) that accompany the pharmaceutical (either ALA or Metvix) specify in detail the technical requirements of the light source that is to the used in this combination therapy. The IFU does NOT however specify which manufacturer or brand of light source should be used. As such there are currently a large number of different manufacturers and brands of light sources in use for PDT, and clinicians working in this field do not differentiate between brands of light sources with respect to efficacy. This situation is partially reflected in the recent review of PDT conducted by NICE (document 31364) in which the clinical papers relating to PDT were systematically analysed. In this no mention was made of the influence of different brands of light sources on treatment efficacy, although there were at least 3 light sources used in the different papers. None of the papers themselves make any distinction between the brands of light sources.

The role of these light sources is to trigger the active ingredient found within the pharmaceutical that has accumulated within the skin cancer. Providing that the technical requirements of the light source are met with respect to the pharmaceutical IFU, it is the active ingredient within the pharmaceutical that drives treatment efficacy and indeed safety. The Ambulight PDT device fully complies with the requirements for light sources that are laid down in the pharmaceutical IFU.

PDT in depth

As mentioned in the previous section, PDT is a three step process. In the first step a pharmaceutical is topically applied to the skin, the pharmaceutical typically used is Metvix®, which is supplied by Galderma.

Metvix cream contains methyl aminolevulinate (MAL), which is an ester of 5-aminolevulinic acid (5-ALA). 5-ALA is found naturally within the body and is an early precursor in the biosynthesis of heme. As part of this naturally occurring synthetic pathway, 5-ALA is converted into a photoreactive porphyrin called PPIX before being converted into heme. In abnormal or tumour cells, this last step in the process to heme is faulty. Addition of 5-ALA will therefore lead to the accumulation of the

photoactive porphyrin PPIX within these abnormal cells. This porphyrin is a photoactive, fluorescing compound and if irradiated with light can react with neighbouring oxygen molecules to produce highly reactive oxygen species (ROS), mainly singlet oxygen, thereby resulting in localised tumour cell damage. If sufficiently destructive, tumour cell necrosis or apoptosis produces the desired clinical cure. The photosensitised production of a toxic effect via the oxygen radical system is termed "photodynamic". Due to the fact that abnormal or tumour cells that preferentially accumulate these photoactive porphyrins, it is these abnormal cells that are predominantly affected by the subsequent photochemical reaction. This means that surrounding healthy cells are unaffected by the PDT process.

Photochemical Reaction

In a typical PDT process, once the cream has been topically applied, it is left in place for a period of three hours. This time allows the cream to be absorbed into the skin and for the abnormal cells to convert the 5-ALA into PPIX and build up a sizable concentration of PPIX. Upon irradiation with light a photochemical reaction is activated between PPIX and oxygen. This leads to the production of singlet oxygen, which causes damage to cellular components, particularly cell membranes.

A photochemical reaction is a chemical reaction which is induced by light. The basic requirements for a light source to induce a photochemical reaction are:

- The energy of the light source must correspond to an electronic transition between orbitals of the reactive species.
- The emitted light must be able to reach the targeted reactive species without being blocked by the medium or other functional groups present.

We can therefore summarise the PDT photochemical reaction in the skin as follows;

PPIX + Oxygen + light = creation of singlet oxygen which damages nearby cells.

From these initial scientific premises, a number of conclusions can be drawn about the PDT process in general. These are as follows;

1. If light is used to activate the reaction, then this reaction will continue in the presence of light until the initial chemicals are depleted.
2. The quantity of singlet oxygen produced by this photochemical reaction is directly proportional to the amount (or dose) of light incident on the reactive species. (assuming the initial chemicals are not exhausted)
3. A given light source will produce the same quantity of ROS at different irradiances providing that the applied dose of light remains the same. (assuming the initial chemicals are not exhausted)

There is a body of scientific literature to suggest that at high irradiances the oxygen is depleted faster than can be supplied by the local vascular system thereby resulting in an unused quantity of PPIX and an inefficient reaction. Langmack (2001) has also looked at the role of tumour oxygenation in PDT. He concluded that lower irradiance PDT should be as effective as high irradiance PDT. He went on to trial a device with an irradiance of 7 mw/cm^2 on 22 patients with 32 lesions. He observed a complete response rate of 84% at 12 months which is comparable with existing PDT protocols.

Total Effective Dose

One of the basic requirements for a photochemical reaction was described in the previous section as '*The emitted light must be able to reach the targeted reactive species without being blocked by the medium or other functional groups present*.' Typically in PDT (and in the Metvix IFU) a wavelength of

570-670 nm is employed. However this wavelength is essentially a compromise between PPIX absorption and light transmission through skin tissue (Moseley 1996)

The effectiveness of a light source in activating a PDT photochemical reaction within the skin is dependent upon three factors;

1. The output spectrum of the light source. (spectral irradiance)
2. The transmission spectrum of the skin. (this may be depth dependent)
3. The absorption spectrum of the porphyrin.

If we were to take a look at the transmission spectrum of skin at a depth of 2mm the following data is obtained.

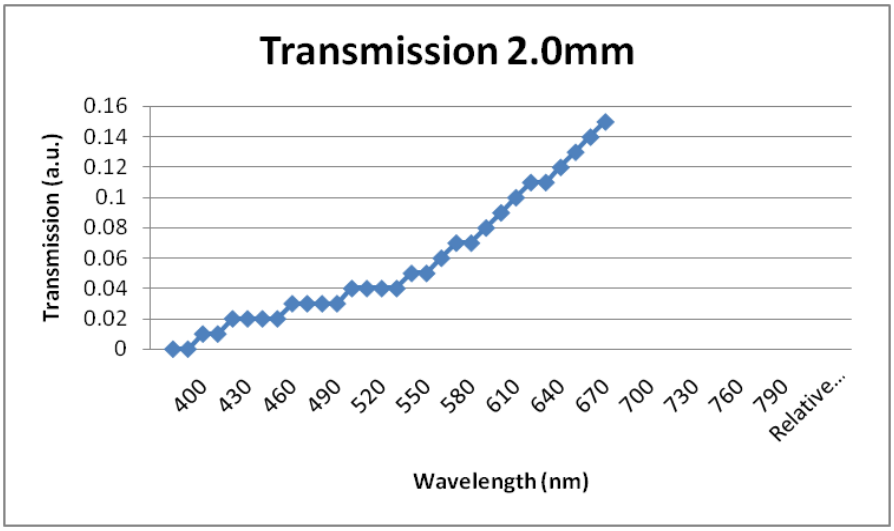

Figure 2 Optical transmission spectrum for human skin at a depth of 2mm.

From analysis of the data in **Figure 2** a number of conclusions can be drawn.

- The absorption of photons within the skin varies with increasing wavelength.
- Any two light sources that emit photons of the same wavelength will have the same optical transmission through the skin.

In order to choose the optimum wavelength of light for a PDT photochemical reaction you might conclude that longer wavelengths of light were more suitable than shorter ones. However this graph does not show the entire picture. **Figure 3** shows the absorption spectrum for the PPIX porphyrin in human skin. From this you can see that the most effective wavelength of light for activating the PPIX Porphyrin is actually at shorter wavelengths.

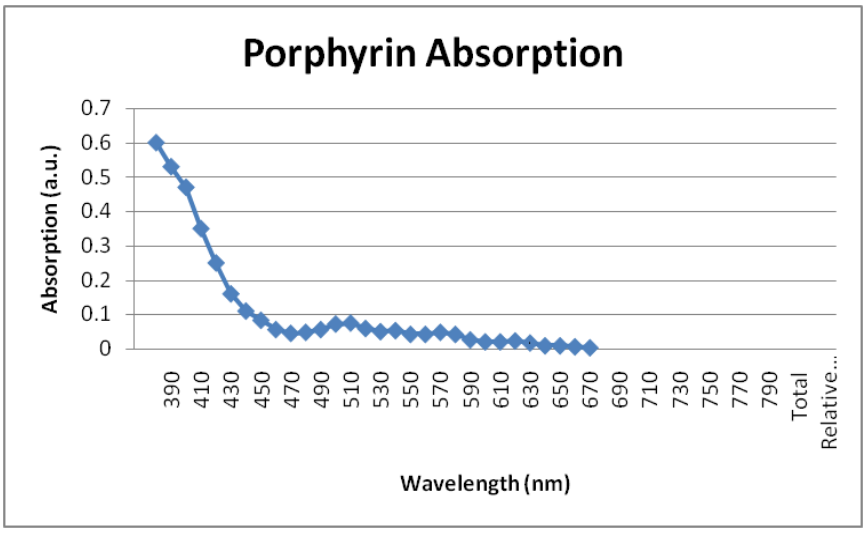

Figure 3 Optical absorption spectrum for a PPIX porphyrin in human skin.

To fully appreciate which wavelengths of light a light source must supply to a treatment area in order to achieve the most effective dose, the spectra in Figure **2** and Figure **3** must be multiplied together. The effects of this are shown in Figure 4.

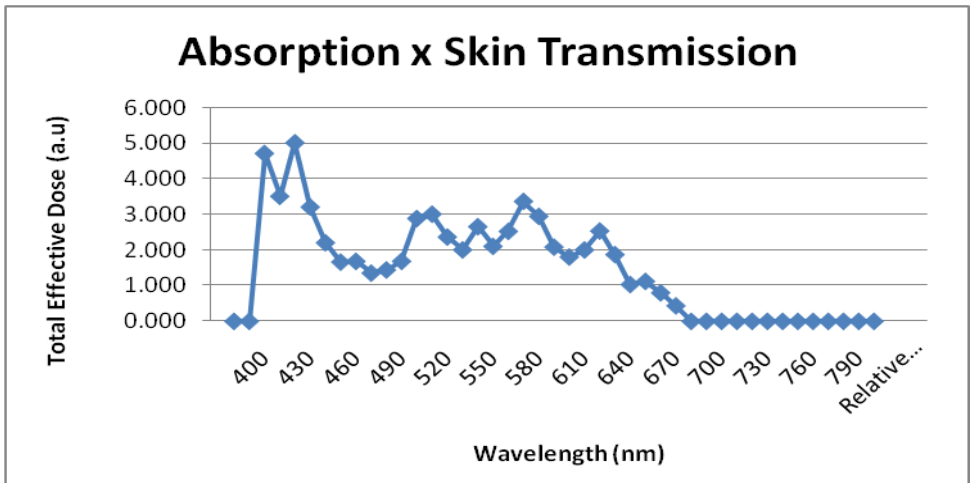

Figure 4 Total effective dose spectrum for a PPIX porphyrin in human skin (2 mm depth).

Figure 4 therefore illustrates which wavelengths of light are most effective at activating a PDT photochemical reaction. Given that (for a fixed wavelength) a photon of light is identical no matter where it originates, the data in **Figure 4** is independent of the light source used. i.e. The data in this figure is true for all light sources.

History of PDT Use – Light Sources

Of the three essential components of PDT (drug, light and oxygen), light is the main subject of this review. Over the last fifteen years of development of PDT, there has been considerable changes within the types of light sources used, due to technical developments such as, cost, size, power consumption and useability. However it should be noted that there has not been a significant change in efficacy due to variations in the light source. Given the discussions in the previous section for total effective dose, whereby it was demonstrated that for a given wavelength of light the PDT effective dose is the same, this is not a surprising result.

Although cellular PPIX has a large absorption peak in the blue region and a lesser peak in the red area, irradiation for PDT is nearly always conducted with a red light source. The reason for this is explained by the fact that red light penetrates skin lesions more deeply than blue light. Although blue light has been used for the most superficial of skin lesions, i.e., actinic keratosis, the great majority of NMSC studies have been conducted with red light (600 – 700 nm) (Braathen, et al, 2007).

A wide range of red light sources has been used in PDT (Moseley 2003; Brancaleon & Moseley, 2002). These are shown in Table 1. In the early days of PDT, a simple low cost tungsten bulb slide projector was used with a red plastic filter. Later, various lasers were employed and such incoherent light sources as the xenon arc, metal halide, light emitting diodes and even sunlight have been employed (Moseley & Brancaleon, 2003) (Figure **5**).

Although lasers are more commonly used for endoscopically delivered systemic PDT, it is the broad band incoherent light sources that have the advantage of being both less expensive and having a larger area of irradiation. In the last decade, inorganic light emitting diodes (ILED, Gsg Aktilite 16 and 128; manufactured by Photocure ASA, Hoffsveien 48, NO-0377, Oslo, Norway) have become increasing popular as a source of red photons, particularly when treating Bowen's disease (BD) and basal cell carcinoma (BCC) (Morton et al, 2002).

Throughout the continuing development phase of PDT, not only has a wide range of red light sources been effective (Figure **5**) but also the dose administered and the irradiance used, have varied without much apparent change in the efficacy of the treatment. This strongly suggests a significant degree of red light overdose/redundancy in most treatment trials, a view which is reasonable when the fluorescent kinetics of PPIX are considered. It is also clear, not only that PPIX is easily inactivated at high irradiances during the PDT process rendering it inactive, but also the other essential PDT component, oxygen, is in short supply providing another rate limiting step. Some have estimated that up to 95% of photons applied in PDT are wasted during the process. Not only does the dose of red light vary in different clinical trials (10 J/cm^2 to 540 J/cm^2) (Moseley et al, 2006), but also the irradiance ranges from a low value of 7 mW/cm^2 (Langmack et al, 2001) to 150 mW/cm^2 Diomed laser (Moseley et al, 2006).

In the study of Langmack et al (2001) a low dose, low irradiance light emitting diode lamp was used to treat 32 sBCCs with a dose of 12.6 J/cm^2 at a low fluence rate of 7 mW/cm^2. The clearance rate at one year was 84%. Interestingly, pain was only a minor feature with none of their patients requiring local anaesthesia. In this work they have a mathematical model which suggests that using a slide projector as a source, they calculated a dose of 30 J/cm^2 would be expected to produce as good an effect as 150 J/cm^2.

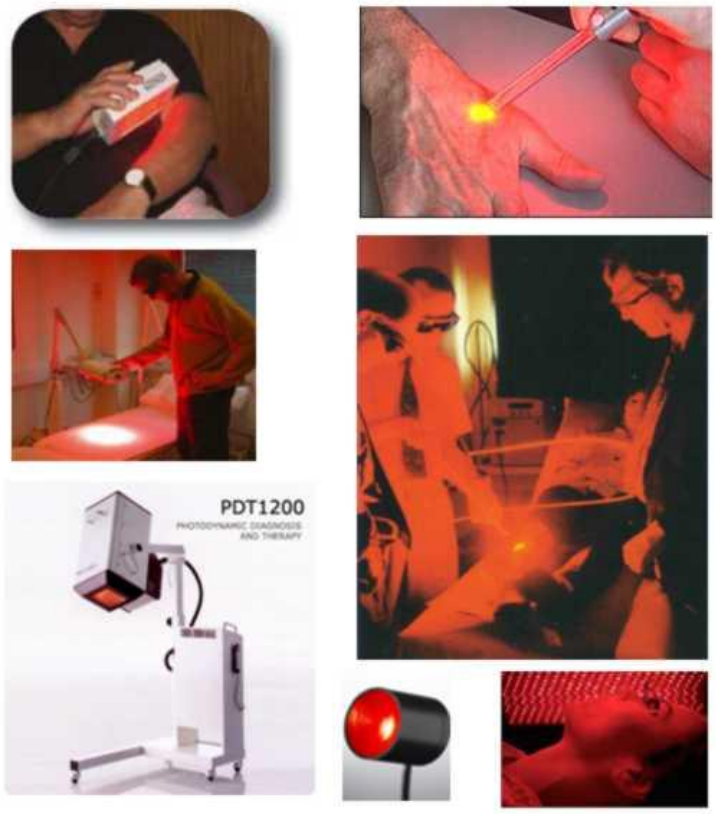

Figure 5 Illustration of the wide range of red light sources that have been used in PDT, all with similar efficacy rates.

In the Scottish PDT Centre, comparative analysis of a xenon arc lamp, laser, metal halide and halogen sources in the clearance of Bowen's disease and sBCCs was achieved in the majority of cases (88 to 100%), whichever lamp was used (Ibbotson et al, 2004).

It is of interest that the similarities in therapeutic outcomes indicate "a range of light sources, doses and irradiances can be used in ALA PDT" and that "this range is effective". Strength of recommendation (A11) (Morton et al, 2008), whereas stated by other workers "topical ALA PDT seems to be performed quite successfully at a wide range of fluences and fluence rates" (Langmack et al, 2001). On the same theme of the efficacy of low irradiance PDT, recently the use of daylight has been assessed and in one study has been found to be effective. Twenty-nine AK patients treated with MAL had exposure to three hours of daylight. Another area of AK within the same patient was treated with conventional red light LED (37 J/cm^2). No efficacy difference was noted between the two treatments. Interestingly, pain was markedly less in the lower irradiance daylight group (Wiegell et al, 2008).

Unpredictability in UK weather patterns could lead to unpredictability and practicality issues of treatment light dose. HCP's could also be giving conflicting public health advice regarding sun exposure. Therefore a controlled, easy to manage light dose would be preferential.

However the point again is emphasised that over a wide range of light intensity and dose, efficacy is equivalent and reduced pain a feature of lower irradiance devices.

Table 1: Overview of light sources used in PDT (adapted from Moseley, 2003)

Type	Specific types	Emission wavelength (nm)	Irradiance (mW/cm^{-2})	Maximum field diameter (cm)

Laser	Argon dye	630	10-500	10
	Copper vapour dye	630	10-500	10
	Nd:YAG-KTP dye	630	10-500	10
	Semiconductor diode	630 ± 5	10-500	10
LED array	PRP 100	630 ± 5	<500	4
Xenon arc	Paterson PTL	630 ± 15 (filter)	10-130	8
Metal halide	Waldmann 1200	600-750	10-200	15
Tungsten/halogen	Projector (modified)	570-1100	<200	~15
LED	Photocure Curelight	570-670	<150	5.5
LED (Langmack et al, 2001)	Actilite 128	635	7	7
OLED Ambicare Health	Organic LED	550-750	5	2
Sunlight/Daylight in Denmark (Wiegell et al, 2008 & 2009)		290-670	variable	>10

Adapted from Table 2 in Guidelines for Topical Photodynamic Therapy: Report of a Workshop of the British Photodermatology Group, Morton et al, BJD 2002, 146: 552-567.

Overview of Safety

It should be noted that the Ambulight PDT product is simply a light source for activating the photochemical reaction of a separate drug within the skin. Light at this wavelength and irradiance is not considered hazardous. Further the aim of the review by NICE is to review the Ambulight device and not PDT in general. However for completeness a discussion of safety is included below and relates to safety of the drug once it is activated by the light source.

Risks relating to the device and its protocol for use have been addressed in the development phase and have been considered fully through an extensive risk analysis process. The protocol relating to use of the Ambulight does not raise any further significant safety issues. It should also be noted that the product already has a CE mark.

A systemic literature review was conducted using Medline, Embase and the Cochrane Clinical Library. A grading of the quality of evidence was conducted using a standard scoring system. Specific areas assessed were efficacy, adverse effects, i.e., safety/tolerability and patient satisfaction.

Two recently published articles that have looked closely at these areas with grading of evidence have particularly been drawn upon (Braathen et al, 2007; Morton et al, 2008)

Adverse Effects

Common and non-Serious

Acute

PDT has few acute adverse effects (Morton 2008). Occasionally marked localised erythema, urticaria and even rarely blistering can occur. In one study post treatment crusting of the area was noted in 9%, pustular reaction in 6%, erosions in 1.2% and pigmentary changes in 1%.

Chronic

The incidence of scarring / pigmentary change appears low (Choudry et al, 2003; Monfrecola et al, 2002).

A mild to moderate increase in pigmentation is occasionally seen in PDT treated psoriasis lesions, although in large studies hypopigmentation can uncommonly occur. In a similar fashion, localised hair loss following PDT appears an uncommon, yet recognised, phenomenon (Morton et al, 2001).

Serious or Significant Adverse Events

Throughout the literature it is pain during therapy that causes the most problems and is perhaps the most serious barrier to the use of the therapy. Pain can affect up to 80% of patients undergoing skin PDT (Lehmann, 2007). In approximately 20% of patients this will be severe requiring some medical intervention (Grapengiesser et al, 2002; Sandberg et al, 2006).

Various techniques have been tried to reduce pain during PDT. These include skin cooling during therapy with refrigerated air (Pagliaro et al, 2004), topical and injected local anaesthesia and nerve block. Those patients who have severe pain appear resistant to such simple topical methods. The sensation described by patient's ranges from a burning stinging unpleasant experience to excruciating and intolerable, the worse pain I've ever had, confined to the area of ALA/Metvix and light illumination. One way of reducing pain is the use of a low intensity light source (Wiegell et al, 2008; Ibbotson et al, 2004; Langmack et al, 2001). It should be noted that use of analgesic sources such as the cool air dispenser further reduce the widespread availability of PDT.

Pulsing or pausing (Wiegell, Haedersdal, Wulf 2009) also has the effect of reducing pain. This area has recently been comprehensively reviewed (Morton et al, 2008).

Another potentially serious adverse effect of erosive pustular dermatosis of the scalp has followed PDT in a single case report. Although there was an association, it is as yet unclear whether this was a true cause and effect relationship (Guarneri and Vaccaro, 2009).

The potential problem of contact allergic dermatitis has recently been addressed (Korshoj et al, 2009). In a group of patients treated at least five times with Metvix PDT, patch testing with Metvix was conducted. Positive patch tests were obtained in 7 / 20, indicating in this single study a high sensitisation potential. Further study is required to quantify the risk.

Regarding carcinogenicity as a hazard of the treatment, it seems unlikely this is a problem as the biological site of action is not DNA based and there is also a lack of clinical evidence of risk in the large number of patients treated (Morton et al, 2008).

Risks of Under Treating

Actinic keratosis is not a malignancy per se although can over time develop into a squamous cell carcinoma. Only a minority (1%) of actinic keratoses appear to transform in this way. Superficial basal cell carcinomas, in the majority of cases, do not metastasise and therefore are considered to be locally malignant. Bowen's disease (intraepidermal squamous cell carcinoma) is similar to superficial basal cell carcinoma in that it does not metastasise and has to transform into a squamous cell carcinoma to do so.

A delay in treating all three of these conditions is extremely unlikely to present a serious risk to a patient. In fact, standard outpatient therapy for all three lesions includes a variety of topical treatments such as liquid nitrogen, Efudix (5-fluorouracil) and Aldara (Imiquimod). All of these forms of therapy have a recognised failure rate and quite simply physicians move from one to another or eventually to PDT, until success is achieved. This is quite different from the situation that one sees

with malignant melanoma (superficial spreading or nodular) where complete excision with a safety margin is considered the treatment of first choice. With these types of malignant melanoma there would indeed be a risk of metastases with ineffective treatment. Of course it can be seen that photodynamic therapy, which is a routine therapy for actinic keratoses, Bowen's disease and superficial basal cell carcinoma, is recognised to have a failure rate. Patient management involves careful monitoring of the success of therapy and switching to alternative treatments if treatment failure occurs. It should be noted that the Ambicare Health device is not intended to treat malignant melanoma.

2. Comparison with Existing PDT Treatments and Light Sources

In order to determine what clinical data should be included in the systematic review of clinical data, the following sections analyse the difference between the Ambulight device and the leading light source currently on the market. There is also an analysis of the differences between the pharmaceutical IFU and the Ambulight IFU.

Comparison between Ambicare Health Device and Existing Product

Proposed Ambicare Health Device

In order to further determine which aspects should be considered in the clinical data review, the new Ambulight PDT light source will be compared to one of the market leading products (Aktilite CL 128). Given that this existing light source has a great deal of clinical data published for it and as such its efficacy is well understood; highlighting differences between this product and the Ambicare Health product will establish which items to include in this clinical data review.

The Ambicare Health light source is a portable device that is worn by the patient. It is in two parts; the first is a battery pack that is either worn about the neck on attached to a belt. The second part is a light emitting plaster that attached via adhesive to the treatment site.

Figure 6 Illustration of the Ambicare Health skin cancer plaster. The device comes in two parts; the first is the battery pack that is worn on the belt and the second is the light emitting plaster.

The adhesive plaster consists of an array of LEDs which emit light with a peak wavelength of 640nm and a Full Width at Half Maximum (FWHM) of 25nm. The ouput spectrum of the LEDs is given in Figure **7** below.

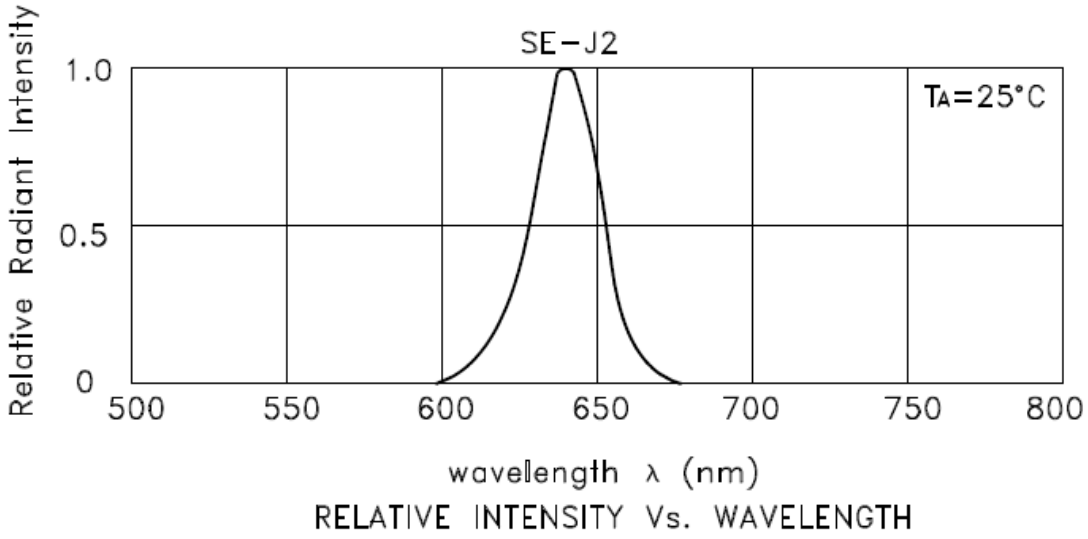

Figure 7 Optical output spectrum of the LEDs used in the Ambicare Health light emitting plaster. The peak wavelength is at 640nm with a FWHM of 25nm.

The Ambicare Health light emitting plaster is capable of delivering a light dose of 75 J/cm^2 at an irradiance of 7 mW/cm^2.

Existing Comparative Device

The Aktilite CL128 lamp (Figure **8**) is table or stand mounted and used in PDT for illuminating large treatment areas. The device employs light emitting diodes (LEDs) and emits red light at approximately 635 nm (FWHM 18nm), as shown in the light spectrum below (Figure **9**).

Figure 8 Photograph of the Aktilite CL128 stand based PDT lamp.

The light dose can be adjusted at the control panel and can be varied from 1-99 J/cm^2. Calibration by the operator is not needed, and the illumination time is calculated automatically for the recommended working distance of 50 to 80 mm (2 to 3.2 inch). The illumination time is the same for working distances in this range. The Aktilite CL128 gives a homogenous light field of 80 x 180 mm (3.2 x 7.1 inch).

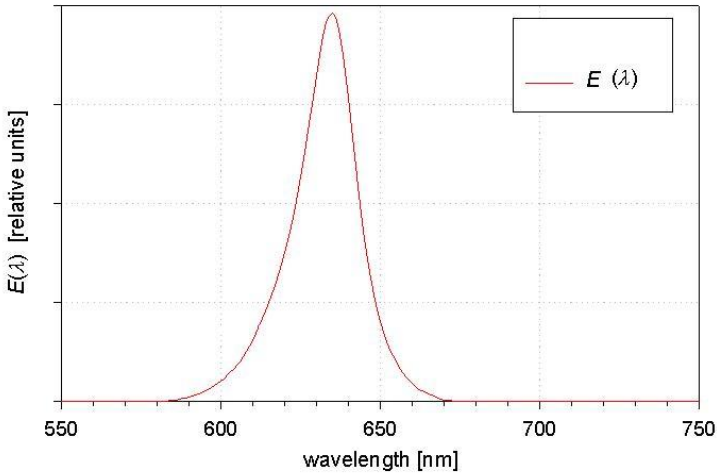

Figure 9 Optical output spectrum from the Aktilite CL128 lamp. The spectrum has a peak at 635nm with a FWHM of 18nm.

Analysis of Differences between Ambicare Health Light Source and Existing Light Source

From the overview of the two products included above, it is apparent that the two devices have a great deal in common. The features of the two products will be discussed in detail so that a picture of their differences can be built up.

Portability

The CL128 device is a large static device that should not be moved during treatment. The lamp is relatively impractical to move and the patient needs to be transported to the location of the lamp for treatment. The Ambicare Health device is small and lightweight and can easily be transported to the location of the patient. The potential exists with Ambulight PDT for movement of both patient and device during treatment.

The portability of the product does not affect the ability of the light source to deliver light to the patient. As such the portability of the light source does not affect the efficacy of the PDT treatment. The device is designed to be used in an ambulatory setting and a full risk analysis of such treatment was conducted during the development phase of the product. No significant risks were identified as arising from the ambulatory nature of the product.

The portable nature of the Ambulight is seen as offering many benefits to the patient and to HCPs whilst still retaining the efficacy of PDT as a treatment.

Proximity to Patient

The CL128 device shines light onto the patient from a distance of 50-80 mm. However the Ambicare Health device is in contact with the patient during use.

In terms of the ability of the light source to deliver light to the treatment site there are no differences between the two products due to the fact that the Ambicare Health light source is in contact with the patient.

Light Delivery

There are a number of different variables that need to be considered when looking at the delivery of light from the light sources to the treatment area. The first item to consider relates to the wavelengths of light that are emitted from each device. Inspection of the output spectra of the two devices shows that both are remarkably similar. The CL128 emits light with a peak at 635 nm FWHM of 18nm whilst the Ambicare Health plaster emits light at 640 nm FWHM of 25 nm. It is clear from this that there is a great deal of overlap between the two spectra. Furthermore, taking each spectra and multiplying them by the total effective dose spectra shown in **Figure 4** highlights that there are no significant differences in spectra between the two devices.

The Ambicare Health device is able to deliver the required treatment dose of 75 J/cm^2 to the treatment area whilst the CL128 is able to vary the dose between 1-99 J/cm^2. In this regard the two devices are not significantly different to each other except for the fact that the Ambicare Health device can reduce operator error since it is set to deliver exactly the reqired light dose.

A summary and comparison of the product characteristics of the two devices is included below.

Product Feature	Ambulight Light Source	Aktilite CL128	Significant Difference	Clinical Data Required
Portability	Yes	No	No	No
Proximity to Patient	In Contact	Remote	No	No
Wavelength of Light	640nm FWHM 25nm	635 nm FWHM 18nm	No	No
Light Dose	75 J/cm2	1-99 J/cm2	No	No

Figure 10 Summary and comparison of the product characteristics of the Ambicare Health light source and the Aktilite CL128.

Comparison between Pharmaceutical Protocol and Ambulight Protocol

In order to further determine which aspects should be considered in the clinical data review, a systematic comparison between the pharmaceutical IFU and the Ambulight IFU is included below.

Established Metvix IFU Protocol

The protocol for Metvix in the EU is as follows and was taken from the information leaflet incorporated with the product. It should be noted that for ease of analysis in this report the protocol has been broken down into numbered sections

1. For treatment of actinic keratoses (AK) one session of photodynamic therapy should be administered.
2. Treated lesions should be evaluated after three months and if needed, treatment should be repeated with a second therapy session.
3. For treatment of basal cell carcinoma (BCC) and Bowen's disease two sessions should be administered with an interval of one week between sessions.
4. Before applying Metvix cream, the lesion surface should be prepared to remove scales and crusts and roughen the surface of the lesions.
5. Nodular BCC lesions are often covered by an intact epidermal keratin layer which should be removed.
6. Exposed tumour material should be removed gently without any attempt to excise beyond the tumour margins.
7. Apply a layer of Metvix cream (about 1 mm thick) by using a spatula to the lesion and the surrounding 5-10 mm of normal skin.
8. Cover the treated area with an occlusive dressing for 3 hours
9. Remove the dressing, and clean the area with saline
10. and **immediately expose the lesion to red light with a continuous spectrum of 570-670 nm and a total light dose of 75 J/cm^2 at the lesion surface**.
11. **Red light with a narrower spectrum giving the same activation of accumulated porphyrins may be used**.
12. **The light intensity at the lesion surface should not exceed 200 mW/cm^2.**
13. **Only CE marked lamps should be used, equipped with necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and UV radiation.**

14. **It is important to ensure that the correct light dose is administered. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface and illumination time. These factors vary with lamp type, and the lamp should be used according to the user manual. The light dose delivered should be monitored if a suitable detector is available.**

15. Patient and operator should adhere to safety instructions provided with the light source. During illumination patient and operator should wear protective goggles which correspond to the lamp light spectrum.

16. Healthy untreated skin surrounding the lesion does not need to be protected during illumination.

17. Multiple lesions may be treated during the same treatment session.

18. Lesion responses should be assessed after three months, and at this response evaluation, lesion sites showing non-complete response may be retreated if desired.

19. It is recommended that the response of BCC and Bowen's disease lesions be confirmed by histological examination of biopsy material. Subsequently, close long term clinical monitoring of BCC and Bowen´s disease is recommended, with histology if necessary.

20. Contraindications

    a. Hypersensitivity to the active substance or to any of the excipients which includes arachis oil.

    b. Morpheaform basal cell carcinoma.

    c. Porphyria.

21. Special warnings and special precautions for use

    a. Metvix should only be administered in the presence of a physician, a nurse or other health care professionals trained in the use of photodynamic therapy with Metvix.

    b. Metvix is not recommended during pregnancy.

    c. Thick (hyperkeratotic) actinic keratoses should not be treated with Metvix. There is no experience of treating lesions which are pigmented, highly infiltrating or located on the genitalia with Metvix cream. There is no experience of treating Bowen´s disease lesions larger than 40 mm. As with cryotherapy and 5-FU therapy of Bowen´s disease, response rates of large lesions (>20 mm in diameter) are lower than those of small lesions. There is no experience of treating Bowen´s disease in transplant patients on immunosuppressive therapy or in patients with a history of arsenic exposure.

    d. Methyl aminolevulinate may cause sensitization by skin contact resulting in application site eczema or allergic contact dermatitis. The excipient cetostearyl

alcohol may cause local skin reactions (e.g. contact dermatitis), methyl- and propyl parahydroxybenzoate (E218, E216) may cause allergic reactions (possibly delayed).

e. Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure of the treated lesion sites and surrounding skin should be avoided for about 2 days following treatment.

f. Direct eye contact with Metvix cream should be avoided.

Ambulight PDT Device IFU Protocol

The IFU protocol for the Ambulight PDT light source is included below.

Device Alignment and Lesion Preparation

1. Before preparing the lesion, the position and orientation of the light source on the skin should be determined.

2. The location of the lesion should be checked against the permitted locations as described in this IFU.

3. Areas that are covered with hair should be shaved prior to the cream application.
4. The alignment template should be placed on the skin over the lesion and aligned such that the lesion sits in the middle of the circle on the template.

5. The lesion should be no greater than 24mm in diameter at its widest point and fit completely within the circle of the template.

6. For lesions that are located on curved body surfaces, the template should be rotated around the lesion such that the hinge of the device allows it to bend around the body curve. *See Appendix 1 for further details*

7. Dots or lines should be made on the skin using a pen to illustrate the location of the template over the lesion

8. Before applying the pharmaceutical cream, the lesion surface should be prepared to remove scales and crusts and roughen the surface of the lesions. Please refer to the pharmaceutical instructions for a protocol of how this should be achieved.

9. The pharmaceutical cream should be applied in an even 1mm thick layer across the extent of the lesion *(see item 9)*. This ensures that the cream will be absorbed into the skin and therefore becomes transparent before the light source is activated. To achieve the required thickness of cream it should be applied to the skin in a set manner.

10. Parallel lines of cream taken from a standard pharmaceutical tube should be deposited across the lesion. These lines should be spaced at a distance of 5mm and should extend past the lesion margins by a distance of 5-10mm.

11. Once the cream has been applied in the manner described above the entire area should be covered with a transparent occlusive dressing (such as Tegaderm®). This dressing should have

dimensions of at least 3 cm x 3 cm. Slight pressure should then be applied to the area to ensure that a 1mm thick continuous layer of pharmaceutical covers the lesion and extends beyond the lesion margin to a distance of 5mm.

12. The battery unit should be secured to the patient via the supplied belt clip (or lanyard).

13. The adhesive liner on the light plaster should be unpeeled with the adhesive release tab to expose the adhesive.

14. The light plaster should then be placed over the lesion and occlusive dressing layer such that it aligns with the marks that were made with the alignment template. See Appendix 1 for additional information on alignment of the plaster.

15. Instances where the power cord may get snagged during use require that the path of the power cord from the battery pack to the light source go under the clothes of the patient. The power cord should be attached to the patient at distances of 25cm using adhesive strips. The adhesive strips should be placed in such a manner that the cord has enough slack to ensure it does not impede the normal movement of the patient.

Device Operation

16. Once attached, the battery pack should be turned on by pressing the on/off button.

17. It must be verified that a green light is visible on the battery pack before proceeding further.

18. The device is programmed so that the light source does not come on until three hours after the battery pack was initially turned on.
The entire treatment time is 6 hours;

3 hours wearing plaster with light off + 3 hours wearing plaster with light on.

19. When the green light starts to flash, the treatment has successfully completed. The light source, battery pack and occlusive dressing may be removed.

20. Once removed, the treatment area should be treated according to the pharmaceutical instructions.

Notes on use

1. To verify that the device is working correctly and that the timer is counting the green light will remain lit on the battery pack.
2. If the device encounters a problem and is unable to perform the treatment, the green LED will become extinguished and the red LED will light up.

3. After the initial three hour wait, the light source will automatically activate and illuminate the lesion.

4. The device will supply light with a wavelength of 640 nm and will deliver a dose of 75 J/cm2 to the lesion.

5. The device will illuminate the lesion for a period of three hours and will ensure that the correct dose has been administered.

6. Healthy untreated skin surrounding the lesion does not need to be protected during illumination.

7. Multiple lesions may be treated during the same treatment session, each lesion must be treated with a different Ambulight : PDT lightsource.

Differences between Existing Light Source Protocol and Ambicare Health's Protocol

The following is a comparison between the two protocols; only numbered items where the Ambicare Health protocol deviates from the Metvix one are included in this analysis. Items from the existing drug protocol with be labelled M1 and items from the new Ambicare Health protocol will be numbered L1

1. M7, L8, L9, L10. These deviations relate to how the cream is applied. In the existing Metvix protocol, the cream is applied with a spatula to a thickness of 1mm, and then covered with a Tegaderm sheet. In the Ambicare Health protocol a 1mm thick layer is also applied, however to achieve this thickness an extra step in the protocol is added. Given that the end result is the same (a 1mm thick layer of Metvix) it is reasonable to say that there will be no difference in treatment efficacy between the two protocols.

2. M9, M10, L12-L20. These deviations relate to removal of the cream at the end of the absorption period. In the Metvix protocol the cream is removed three hours after it is applied. The area is then cleaned with saline solution before the light is administered. In the Ambicare Health protocol, the cream and the Tegaderm are kept in place, and the light is shone through both, after the three hour absorption time. Equivalence to the existing protocol relies on a number of factors;

    a. **The Tegaderm sheet does not block a significant amount of light that is shone through it.** The transmission of light through a Tegaderm sheet has been measured by Ambicare and is not seen as a significant factor.

    b. **The 1mm thick layer of Metvix does not block a significant amount of light that is shone through it.** The transmission of light through the layer of cream has been measured by Ambicare and is not seen as a significant factor.

    c. **The cleaning with saline does not affect the lesion physically.** The use of saline is simply to remove the cream from the lesion. Any changes of the chemical or biological composition of the treatment area are unlikely to significantly affect the treatment efficacy. This is therefore judged to not be a significant change. Non-removal of the Metvix by the saline is taken into account in item 'b' above.

    d. **The delivery of pharmaceutical beyond three hours and indeed during illumination does not have a significant effect on treatment efficacy.** This will be addressed via a review of the clinical literature.

Conclusions

Having concluded this review, the two protocols work in alignment with each other, however a systematic review of the literature will be conducted to ensure that the extended cream application time used in the Ambulight protocol is safe. It should be noted that these differences have been fully addressed in the technical file for the product as part of its CE mark.

3. Overview of Existing Clinical Data

Before the systematic examination of the clinical data is performed, an overview of the clinical data that has so far been generated using the Ambulight device will be presented and analysed. This data falls into two parts;

- The first set of data is from a pilot trial that was performed using a prototype Ambulight PDT device. The results from this pilot trial have been written up and accepted for publication in the peer reviewed journal British Journal of Dermatology (BJD).
- The second set of data was collected from use of the device at Ninewells hospital in Dundee. The Ambulight is currently being used in a number of HNS hospitals across the UK, for every treatment data is collected on the use of the device. This data includes treatment efficacy and data relating to the quality of life for the patient. One of the main indicators that is collected in this area is the collation of pain data during treatment.

Pilot Trial Overview

Participants

Twelve patients referred to the PDT hospital clinic with histologically proven Bowen's disease or sBCC (all $\leq$2 cm diameter) were invited to participate in the study. The study was approved by the Tayside Ethics Committee and written informed consent was obtained from all participants. The portable device was safety approved by the Medical Physics Department, Ninewells Hospital, Dundee.

Treatment Method

Within the hospital PDT clinic, each lesion was prepared by gentle superficial curettage, without local anaesthesia. 50 mg/cm^2 of Aminolevulinic acid (ALA) (20% w/w) cream; Crawford Pharmaceuticals, was applied under Tegaderm™ for four hours. The remaining cream was wiped clear and a self-adhesive Silicone Gel layer (Cica-Care ®) was applied on to the lesion. The portable light source was then applied for three hours. All subjects had treatment repeated after one month, i.e., a total of two treatments per lesion. Patients were followed up at 6 & 12 months following their last treatment.

Outcome Assessment

Three assessment measures were used in the study

i. Efficacy: Lesions were clinically assessed at 6 and 12 months following the last treatment and any evidence of residual disease, documented. Lesions that failed to respond were surgically excised.

ii. Protoporphyrin 9 (PPIX) fluorescence: At the time immediately prior to OLED application (4 hours after the application of ALA cream), PPIX fluorescence of the lesion was assessed using a conventional Wood's light source (UVP Inc., Upland, California, USA) and scored on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = marked).

iii. Numerical Rating Scale (NRS): Patients were asked to score maximal pain/ discomfort experienced immediately after treatment using the NRS (0-10).

Light Source Overview

This consisted of two parts connected via an electrical cable:

i. Power Supply: Contained 8 rechargeable Ansmann 2600mAh AA batteries and electronics to deliver a current of 280mA to the light source. The pack weighed 390 gm and could either be carried in a belt pouch or the patient's pocket.

ii. Lighting element: The light emitting device consisted of a custom made Organic Light Emitting Diode (OLED) manufactured by Osram Opto Semiconductors. The light source used in this study consisted of a flat light emitting area that was circular in shape and 2cm in diameter. This type of light emitting element exhibited high output uniformity. The light source had aluminium foil backing on all 4 sides which with adhesive tape, fixed the device to the patient as shown in Figure **11**1. The emission spectrum of the light source was measured using an Oriel CCD 77400 and is shown in Figure **12**2. The power output of the light source was measured using a Gigahertz Optik P9710 irradiance meter with a RW-3703-2 sensor. The device was chip controlled and programmed to deliver the desired fluence and fluence rate. For the purpose of this study the devices were applied for three hours such that a total light dose of between 45 and 60 J/cm^2 was delivered per lesion (fluence rate - 5 mW/cm^2).

Figure 11 photographs of the portable PDT light source showing, a) the two parts of the device, b) the light source attached to the patient, c) the power pack worn around the waist.

Irradiance Considerations

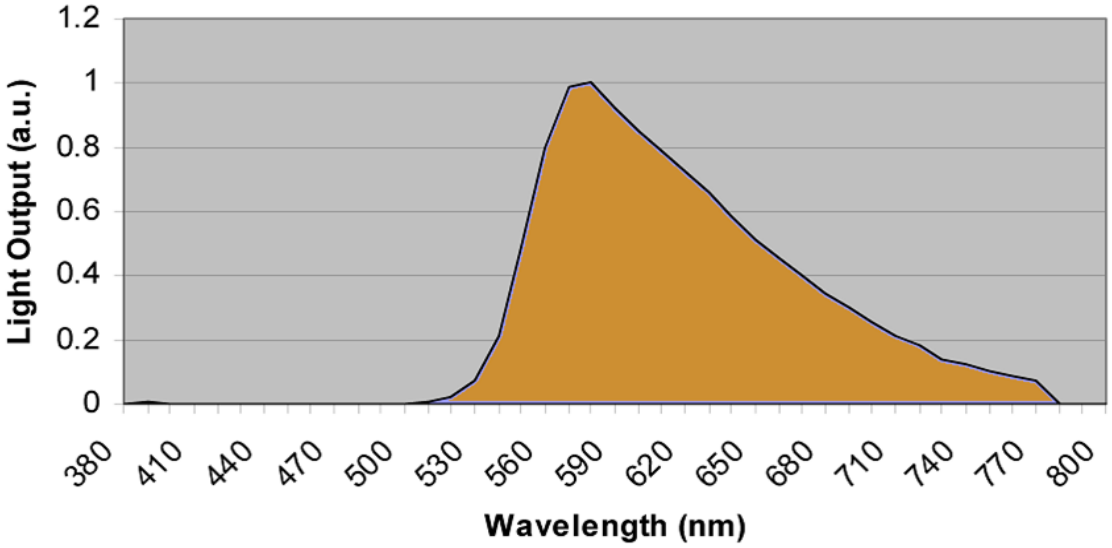

Figure 12 optical output spectrum from the portable PDT light source.

Trial Results

Twelve patients (median age 69 years) with a histological diagnosis of Bowen's disease (8) or sBCC (4) were enrolled and completed the study. The median lesion diameter was 1.1cm (range 0.6-1.9cm).

At six months, 9 out of the 12 had a complete response with a further two relapsing at the 12 months follow-up. Of the five without clearance at 12 months, a peripheral margin failure was evident in four (**Figure 13**) and the other, despite initial biopsy showing a superficial lesion, was noted to have a residual nodular component. There was no apparent relationship between degree of fluorescence and likelihood of response or failure, to treatment. The median fluorescence score for both treatments was 2 (moderate). Furthermore, degree of fluorescence did not seem to be associated with level of pain experienced i.e. lesions with marked fluorescence were not more painful during treatment.

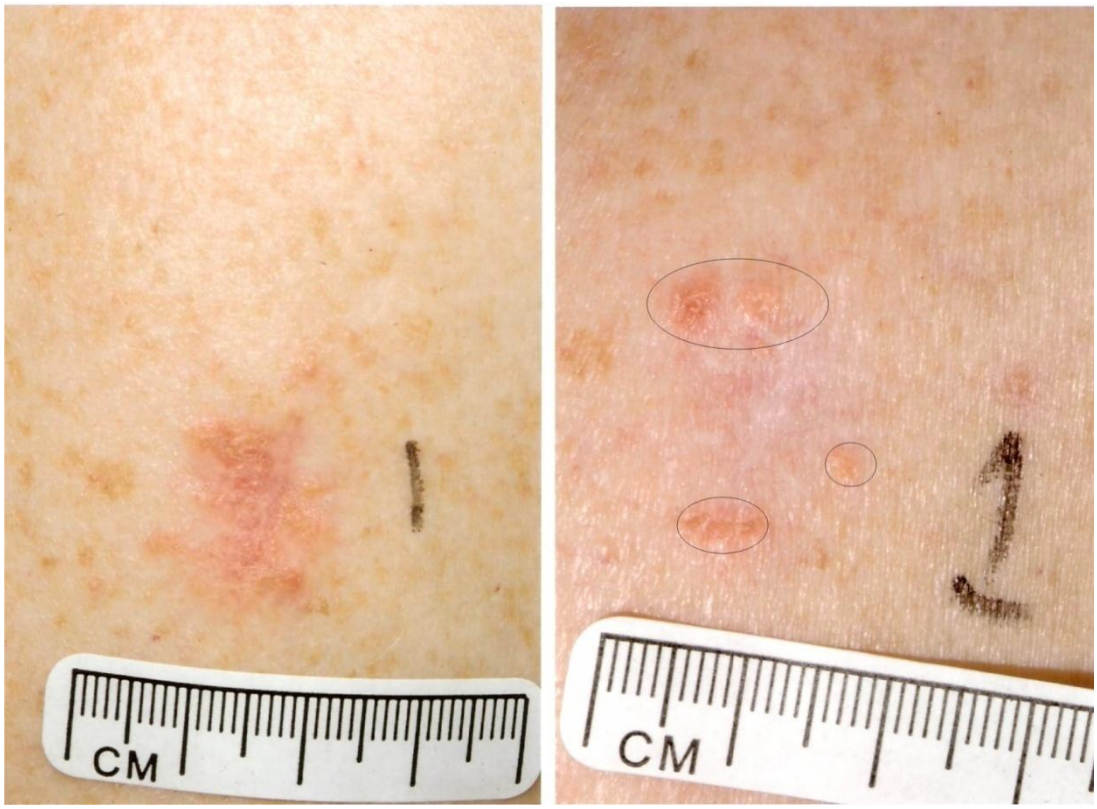

Figure 13 photographs of before and after treatment for a typical lesion in this trial. Note in the right hand image the peripheral failure of treatment.

All the 12 subjects scored pain as ≤2 using the NRS (median score=1; range 0-2). None of the pilot study patients required pain relief in the form of local anaesthesia or cool air treatment during therapy. One subject (No.7) who had experienced excessive pain with PDT previously, commented on the lack of discomfort with the OLED device. The NRS scores of the 12 patients were compared with pain data from 50 consecutive patients from the routine PDT clinic (who were treated with Aktilite inorganic LED source (Photocure™); dose 75 Jcm^{-2}), who were scored in a similar manner. The median NRS score for the conventional PDT cohort was 6 (range 1-10). Eleven of these 50 patients required local analgesia (topical or intralesional lignocaine). Moreover all these patients required cool air treatment (Cynosure Smartcool™).

Table 2 Clinical data results from pilot trial with portable PDT light source.

No.	Sex	Age	Lesion	Diameter (cm)	Site	Dose 1 (J/cm2)	Fluorescence	Dose 2 (J/cm2)	Fluorescence	Median NRS	3 month review	6 month review	9 month review	12 month review
1	F	76	BD	1.1	Leg	60.4	Moderate	49	Moderate	2	Clear	Clear	Clear	Clear
2	M	60	BD	1.1	Shoulder	44.5	Moderate	52.2	Mild	1	Fail*	n/a	n/a	n/a
3	M	78	sBCC	1.7	Mid Back	48.4	Marked	53.2	Moderate	1.5	Clear	Clear	Fail	n/a
4	F	68	BD	1.2	Leg	44.9	Moderate	51.3	Mild	1	Clear	Clear	Clear	Clear
5	M	68	sBCC	1.6	Shoulder	47.5	Moderate	50.5	Moderate	1	Clear	Clear	Clear	Fail*
6	F	66	BD	0.7	Leg	49.7	Mild	49.4	Mild	1	Clear	Clear	Clear	Clear
7	F	50	sBCC	1.5	Mid Back	49.1	Marked	50.9	Moderate	1	Clear	Clear	Clear	Clear
8	F	69	BD	1.7	Leg	49.1	Moderate	49.2	Mild	1	Clear	Fail*	n/a	n/a
9	F	65	BD	1	Leg	50.3	Moderate	49.2	Mild	1	Clear	Clear	Clear	Clear
10	F	74	BD	0.6	Leg	50.9	Mild	52.9	Moderate	1	Clear	Clear	Clear	Clear
11	F	81	sBCC	1.9	Chest	53.3	Marked	48.1	Mild	1.5	Fail*	n/a	n/a	n/a
12	F	74	BD	1.1	Leg	55.3	Moderate	50.2	Mild	2	Clear	Clear	Clear	Clear

* Failure at Peripheral Margin

Interpretation of Results

Despite the OLED-PDT efficacy results being at the lower end of published conventional PDT response range, it was interesting that the majority of lesions that failed to clear were ≥ 1.5 cm in diameter (Table 2). The peripheral pattern of failure may be relevant as it suggests that treatment of ≥ 1.5 cm lesions with a 2 cm device may have been overambitious and that a more accurate

alignment of the device to the lesion is required. Only one lesion <1.5cm was not clear at 12 months follow-up.

As a consequence of these peripheral failure results, Ambicare Health has included a measurement and alignment template in the box with each device. This template allows the size of the lesion to be checked and for the device to be aligned to the lesion. This will ensure that the device cannot fail due to the lesions being too large or to inaccurate alignment of the plaster to the lesion. Details of this alignment method are included in the technical file of the Ambulight.

Of further interest in this pilot study was that despite irradiation for 3 hours, treatment was well tolerated with only mild discomfort reported. This is in contrast to the vast majority of PDT treatments whereby pain is a significant factor, the mechanism of which is yet to be explained. There is a suspicion of a neuropathic pathway as ALA is known to be directly taken up by gamma-amino butyric acid (GABA) nerve receptors. There is also an idiosyncratic element with marked intersubject variation; some patients describing excruciating, shooting, burning pain, which makes treatment intolerable. It has been shown previously that the degree of pain depends upon the light source used and the intensity of light delivery.

Conclusions from Pilot Study

The efficacy of this trail was in agreement with the lower end of the published range for PDT treatments. There are solid arguments relating to the ratio of lesion size to light source and to the accuracy of the plaster alignment. Given that the light source treated the central parts of all the lesions, but failed at the perimeters it is reasonable to expect that the relative alignment and size of the devices was the sole reason for the failures. It should also be noted that there were no significant adverse events in this study.

Given restrictions with sample size it is hard to draw definitive conclusions from this study. However on balance, this pilot study demonstrates that it is unlikely that a low irradiance PDT device that is in contact with a treatment site will be significantly less safe or less effective than an existing high irradiance lamp.

Ongoing Collation of Clinical Data using the Ambulight PDT

The Ambulight PDT device has been further used at Ninewells and the data from the treatments collected. As the device is very new, little data has yet been gathered relating to on-going treatment efficacy, although this is being collected. Data on the pain experienced during each treatment is regularly recorded at Ninewells regardless of the light source used. This pain evaluation is recorded on a Visual Analogue Scale (VAS) from 1-10.

Patient Number	Lesion Number	Diagnosis	Treatment Type	Date Of Treatment				Pain Score			
				Rx1	Rx2	Rx3	Rx4	Rx1	Rx2	Rx3	Rx4
1	1	SBCC	Ambulight	24.05.10	07.06.10			1.0	2.5		
	2	SBCC	LED 16 (2)	24.05.10	07.06.10			6.5	1.5		
	3	SBCC	Ambulight	07.06.10	14.06.10			1.0	2.5		
2	1	SBCC	Ambulight	23.02.10	21.03.10			3.0	5.0		
3	1	BCC	Ambulight	07.04.10	14.04.10			2.0			
4	1	Bowens	Ambulight	01.02.10	08.02.10	27.04.10	04.05.10	1.5	1.7		
5	1	Micronoduler SBCC	LED 16 (2)	27.05.10	16.06.10			5.0	3.5		
	2	SBCC	Ambulight	27.05.10	03.06.10			2.0	7.5		
	3	BCC	Ambulight	27.05.10	03.06.10			2.0	7.5		
6	1	SBCC	Ambulight	21.12.09	31.12.09			2.5	1.3		
	2	SBCC	LED 16 (1)	21.12.09	31.12.09			4.0	1.7		
7	1	Bowens	Ambulight	08.04.10	15.04.10			5.0			
8	1	AK	Ambulight	21.04.10				0.3	n/a - AK		
	2	AK	LED 128	21.04.10				6.0	n/a - AK		
	Area 3	AK	PDT 1200	28.05.10				5.0	n/a - AK		
	Area 4	AK	PDT 1200	11.05.10				5.0	n/a - AK		
9	1	SBCC	LED 16 (1)	06.05.10	13.05.10			3.3	6.4		
	2	SBCC	Ambulight	06.05.10	13.05.10			3.0	6.0		
	3	SBCC	LED 16 (2)	06.05.10	13.05.10			4.7	7.2		
10	1	SBCC	LED 16 (2)	04.03.10	11.03.10			2.0	7.6		
	2	Bowenoid AK	Ambulight	04.03.10	11.03.10			0.0	2.0		
11	1	Bowens	Ambulight	11.03.10	17.03.10			2.0	7.0		
12	1	SBCC	Ambulight	21.01.10	03.02.10			1.0	1.0		
	2	SBCC	LED 128	21.01.10	03.02.10			6.5	6.0		
	3	SBCC	LED 128	21.01.10	03.02.10			6.5	6.0		
13	1	SBCC	Ambulight	17.06.10				2.5	4.0		
	2	Bowenoid AK	LED 16 (1)	17.06.10				9.0	10.0		
14	1	SBCC	Diomed	02.11.06	07.11.06	01.04.08	09.04.08	5.0	8.0	7.5	8.1
	2	Bowens	Ambulight	01.07.10	08.07.10			1.0	4.0		
15	1	SBCC	LED 128	08.07.10	15.07.10			8.0	10.0		
	2	SBCC	Ambulight	08.07.10	15.07.10			0.0	0.0		
	3	Bowens	LED 128	08.07.10	15.07.10			6.0	5.0		
	4	Bowens	LED 128	08.07.10	15.07.10			6.0	5.0		
16	11	BCC	LED 128	07.07.10	14.07.10			9.0	8.5		
	12	BCC	LED 128	07.07.10	14.07.10			9.0	8.5		
	13	BCC	Ambulight	07.07.10	14.07.10			7.0	8.0		
	8,9 &10	Bowenoid AK	Cryo	07.07.10				6.5	n/a - AK		

Although there has not been sufficient time to follow up these patients and assess long term efficacy, each patient is assessed post treatment to establish the level of photo-toxic inflammation. This is essentially the amount of oedema and erythema present immediately post treatment, and is a measure of the damage done to the area by the PDT process. It is in part a proxy for treatment efficacy. The clinicians at Ninewells have not seen any difference in post treatment inflammation between the Ambulight light sources and the other existing light sources that are on the market.

4. Items to be Addressed by Clinical Data Review

Irradiance of Light Source

In the Metvix Instructions for Use (IFU) and protocol, only a total light dose and wavelength range are mentioned, the Ambulight PDT device therefore completely complies with the drug IFU when it comes to supply of the light to activate the photochemical reaction.

However, in order to reduce costs, in most clinical settings, it is common for the prescribed light dose to be delivered as quickly as possible. This means that most light sources deliver light at high irradiance with the total dose being delivered in 10-20 minutes. This corresponds to an operational irradiance range of 50-200 mW/cm^2, and this is the range in which the bulk of their clinical trials have been performed. The Ambulight PDT light source operates at 7 mW/cm^2 for 3 hours.

Given the arguments laid out above relating to total effective dose and the properties of photochemical reactions, it is reasonable to assume that it is the total dose of light administered that is the critical parameter rather than irradiance when considering efficacy. However for completeness, a search of the clinical literature was performed to examine the data relating to safety and efficacy at a reduced irradiance. It should be noted that an assessment of the risks relating to under treatment are included elsewhere in this report (p8-9).

Extended Cream Application Time

In the comparison of the Ambicare Health treatment protocol against the pharmaceutical protocol only one factor that was relevant to either the safety of efficacy of the treatment that required analysis of the clinical data was highlighted. This single difference in protocols related to keeping the drug in situ for a length of time greater than three hours. It therefore follows that the literature will also be analysed to determine the safety and efficacy of this extended cream application time.

Literature Search Methodology and Ranking Methods

Three literature databases were searched: Medline, Embase and the Cochrane Library of Systematic Reviews. Below are the search criteria that were employed to find the relevant clinical literature for the two areas requiring examination; Irradiance and cream application. It should be noted that the previous section on adverse events was also subject to systematic review to ensure that the a state of the art representation of adverse events were reported.

Irradiance

((Photodynamic therapy OR aminolaevulinic acid OR Metvix) (treatment OR therapy) AND (light source) AND (irradiance OR fluence rate))

Application Times

((photodynamic therapy OR aminolaevulinic acid OR Metvix) AND (application times))

Adverse Effects Search

((Photodynamic therapy OR aminolaevulinic acid OR Metvix) (treatment or therapy) AND (skin or dermatological) AND adverse effects))

Results of the Literature Search and Criteria for Acceptance

From searching the listed databases with the above search terms, the papers were read and sorted for acceptability. The ONLY criteria for rejecting papers for inclusion in this report were the ones laid out in the MED-DEV guidance 2.7.1 (section 4.3.1 d) on the basis of either; clinical, technical or biological aspects.

The remaining papers were then analysed and are summarised below. An expert judgement was then made on the strength of these papers and this judgement is summarised in the statement. The strength of the statement is given a rating. The criteria are listed below.

Strength of recommendations

A There is good evidence to support the use of the procedure
B There is fair evidence to support the use of the procedure
C There is poor evidence to support the use of the procedure
D There is fair evidence to support the rejection of the use of the procedure
E There is good evidence to support the rejection of the use of the procedure

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial
II-i Evidence obtained from well-designed controlled trials without randomization
II-ii Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one centre or research group
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.

III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees

IV Evidence inadequate owing to problems of methodology (e.g., sample size, or length of comprehensiveness of follow-up or conflicts in evidence)

Irradiance as a factor in PDT Efficacy – Literature Review

Using EMBASE and Medline databases (1996 – 2009), a search was conducted (photodynamic ADJ therapy OR aminolaevulinic ADJ acid OR metvix) AND (light ADJ source OR laser OR LED ADJ OR incoherent) AND (irradiance OR fluence rate), which revealed 155 and 175 titles respectively. The majority of assessed publications were in the areas of laboratory study or systemic PDT.

Only one review article that focused on light sources for cutaneous PDT was detected. This describes a wide range of light sources employed in publications and their range of irradiances. The table presented within that article has been adapted to include more recent lower irradiance sources/peer reviewed publications (Moseley 2003).

The laboratory based PDT literature reveals an interest in the concept that too high doses and irradiances are often given in PDT. Cellular and *in* vivo lab work does convincingly support that for a given dose, low irradiance PDT, i.e., the same dose delivered over a longer period of time, causes more tumour cell damage than a high irradiance regime for the same dose (Iinuma et al, 1999; Foster et al, 1993; Robinson et al, 1998; Veenhuizen and Stewart, 1995). This is explained by the various workers on the basis that oxygen (essential to the PDT effect) has a limited availability, i.e., if a dose of light is given too rapidly it quickly consumes the available oxygen. In addition, there is the issue of photobleaching of the photosensitiser rendering it ineffective. High dose, high irradiance regimens, it is suggested, may have a significant element of overkill.

The majority of published PDT clinical trials do provide irradiance data. Lasers are at the top end of the high irradiance range (up to 500 mW/cm^2) and LEDs at the lower end (5-150 mW/cm^2) (Table 1, page 11). A significant criticism of published figures is the lack of information regarding radiometer calibration which will vary between Centres. Nevertheless, although it is not always possible to comment on the relative irradiances between many of the studies conducted, it should be noted that the majority of trial data is for treatments with irradiances well above the Ambicare Health device.

With regard to specific clinical trials, although the majority of the literature is high irradiance related work. Two specific publications have looked at low irradiance regimes. The first of these (Langmack et al, 2001) determined a numerical model taking into account 5-ALA concentration, bleaching, fluence rates and oxygen concentrations. This model predicted that low fluence rate PDT would be as effective as higher irradiances if conducted over the same period of time, i.e., the same dose was given. To test the validity of their model, they built an LED device with a low fluence rate (7 mW/cm^2) which was used in an open trial manner to treat 32 superficial basal cell carcinomas on 22 patients with a total dose of 12.6 J/cm^{-2}). At one year the clearance rate was 85%, which is equivalent to higher irradiance publications. It should be noted however that this was an open study and clearance rates for >one year were not reported, and it is interesting, although not quantified, that they did comment that PDT associated pain was mild.

In another clinical study from Copenhagen, Wiegell et al (2008) employed a randomised controlled, within subject, comparison trial of low irradiance PDT using sunlight, which was directly compared with a conventional higher irradiance LED PDT. Thirty patients with actinic keratoses had areas randomised to both high and low irradiance regimes. An effective light dose was calculated for the

high (1.2 J/cm^{-2}) and low dose (1.9 J/cm^{-2}), i.e., were roughly equivalent. The main difference between the conventional PDT and the sunlight exposure was the time of light administration with sunlight ($2_{1/2}$ hours exposure) having an irradiance of approximately one-fifth that of the LED source. The results at three months (i.e., a relatively short follow-up period), reveals high and low irradiance regimes to be roughly equivalent. Both produced similar erythema and crusting post treatment. Measured pain scores were considerably less in the lower irradiance (sunlight) group.

A further open study of at home sunlight PDT by the same Danish group found low irradiance PDT (4 hours outdoor exposure) to be effective in 30 actinic keratoses treated at home (Wiegell 2009).

Although searched for, no clinical work has defined the lower limit of effective irradiance using a red light source. Such a threshold must exist.

Statement

There does therefore seem to be, an albeit limited, amount of theoretical and laboratory data to support the concept of low irradiance PDT. Only one randomised controlled trial looking specifically at this parameter has been conducted. This data supports the conclusion that low irradiance is safe and effective.

Level of Evidence: B II-i

ALA/Metvix Cream Application Time Prior to Illumination - Literature Review

Using EMBASE and Medline databases (1996 – 2009), a search was conducted (photodynamic ADJ therapy OR aminolaevulinic ADJ acid OR metvix) AND application ADJ times) revealed a range of peer reviewed articles, 15 and 21 respectively. No systematic review on this topic was found in the Cochrane Library. Those peer reviewed publications involving clinical aspects and methods of application significantly different from those used in routine PDT, were rejected (e.g., those related to hypericum, hexyl aminolaevulinic acid and bioadhesive ALA patches).

The ALA or Metvix Cream application time pre-irradiation (with either red or blue light) must be an important treatment parameter. It is therefore surprising that a literature search fails to reveal the source data for current recommended application times of Metvix (3 hours) and ALA (4 hours). Although this may simply be due to the fact that such data was generated by the manufacturer and never published, personal communication with the companies suggests that the recommended time of application was to a large extent an arbitrary decision.

This impression is supported by a recently conducted large open randomised parallel multi-centre study (Braathen et al 2008) of 112 patients with 384 actinic keratoses. This work evaluated the effect of varying the Metvix application time (one hour vs three hours) on treatment outcome. Follow-up, when conducted at two and three months, indicated equivalent efficacy, with a slightly greater benefit in the one hour group (96% vs 87%), with recurrence rates at 12 months being 19% and 17% respectively. This large study suggests that a one hour application may be sufficient. This particular work was significant in that it was funded by the Metvix manufacturer (Photocure), highlighting their uncertainty regarding application time and so suggesting a probable large window of opportunity for the time of cream application prior to irradiation.

A number of points do emerge from other published work. A particular study (Ibbotson et al 2006) looked at the time to reach peak PPIX tissue fluorescence vs application time in 21 normal volunteers. The application times in this study ranged from one to six hours and revealed no significant difference in the time to reach maximum PpIX fluorescence. These results are compatible

with the findings above (Braathen et al 2008). Also of interest in that study, was the strong element of intra-subject variation when the investigation was repeated. If tumours have similar characteristics, it could go some way to explain why widely varying ALA application times produce similar efficacy results. For example, published work looking at actinic keratosis, superficial basal cell carcinomas and Bowen's disease, use times of application of one hour (Smith et al 2003), six hours (Berroeta et al 2007), eight hours (Dijkstra et al, 2001), six to 12 hours (Yang et al 2003), and even 14 to 18 hours (Piacquadio et al 2004) prior to irradiation. All these studies had a similar therapeutic efficacy. This variability suggests that effective PDT is associated with a wide range of application times. There appears to be no particular adverse effects reported with the longer application times, i.e., >3 hours.

Statement

A wide range of application times for Metvix and ALA Cream prior to irradiation are associated with approximate equal efficacy. No evidence exists to suggest that adverse effects are more common with longer cream application times.

Level of Evidence: B II-ii

Conclusions of Literature Reviews

When considering the safety issues of the Ambulight PDT light source it is important to distinguish between the existing adverse effects of the pharmaceutical (see Adverse effects P13-15) and the way in which the light source moderates these effects. The literature search failed to reveal that there are additional safety issues of using a low irradiance light source. The worst case scenario is that the device under treats the patient. A statement on the implications of under treatment is included in this report (p8-9). In Summary a delay or under treatment to the patient is unlikely to have a significant impact on the health or quality of life of the patient.

The major problem with PDT appears to be pain during therapy which can persist for sometime after treatment. In this respect the low irradiance regime, whether it is using an LED (as is the focus of this paper) or any other light source, appears to greatly reduce this adverse effect.

It should also be noted that the pilot trial presented earlier in this review did not report any safety issues associated with a low irradiance light source.

Although there is limited data on cream application times of >3 hours, there is data for application times as great as 18 hours. There are no reported safety issues with longer application times and given the widespread use of Metvix, it seems unlikely that a cream application time of 6 hours will prove to raise significant safety concerns.

Efficacy issues raised by the literature search revolve around under treating the patient and are covered in the previous section.

Conclusions from Analysis of Literature

This report has demonstrated that a wide range of different PDT red light sources of similar efficacy exist. This is unsurprising as a red light photon is the same reagent whatever its source.

The role of these light sources is to trigger the active ingredient found within the pharmaceutical that has accumulated within the skin cancer. It is the active ingredient within the pharmaceutical that drives treatment efficacy and indeed safety.

The Ambicare Health PDT device delivers the same dose, at the same wavelength as more routinely used red light sources, but does so over a longer period of time (i.e., at a lower irradiance). Laboratory and clinical work suggests that lower irradiance devices may even be more effective per dose than higher irradiance sources.

This report concludes that there is sufficiently suitable proxy data from the systematic literature search to suggest that the Ambulight PDT device is a safe and effective light source, equivalent to others currently being routinely used for PDT.

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