



# Kansas City

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## Dermatologic Applications of Photodynamic Therapy

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**Origination:** 8/2007

**Last Review:** 3/2014

**Next Review:** 3/2015

### **Policy**

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Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for photodynamic therapy when it is determined to be medically necessary because the criteria shown below are met.

### **When Policy Topic is covered**

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Photodynamic therapy may be considered **medically necessary** as a treatment of:

- Non-hyperkeratotic actinic keratoses of the face and scalp.
- Superficial basal cell skin cancer only when surgery and radiation are contraindicated.
- Bowen's disease (squamous cell carcinoma in situ) only when surgery and radiation are contraindicated.

### **When Policy Topic is not covered**

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Photodynamic therapy is considered **investigational** for other dermatologic applications, including, but not limited to, acne vulgaris, non-superficial basal cell carcinomas, hidradenitis suppurativa, or mycoses.

Photodynamic therapy as a technique of skin rejuvenation, hair removal, or other cosmetic indications is considered **cosmetic**.

### **Considerations**

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Surgery or radiation is the preferred treatment for superficial basal cell cancer and Bowen's disease (see Rationale). If photodynamic therapy is selected for these indications because of contraindications to surgery or radiation, patients and physicians need to be aware that it may have a lower cure rate in comparison with surgery or radiation.

Photodynamic therapy typically involves two office visits; one to apply the topical ALA, and a second visit to expose the patient to blue light. The second physician office visit, performed solely to administer blue light, should not warrant a separate Evaluation and Management CPT code.

### **Description of Procedure or Service**

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Photodynamic therapy (PDT) refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Photosensitizing agents, administered orally or intravenously, have been used in non-dermatologic applications and are being proposed for use with dermatologic conditions such as actinic keratoses and non-melanoma skin cancers.

Two common photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester methyl aminolevulinate (MAL). When applied topically, they pass readily through the abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. 5-ALA and MAL are metabolized by the underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404–420 nm and 635 nm, respectively) generates reactive oxygen species that are cytotoxic, ultimately destroying the lesion. PDT can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results. PDT with

topical ALA has been investigated primarily as a treatment of actinic keratoses. It has also been investigated as a treatment of other superficial dermatologic lesions, such as Bowen's disease, acne vulgaris, mycoses, hidradenitis suppurativa, and superficial and nodular basal cell carcinoma. Potential cosmetic indications include skin rejuvenation and hair removal.

Actinic keratoses are rough, scaly, or warty premalignant growths on sun-exposed skin that are very common in older individuals with fair complexions, with a prevalence of greater than 80% in fair-skinned people older than 60 years of age. In some cases, actinic keratosis may progress to squamous cell carcinoma (SCC). The available treatments for actinic keratoses can generally be divided into surgical and non-surgical methods. Surgical treatments used to treat one or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodesiccation), and laser surgery. Non-surgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (also known as chemical peels), and dermabrasion. Topical treatments are generally used in patients with multiple lesions and the involvement of extensive areas of skin. Under some circumstances, combinations of different treatment methods may be used.

Non-melanoma skin cancers are the most common malignancies in the Caucasian population. Basal cell carcinoma (BCC) is most often found in light-skinned individuals and is the most common of the cutaneous malignancies. Although the tumors rarely metastasize, they can be locally invasive if left untreated, leading to significant local destruction and disfigurement. The most prevalent forms of BCC are nodular BCC and superficial BCC. Bowen's disease is a squamous cell carcinoma (SCC) in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive SCC. Lesions may appear on sun-exposed or covered skin. Excision surgery is the preferred treatment for smaller non-melanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-fluorouracil, imiquimod, and cryotherapy. Poor cosmesis resulting from surgical procedures and skin irritation induced by topical agents can be significant problems.

### **Regulatory Status**

In 1999, Levulan® Kerastick™, a topical preparation of ALA, in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, received approval by the U.S. Food and Drug Administration (FDA) for the following indication: "The Levulan Kerastick for topical solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp." The product is applied in the physician's office.

A 5-aminolevulinic acid patch technology (5-ALA Patch) is available outside of the U.S through an agreement between Intendis (part of Bayer HealthCare) and Photonamic GmbH and Co. KG. The 5-ALA patch is not approved by the FDA.

Another variant of PDT for skin lesions is Metvixia® and the Aklilite CL128 lamp, each of which received FDA approval in July 2004. Metvixia® (Galderma, SA, Switzerland; PhotoCure ASA, Norway) consists of the topical application of methyl aminolevulinate (MAL) in contrast to ALA used in the Kerastick procedure, followed by exposure with the Aklilite CL 128 lamp, a red light source (in contrast to the blue light source in the Kerastick procedure). Broadband light sources (containing the appropriate wavelengths), intense pulsed light (IPL), pulsed dye lasers (PDL), and potassium titanyl phosphate (KTP) lasers have also been used. Metvixia is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation (debridement using a sharp dermal curette) in the physician's office when other therapies are unacceptable or considered medically less appropriate.

### **Rationale**

The policy was created in 2001 and was updated regularly with searches of the MEDLINE database. The most recent literature search was for the period November 2012 to December 2, 2013. Key literature is described below and focused on studies evaluating FDA-approved photosensitizing agents.

## Actinic Keratoses

Multiple randomized controlled trials (RCTs) evaluating photodynamic therapy (PDT) for actinic keratoses have been published. Representative trials are described below

### *Placebo-controlled trials*

In a 2003 trial, Pariser and colleagues conducted a randomized, placebo-controlled trial of 80 patients with actinic keratoses. (1) The authors reported that the complete response rate for the methyl aminolevulinate (MAL) group was 89% compared to 38% in the placebo group.

A 2009 double-blind RCT conducted in Germany by Hauschild and colleagues evaluated PDT with 5-aminolevulinic acid (5-ALA) using a self-adhesive patch. (2) Eligibility criteria included Caucasian patients, age 18 years and older with skin type I-IV and actinic keratoses on the head and of mild or moderate grade, as defined by Cockerell (maximum diameter of 1.8 cm and interlesional distance of at least 1 cm). Patients were randomly assigned to receive 5-ALA patches containing 8 mg 5-ALA or identical placebo patches. Patches were square, measuring 4 cm<sup>2</sup>, and patients received 3–8 of them, depending on their number of study lesions. The primary efficacy outcome was the complete clinical clearance rate 12 weeks after PDT. A total of 99 of 103 randomized patients were included in the primary efficacy analysis. The complete clinical clearance rate on a per patient basis (all lesions cleared) was 62% (41 of 66) in the 5-ALA patch group and 6% (2 of 33) in the placebo patch group; there was a statistically significant difference favoring PDT.

### *Trials comparing PDT to an alternative intervention*

In 2006, Morton and colleagues published an industry-sponsored, 25-center randomized left-right comparison of single photodynamic treatment and cryotherapy in 119 subjects with actinic keratoses on their faces or scalps. (3) At a 12-week follow-up, PDT resulted in a significantly higher rate of cured lesions compared with cryotherapy (86.9% vs. 76.2%, respectively, cured). Lesions with a non-complete response were retreated after 12 weeks; a total of 108 of 725 lesions (14.9%) received a second PDT session; 191 of 714 lesions (26.8%) required a second cryotherapy treatment. At 24 weeks, the groups showed equivalent clearance (85.8% vs. 82.5%, respectively). Skin discomfort was reported to be greater with PDT than with cryotherapy. Investigator-rated cosmetic outcomes showed no difference in the percentage of subjects with poor cosmetic outcomes (0.3% vs. 0.5%, respectively), with more subjects rated as having excellent outcomes at 24 weeks after PDT (77.2% vs. 49.7%, respectively). With PDT, 22.5% had cosmetic ratings of fair or good compared to 49.9% for cryotherapy.

In 2010, Szeimies and colleagues in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch to cryotherapy. (4) The study had the same eligibility criteria and primary outcome as the Hauschild et al. study, (2) described above. A total of 148 patients were randomly assigned to the 5-ALA patch group, 49 to a placebo group, and 149 to a cryotherapy group.

The study used a test of non-inferiority of PDT versus cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT and cryotherapy, leaving 283 patients. The rate of complete clearance of all lesions was 67% (86 of 129) in the 5-ALA group, 52% (66 of 126) in the cryosurgery group, and 12% (5 of 43) in the placebo group. The clearance rate was significantly higher in the 5-ALA patch group than either the cryosurgery group or placebo patch group. Results were similar in the analysis of clearance rates on a lesion basis. The 360 patients with at least 1 lesion cleared at 12 weeks were followed up for an additional 9 months; 316 completed the final visit 1 year after treatment. The overall clearance rate on a lesion basis was still statistically higher in the 5-ALA patch group compared to placebo (in both studies) and compared to cryosurgery (in the second study). Thirty-two percent of patients in the 5-ALA group from the first study and 50% of patients in the 5-ALA group from the second study were still completely free from lesions. The corresponding figure in the

cryosurgery group was 37%. In the safety analysis, there were high rates of local reaction to patch application and cryotherapy at the time of treatment, but no serious adverse effects due to study intervention were documented. The photodynamic therapy patches used in the German studies have not been cleared by the FDA for use in the United States.

A 2012 randomized pilot study from Spain compared PDT using methyl aminolevulinate (MAL) alone, imiquimod alone, and the combination of the 2 treatments. (5) Patients with non-hyperkeratotic actinic keratoses on the face and/or scalp were randomly assigned to 1 of 3 groups: 1) 1 session of PDT with MAL (n=40); 2) self-administered imiquimod 5% cream for 4 weeks (n=33); or 3) PDT, as above, followed by 4 weeks of imiquimod cream (n=32). Follow-up occurred 1 month after PDT (group 1) or 1 month after the end of treatment with imiquimod (groups 2 and 3). The primary outcome measure, complete clinical response, was defined as the total absence of actinic keratoses by visual evaluation and palpation. Complete clinical response was achieved by 4 (10%) of patients in group 1, 9 (27%) of patients in group 2, and 12 (37.5%) of patients in group 3. There was a statistically significantly higher rate of complete response in the PDT plus imiquimod group compared to PDT only (p=0.004). A limitation of the study was that the PDT-only group was followed for a shorter amount of time, which could at least partially explain the lower rate of complete response.

In 2012, Scola and colleagues in Germany published findings from a randomized split-area comparison of 5-ALA PDT and carbon dioxide laser ablation in 21 patients with multiple actinic keratoses. (6) Seventeen of the 21 patients had lesions located on the face or scalp and, in the other 4 patients, lesions were on the back of the hand or forearms. The primary efficacy outcome was the reduction in the number of actinic keratoses. At baseline, the median number of actinic keratoses was 6 (range 4-28) in the PDT group and 8 (range 3-34) in the laser ablation group. The median number of actinic keratoses in the PDT was 0 (range 0-12) at the end of the 4-week treatment period and 1 (range 0-5) at the 3-month follow-up. Comparable numbers in the laser ablation group were 2 (0-7) actinic keratoses at 4 weeks and 2 (range 1-7) in the laser ablation group. The reduction in the number of actinic keratoses did not differ significantly between groups at 4 weeks, but there was a significantly greater reduction in the quantity of actinic keratoses at 3 months in the PDT group (p=0.016). The investigators reported that there were more adverse events associated with PDT, but they did not provide details on rates of these adverse events.

Section summary: Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with hyperkeratotic actinic keratoses on the face or scalp compared to placebo or other active interventions. One trial reported superior outcomes with a combination of photosensitizing agents compared to a single agent. However, this was a preliminary study and the superiority of combined treatment compared to PDT alone needs to be confirmed in larger numbers of patients followed for similar amounts of time.

### Basal Cell Carcinoma (BCC)

A 2007 Cochrane review evaluated surgical, destructive (including PDT), and chemical interventions for basal cell carcinoma. (7) The authors concluded that surgery and radiotherapy appeared to be the most effective treatments, with the best results being obtained with surgery. In addition, they stated that cosmetic outcomes appear to be good with PDT, but additional data with long term follow-up are needed. The Cochrane review did not distinguish between BCC subtypes.

### *Superficial BCC*

A 2012 systematic review by Roozeboom and colleagues examined randomized and non-randomized trials evaluating treatments for superficial basal cell carcinoma. (8) A total of 16 studies were identified that evaluated PDT for treating BCC; 6 of the studies were RCTs. There was significant heterogeneity among studies (p<0.0001). A pooled estimate of complete response after treatment with PDT in 13 studies (PDT arms only) was 79% (95% confidence interval [CI]: 71% to 87%). In 3 studies that

compared illumination regimens, only 1 arm was included, and in 2 studies that compared PDT agents, both arms were included.

A representative RCT was published in 2008 by Szeimies and colleagues. (9) This was an industry-sponsored multicenter open trial comparing MAL-PDT with surgery for small (8–20 mm) superficial BCC in 196 patients. At 3 months after treatment, 92% of lesions treated with MAL-PDT showed clinical response, compared with 99% of lesions treated with surgery (per protocol analysis). At a 12-month follow-up, no lesions had recurred in the surgery group, and 9% of lesions had recurred with MAL-PDT. Approximately 10% of patients discontinued MAL-PDT due to an incomplete response or adverse event, as compared with 5% of patients in the surgery group. Cosmetic outcomes were rated by the investigators as good to excellent in 94% of lesions treated with MAL-PDT in comparison with 60% following surgery.

Another trial, published in 2008 by Basset-Sequin and colleagues, compared PDT with cryotherapy for superficial BCC. (10) This multicenter European study included 120 patients, aged 18 and older, with previously untreated primary superficial BCC. Sixty patients with 114 lesions were randomly assigned to treatment with MAL-PDT (1 treatment), and 58 patients with 105 lesions were randomly assigned to cryotherapy (2 freeze-thaw cycles). Patients who had not responded at 3 months received 2 further MAL-PDT sessions (n=20) or repeat cryotherapy (n=16). The primary outcomes were measured 3 months after the last treatment and included 58 patients with 103 lesions in the MAL-PDT group and 57 patients with 98 lesions in the cryotherapy group. The overall response 3 months after the last treatment on a per lesion basis was 100 of 103 (97%) in the MAL-PDT group and 93 of 98 (94.9%) in the cryotherapy group; the difference was not statistically significant. Results were not reported on a per patient basis. Findings were similar for lesions treated once or repeatedly. Treatment groups did not differ in the recurrence rates at any time during follow-up; at 5 years, the overall lesion recurrence rate was 22% with MAL-PDT and 20% with cryotherapy. There was, however, a better cosmetic outcome with MAL-PDT. The percent of lesions rated by investigators as having an excellent cosmetic appearance at 3 months was 30% in the MAL-PDT group and 4% in the cryotherapy group ( $p=0.0005$ ), and at 5 years was 60% in the MAL-PDT group and 16% in the cryotherapy group ( $p=0.00078$ ). There was a high rate of local, transitory adverse events, mainly pain; no patients discontinued the study due to treatment-related adverse events. This study did not compare cryotherapy to standard surgical or radiation therapy.

Section summary: A Cochrane review of RCTs concluded that surgery and radiotherapy are the most effective treatments for patients with BCC. RCTs have found not found statistically significant differences in the clinical response rate with PDT compared to cryotherapy. This suggests, but does not conclusively demonstrate, similar efficacy. In addition, cosmetic outcomes have been better after PDT compared to cryotherapy.

### *Nodular BCC*

A pair of placebo-controlled trials were published by Foley and colleagues in 2010. (11) The trials were single-blind and industry sponsored; both evaluated MAL-PDT and included primary nodular BCC that were 5 mm or less in depth. One study was conducted in Australia and the other in the United States, but used the same design and procedures. Patients were randomly assigned to receive treatment with PDT using MAL 160 mg/g or placebo cream. The initial treatment cycle consisted of 2 PDT sessions a week apart. Patients whose lesions showed a partial response at the 3-month follow-up underwent a second treatment cycle.

Combining the 2 studies, 131 patients with 160 lesions were enrolled (there were 66 patients in the Australian study and 65 patients in the U.S. study). Sixty-six patients were assigned to the MAL-PDT group and 65 to the placebo group. After randomization, 10 lesions were excluded because they were found histologically not to be nodular BCCs, leaving 150 lesions (75 per group). A total of 117 of 150 lesions (78%) received 1 complete treatment cycle, and 31 of 150 (21%) received 2 complete treatment cycles. The remaining 2 lesions received only a partial treatment cycle. Overall, the complete clinical

response rate at 6 months, the primary outcome, was 55 of 77 (73%) after MAL-PDT and 20 of 75 (27%) after placebo. (P values were not reported for any of the outcomes). Response rates were higher in smaller lesions (<10mm diameter) than larger lesions (10-20 mm) in both groups. The rate of any local adverse event was 49 of 66 (74%) in the MAL-PDT group and 30 of 65 (46%) in the placebo group. The most common local event was a burning sensation of the skin, which was reported by 19 patients (29%) in the MAL-PDT group and 8 patients (12%) in the treatment group. In addition, 9 serious adverse events were reported by 6 patients, 2 treated with MAL-PDT and 4 treated with placebo. None of the serious adverse effects were determined to be related to the study treatment. The study is limited by a lack of statistical reporting and a comparison only to placebo, not surgery.

Several trials have compared PDT to surgery for treating nodular BCC. In 2008, Mosterd and colleagues published an RCT evaluating 5-ALA PDT for patients with nodular BCC. (12) The study included 149 patients with 173 primary nodular BCC; 85 tumors were assigned to PDT and 88 to surgical excision. Two patients, each with 1 tumor, dropped out before treatment. At 3 months, 78 of 83 (94%) tumors in the 5-ALA-PDT group and 86 of 88 (98%) tumors in the surgery group had resolved completely; this difference was not statistically different. Long-term follow-up data were published in 2013. (13) Investigators reported on 106 tumors with at least 5 years of follow-up. Over 5 years, treatment failure occurred in 2 tumors in the surgery group and 23 tumors in the PDT group. The cumulative probability of tumor recurrence by 60 months was 30.7% (95% CI: 21.5-42.6%) in the PDT group and 2.3% (95% CI: 0.6-8.8%) in the surgical excision group. Both treatment failures in the surgery group were due to incomplete excision of the tumors. Treatment failure rates were higher for thicker tumors. The rate of recurrence-free survival at 5 years was over 90% for tumors greater than 0.7mm thick and between 60- 70% of thinner tumors.

In 2007, Rhodes et al. published a 5-year follow-up of an industry-sponsored multicenter randomized study comparing MAL-PDT to surgery for nodular BCC. (14, 15) A total of 101 adults with previously untreated nodular BCC were randomized to receive MAL therapy or surgery. At 3 months, complete response (CR) rates did not differ between the 2 groups; however, at 12 months, the CR rate had fallen from 91% to 83%, while in the surgery group the CR rate had fallen from 98% to 96%. Of 97 patients in the per protocol population, 66 (68%) were available for 5-year follow-up; 16 (32%) discontinued in the MAL-PDT group due to treatment failure or adverse events versus 6 (13%) in the surgery group. A time-to-event analysis of lesion response over time estimated a sustained lesion response rate of 76% for MAL-PDT and 96% for excision surgery. Cosmetic outcomes were rated as good to excellent in 87% of the MAL-PDT patients and 54% of the surgery patients. Thus, although cosmetic outcomes may be improved, PDT does not seem to be as effective as surgery in terms of the more important clinical outcomes of treatment completion and lesion recurrence.

An observational study published in 2011 by Lindberg-Larsen provides additional data on recurrence rates after treatment with PDT. (16) The study including 90 patients with 157 lesions (n=111 superficial BCC, n=40 nodular BCC and n=6 unknown) were initially treated with MAL-PDT. Each lesion was treated twice, with 1 week between treatments. The authors did not report the initial rate of clinical response. Recurrence was defined as reappearance of a histologically-verified BCC in a previously affected area. The estimated recurrence rate was 11% at 6 months, 16% at 12 months, and 19% at 24 months. There was a significantly higher rate of recurrence for nodular BCC than superficial BCC (e.g., at 12 months, the recurrence rates were 28% and 13%, respectively, p=0.008). Study findings suggest the use of PDT with superficial BCC and not with nodular BCC. However, there may be confounding factors. For example, the authors noted that nodular BCCs were more frequently located on patients with fewer tumors and that patients with more tumors had a lower risk of recurrence.

Section summary: An RCT found a higher response rate after PDT compared to placebo, but also a higher rate of adverse effects, suggesting that PDT may not improve the net health outcome for patients with nodular BCC. Other RCTs have found similar initial clinical benefits with surgery and PDT in patients with nodular BCC, but recurrence rates have been higher after PDT. One observational study found a higher rate of recurrence in patients with nodular BCC treated with PDT than patients

with superficial BCC who had been treated with PDT. Overall, the evidence is insufficient for demonstrating that PDT improves the net health outcome for patients with nodular BCC.

### Squamous Cell Carcinoma (SCC)

#### *Squamous cell carcinoma in situ (Bowen's disease)*

A Cochrane review on interventions for cutaneous Bowen's disease was published by Bath-Hextall in 2013. (17) The investigators identified a total of 7 RCTs evaluating PDT. Four of these compared 2 PDT protocols, 1 compared PDT to cryotherapy, 1 compared PDT to topical 5-fluorouracil (5-FU) and 1 compared PDT to both PDT and 5-FU. The authors did not pool study findings.

The study with the largest sample size (n=225) was a 3-arm trial published in 2006 by Morton and colleagues. (18) This was a multicenter study conducted in 11 European countries. A total of 225 patients were randomized to receive MAL PDT, cryotherapy or 5-FU for treatment of Bowen's disease. Unblinded assessment of lesion clearance found PDT to be non-inferior to cryotherapy and 5-FU (93%, 86%, 83%, respectively) at 3 months and superior to cryotherapy and 5-FU (80%, 67%, 69%, respectively) at 12 months. Cosmetic outcome at 3 months was rated higher for PDT than the standard non-surgical treatments by both investigators and blinded evaluators, with investigators rating cosmetic outcome as good or excellent in 94% of patients treated with MAL-PDT, 66% of patients treated with cryotherapy, and 76% of those treated with 5-FU.

Another representative trial comparing PDT to another intervention in patients with Bowen's disease was published by Salim and colleagues in 2003. (19) Forty patients were randomly assigned to undergo either topical 5-FU or MAL therapy. A total of 29 of the 33 lesions (88%) in the PDT group cleared completely, as compared with 22 of 33 (67%) in the 5-FU group. In the 5-FU group, severe eczematous reactions developed around 7 lesions, ulceration in 3, and erosions in 2. No such reactions were noted in the PDT group.

Section summary: RCTs have found that PDT has similar or higher efficacy compared to cryotherapy and 5-FU for patients with Bowen's disease. In addition, adverse effects/cosmetic outcomes appeared to be better after PDT. There is a lack of RCTs comparing PDT to surgery or radiotherapy in patients with Bowen's disease; as a result, conclusions cannot be drawn about PDT compared to these other treatments.

#### *Non-metastatic invasive SCC*

In 2013, Lansbury and colleagues published a systematic review of observational studies evaluating interventions for non-metastatic cutaneous squamous cell carcinoma. (20) The investigators identified 14 prospective studies evaluating photodynamic therapy. Sample sizes ranged from 4 to 71 patients and only 3 included more than 25 patients. These studies evaluated a variety of different PDT protocols. There was only 1 comparative study, and this study compared 2 different PDT regimens. In a pooled analysis, a mean of 72% of lesions had a complete response to treatment (95% CI: 61.5% to 81.4%). Eight studies addressed recurrence rates in patients who were initial responders. When findings were pooled, the probability of recurrence was 26.4% (95% CI: 12.3% to 43.7%).

Section summary: No RCTs evaluating PDT for treatment of non-metastatic invasive SCC are found. There are a number of small, uncontrolled studies, and these represent insufficient evidence to draw conclusions about the efficacy and safety of PDT for patients with this condition.

### Acne

Several RCTs and non-randomized controlled studies have been published. A randomized single-blind split-faced study was published in 2010 by Orringer and colleagues and was U.S.-based. (21) The study included 44 patients with facial acne. A randomly selected side of the face received the

intervention (combined treatment with topical 5-ALA and a pulsed dye laser [PDL]) and the other side of the face remained untreated. Patients received up to 3 treatments at intervals of approximately 2 weeks. Twenty-nine patients (66%) completed the 16-week study. For most outcomes, there were no statistically significant differences between the treated and untreated sides of the face. This included change from baseline to 16 weeks in the mean number of inflammatory papules, pustules, cysts, closed comedones or open comedones. There was a significantly greater reduction in erythematous macules on the treated compared to the untreated side of the face (a mean reduction of 5.9 and 2.5, respectively;  $p=0.04$ ). In addition, the improvement in mean Leed acne severity score was significantly greater on the treated side of the face (-1.07) than the untreated side (-0.52);  $p=0.001$ . There were few adverse effects, and they tended to be mild. A limitation of the study was the high drop-out rate.

A non-randomized split-faced study from Egypt was published in 2012 by Shaaban and colleagues and included 30 patients with inflammatory and nodulocystic acne. (22) In each patient, the right side was treated with a monthly session of ALA-PDT plus intense pulsed-light (IPL) treatment, and the left side was treated with IPL only. From baseline to the 1-month follow-up, the mean count of facial acne lesions decreased from 9.55 (standard deviation [SD]: 1.1) to 2.1 (SD: 1.68) in the combined treatment group and from 9.8 (SD: 4.8) to 5.01 (SD: 1.7) in the IPL-only group. The difference in lesion count between groups was statistically significant. Limitations of the study were that it was not randomized and did not include a group that received PDT as the sole intervention.

In 2013, Mei and colleagues in China published a parallel group RCT that included 41 patients with moderate to severe facial acne. (23) The trial evaluated the additional value of ALA PDT in patients treated with intense pulsed light (IPL). A total of 21 patients were randomized to 4 weeks of treatment with IPL plus PDT and 20 patients were randomized to IPL plus placebo PDT. The mean reduction in both inflammatory and non-inflammatory lesions was significantly greater in the IPL plus PDT group compared to the IPL-only group at the 4-, 8- and 12-week follow-ups. For example, in the IPL plus PDT group, the mean number of non-inflammatory acne lesions decreased from 31.3 (SD: 7.1) at baseline to 14.0 (SD: 6.2) at the 12-week follow-up. In the IPL-only group, the mean number of non-inflammatory lesions decreased from 28.2 (SD: 4.1) at baseline to 18.6 (SD: 3.1) at 12 weeks,  $p<0.05$ . An improvement of 75-100% in all lesions was attained by 13 patients (62%) in the IPL plus PDT group and 3 (15%) in the IPL-only group. Both treatments were well tolerated and no patients withdrew from the study due to adverse effects of treatment. The study did not evaluate the efficacy of PDT in the absence of IPL therapy.

In some studies, a higher rate of adverse events had been reported. For example, a 2006 study by Wiegell and colleagues in Denmark evaluated patients 12 weeks after MAL-PDT ( $n=21$ ) or a control group ( $n=15$ ). (24) There was a 68% reduction from baseline in inflammatory lesions in the treatment group and no change in the control group ( $p=0.023$ ). However, all patients experienced moderate to severe pain after treatment and 7 of 21 in the treatment group (33% did not receive the second treatment due to pain).

Section summary: There are several small (i.e., fewer than 50 patients) randomized and non-randomized studies evaluating PDT for treatment of acne. These studies tended to find that PDT was at least as effective as a control condition. Some studies have reported higher rates of side effects associated with PDT therapy but others have not. A limitation of this body of evidence is that there are few studies evaluating PDT as the sole intervention, therefore more data are needed that isolate the impact of PDT before conclusions can be drawn about the efficacy of this therapy for treating acne.

#### Other dermatological indications

No controlled studies using FDA-approved photosensitizing agents were identified on PDT therapy for other dermatologic indications. Only case series were identified. Most, such as 2 on hidradenitis suppurativa (25, 26) and one on PDT for patients with interdigital mycoses (27) included fewer than 15 patients each. A large retrospective case series was published in 2011 by Xiao and colleagues in China. (28) A total of 642 patients with port-wine stains were treated with PDT; 507 were included in the



study, and the remainder were excluded because they had had previous treatment for their lesions or were lost to follow-up. After treatment, 26 (5.1%) of patients were considered to have complete clearing, 48 (9.5%) had significant (<75% to <100%) clearing, and 77 (15.2%) had moderate (<50% to <75%) clearing. This single uncontrolled study is insufficient to draw conclusions about the effect of PDT on health outcomes in patients with port-wine stains.

Section summary: There is insufficient evidence that PDT improves the net health outcome in patients with dermatological conditions other than those discussed in previous sections of the document.

## **Summary**

Photodynamic therapy (PDT) refers to light activation of a photosensitizing agent light to produce photochemical effects in the target area. The evidence to date suggests that the net health outcome is better with surgery than with PDT for treating basal cell carcinoma (BCC). For superficial BCC, the evidence is sufficient to conclude that PDT has a similar efficacy to cryotherapy and better cosmetic outcomes. In addition, there is evidence from RCTs that PDT is an effective treatment for selected patients with actinic keratoses of the face and scalp compared to placebo or cryotherapy. There is insufficient evidence that PDT improves the net health outcome for nodular BCC and other dermatological conditions compared to accepted treatments. Thus, PDT may be considered medically necessary for treating selected patients with actinic keratoses, superficial BCC, and Bowen's disease and is considered investigational for all other dermatologic indications.

## **Practice Guidelines and Position Statements**

The 2013 clinical practice guideline on basal cell skin cancers from the National Comprehensive Cancer Network (NCCN) states: "Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical...In patients with low-risk shallow cancers, such as SCC in situ (Bowen's disease) or low-risk superficial BCC, topical therapies such as 5-FU (*5-fluorouracil*), imiquimod, PDT (or fimer sodium or topical amino levulinic acid) or vigorous cryotherapy may be considered even though the cure rate may be lower." (29)

In 2008, the British Association of Dermatologists published guidelines containing the following statement on PDT: "Multicentre randomized controlled studies now demonstrate high efficacy of topical photodynamic therapy (PDT) for actinic keratoses, Bowen's disease (BD) and superficial basal cell carcinoma (BCC), and efficacy in thin nodular BCC, while confirming the superiority of cosmetic outcome over standard therapies. Long-term follow-up studies are also now available, indicating that PDT has recurrence rates equivalent to other standard therapies in BD and superficial BCC, but with lower sustained efficacy than surgery in nodular BCC. In contrast, current evidence does not support the use of topical PDT for squamous cell carcinoma...There is an accumulating evidence base for the use of PDT in acne, while detailed study of an optimized protocol is still required." (30)

The International Society for Photodynamic Therapy in Dermatology published consensus-based guidelines on the use of PDT for non-melanoma skin cancer in 2005. Based on both efficacy and cosmetic outcome, they recommended PDT as a first-line therapy for actinic keratosis. The guideline authors considered ALA to not have sufficient tissue penetration for nodular basal cell carcinoma. Based on 2 randomized, controlled and 3 open-label studies, it was concluded that MAL-PDT can be effective for nodular BCC lesions less than 2 mm in depth, if debulked. The guideline recommended PDT for superficial basal cell carcinoma as "a viable alternative when surgery would be inappropriate or the patient or physician wishes to maintain normal skin appearance." The report concluded that PDT is at least as effective as cryotherapy or 5-FU for Bowen's disease but that there is insufficient evidence to support the routine use of topical PDT for squamous cell carcinoma. (31)

## **Medicare National Coverage**

Centers for Medicare and Medicaid Services (CMS) coverage policy on treatment of actinic keratosis dated November 26, 2001, notes: "Various options exist on treating actinic keratosis. Clinicians should select an appropriate treatment based on the patient's history, the lesion's characteristics, and the

patient's preference for specific treatment....Less commonly performed treatments for actinic keratosis include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy....Medicare covers the destruction of actinic keratosis without restrictions based on lesion or patient characteristics." (32)

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### **Billing Coding/Physician Documentation Information**

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| <b>96567</b> | Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (eg, lip) by activation of photosensitive drug(s), each phototherapy exposure session |
| <b>J7308</b> | Aminolevulinic acid HCl for topical administration, 20%, single unit dosage form (354 mg)  |
| <b>J7309</b> | Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 g  |

In 2011, a HCPCS J code was introduced for Metvixia® (J7309).

### **Additional Policy Key Words**

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N/A

### **Policy Implementation/Update Information**

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8/15/07      New policy. This policy was implemented 8/15/2007.

3/1/08	Policy statement revised to indicate may be medically necessary for superficial basal cell carcinoma or Bowen's disease when surgery or radiation is contraindicated. Title change - "Treatment of Actinic Keratoses and Other Skin Lesions" replaced by "Dermatologic Applications."
3/1/09	No policy statement changes.
3/1/10	No policy statement changes.
3/1/11	No policy statement changes.
3/1/12	No policy statement changes.
3/1/13	No policy statement changes.
3/1/14	No policy statement changes.

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