Photodynamic Therapy for the Treatment of Actinic Keratoses and Other Skin Lesions

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I. Description

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 nondermatologic applications and are being proposed for use with dermatologic conditions such as actinic keratosis and nonmelanoma skin cancers.

For individuals who have nonhyperkeratotic actinic keratoses on the face or scalp who receive PDT, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses on the face or scalp compared with placebo or other active interventions. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have low-risk basal cell carcinoma (BCC) who receive PDT, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular BCC. In the small number of trials available, PDT was more effective than placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have squamous cell carcinoma in situ who receive PDT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events/cosmetic outcomes appeared to be better after PDT. Few RCTs compare PDT with surgery or radiotherapy; as a result, conclusions
cannot be drawn about PDT compared with these other standard treatments. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have nonmetastatic invasive squamous cell carcinoma who receive PDT, the evidence includes observational studies and a systematic review of observational studies. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, and treatment-related morbidity. Conclusions cannot be drawn from small, uncontrolled studies. RCTs are needed to determine the safety and efficacy of PDT for this condition. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acne who receive PDT, the evidence includes RCTs and systematic review. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. The available RCTs have not consistently found significantly better outcomes with PDT compared with comparison interventions and a meta-analysis did not find significantly better results with PDT versus placebo. Several trials have found that PTD is associated with high rates of adverse events leading to cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have noncancerous skin conditions, such as, hidradenitis suppurativa, mycoses, or port wine stains who receive PDT, the evidence includes case series and systematic reviews of uncontrolled series. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Photodynamic therapy (PDT) refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Two common photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester, methyl aminolevulinate (MAL). When applied topically, these agents pass readily through abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. 5-ALA and MAL are metabolized by underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404 to 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 disease, acne vulgaris, mycoses, hidradenitis suppurativa, and superficial and nodular basal cell carcinoma (BCC). 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 people 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). Available treatments for actinic keratoses can be divided into surgical and nonsurgical methods. Surgical treatments used to treat 1 or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodessication), and laser surgery. Nonsurgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (chemical peels), and dermabrasion. Topical treatments are generally used in patients with multiple lesions and involve extensive areas of skin. Under some circumstances, combinations treatments may be used.

Nonmelanoma skin cancers are the most common malignancies in the white population. BCC is most often found in light-skinned people and is the most common of the cutaneous malignancies. Although BCC 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 disease is an 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 nonmelanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-FU, 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 aminolevulinic acid (ALA), in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, was 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 nonhyperkeratotic actinic keratoses of the face and scalp.” The product is applied in the physician’s office. FDA product code: MVF.

A 5-aminolevulinic acid patch technology (5-ALA patch) is available outside of the United States through an agreement between Intendis (part of Bayer HealthCare) and Photonamic. The 5-ALA patch is not approved by FDA.

Another variant of photodynamic therapy for skin lesions is Metvixia® used with the Aktilite CL128 lamp, each of which received FDA approval in 2004. Metvixia® (Galderma, Switzerland; Photocure, Norway) consists of the topical application of methyl aminolevulinate (in contrast to ALA used in the Kerastick procedure), followed by exposure with the Aktilite CL128 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 (FDA product code: ONF), pulsed dye lasers, and potassium-titanyl-phosphate lasers have also been used. Metvixia® is indicated for the treatment of nonhyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used with lesion preparation (débridement using a sharp dermal curette) in the physician's office when
other therapies are unacceptable or considered medically less appropriate. FDA product codes: GEX and LNK.

II. Criteria/Guidelines

A. Photodynamic therapy is covered (subject to Limitations and Administrative Guidelines) for the treatment of:
   1. Nonhyperkeratotic actinic keratoses of the face and scalp
   2. Low-risk (e.g., superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated
   3. Bowen disease (squamous cell carcinoma in situ) only when surgery and radiation are contraindicated.

B. Surgery or radiation is the preferred treatment for low-risk basal cell cancer and Bowen disease (see Scientific Background Section). 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.

C. Photodynamic therapy typically involves 2 office visits: one to apply the topical aminolevulinic acid 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. Photodynamic protocols typically involve 2 treatments spaced a week apart; more than 1 treatment series may be required.

III. Limitations

A. Photodynamic therapy is not covered for the treatment of other dermatologic applications, including but not limited to, acne vulgaris, high-risk basal cell carcinomas, hidradenitis suppurativa, and mycoses, due to the lack of scientific evidence demonstrating improved health outcomes.

B. Photodynamic therapy as a technique of skin rejuvenation, hair removal, or other cosmetic indications is considered not medically necessary due to the lack of scientific evidence demonstrating improved health outcomes.

C. Photodynamic therapy for actinic keratoses is limited to use on nonhyperkeratotic lesions on the face and scalp. Use for hyperkeratotic lesions and use on other body areas is not covered due to the lack of scientific evidence demonstrating improved health outcomes.

IV. Administrative Guidelines

Precertification is not required for this service. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

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<th>CPT Code</th>
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<td>96567</td>
<td>Photodynamic therapy by external application of light to destroy</td>
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Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day

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V. Scientific Background

The evidence review was created in November 2001 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through October 26, 2016. Key literature is described next and focuses on studies evaluating U.S. Food and Drug Administration (FDA)–approved photosensitizing agents.

ACTINIC KERATOSES

Efficacy of Photodynamic Therapy Compared with Placebo
Several randomized controlled trials (RCTs) have been published. For example, in 2003, Pariser et al conducted a randomized, placebo-controlled trial of 80 patients with actinic keratoses. The authors reported that the complete response (CR) rate for the methyl aminolevulinate (MAL) group was 89% compared with 38% in the placebo group.
A 2009 double-blind RCT conducted in Germany by Hauschild et al evaluated photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) using a self-adhesive patch. Eligibility criteria included Caucasian patients, age 18 years and older with skin type I-IV (pale to olive complexion) and actinic keratoses on the head and of mild or moderate grade, as defined by Cockerell (maximum diameter, 1.8 cm; interlesional distance, 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 cm², and patients received 3 to 8 of them, depending on the 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. Complete clinical clearance rate on a per patient basis (all lesions cleared) was 62% (41/66) in the 5-ALA patch group and 6% (2/33) in the placebo patch group; there was a statistically significant difference favoring PDT.

**Efficacy of PDT compared with alternative intervention**

A number of published RCTs compare PDT with other therapies, and a systematic review of these studies has been published. Patel et al (2014) reviewed RCTs with at least 10 patients that addressed the efficacy of topical PDT compared with an alternative (ie, non-PDT) treatment of actinic keratosis. A total of 13 studies with 641 participants met the review’s inclusion criteria. Studies compared PDT with cryotherapy (n=6), fluorouracil (n=2), imiquimod (n=4), and carbon dioxide laser (n=1). Seven studies used ALA and the other 6 used MAL as the PDT sensitizer. Most studies focused on lesions located on the face or scalp. No studies in the review was double-blind. In 12 of the 13 studies, primary outcome was a measure related to the clearance rate of lesions. Data from 4 RCTs comparing PDT and cryotherapy were suitable for meta-analysis. The pooled lesion response rate 3 months after treatment was significantly higher with PDT than with cryotherapy (pooled relative risk [RR], 1.14, 95% confidence interval [CI], 1.11 to 1.18). Due to heterogeneity among the interventions, other data were not pooled.

Representative RCTs are described next.

In 2006, Morton et al published an industry-sponsored, 25-center, randomized, left-right comparison of single PDT and cryotherapy in 119 subjects with actinic keratoses on the face or scalp. At 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-CR were retreated after 12 weeks; a total of 108 (14.9%) of 725 lesions received a second PDT session; 191 (26.8%) of 714 lesions required a second cryotherapy treatment. At 24 weeks, 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 with 49.9% for cryotherapy.

In 2010, Szeimies et al in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch to cryotherapy. The study had the same eligibility criteria and primary outcome as the Hauschild et al study, previously described. 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 noninferiority of PDT versus cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT and cryotherapy. 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. Clearance rate was significantly higher in the 5-ALA patch group than either comparator group. Results were similar in the analysis of clearance rates on a per 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. Overall clearance rate on a lesion basis was still statistically higher in the 5-ALA patch group compared with placebo (in both studies) and 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.

A 2012 randomized pilot study from Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments. Patients with nonhyperkeratotic 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 CR in the PDT plus imiquimod group compared with 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 CR.

**Efficacy of Different PDT Protocols**

Several RCTs have compared different approaches to applying PDT in the treatment of actinic keratoses. No clear evidence of superiority of one approach over another emerges from this body of evidence, and some of the alternative approaches (e.g., daylight PDT) are not FDA-cleared.

**Section Summary: Actinic Keratoses on the Face or Scalp**

Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses on the face or scalp compared with placebo or other active interventions. There is insufficient evidence that any PDT protocol is superior to any other protocol.

**BASAL CELL CARCINOMA**

A 2007 Cochrane review evaluated surgical, destructive (including PDT), and chemical interventions for basal cell carcinoma (BCC). The authors concluded that surgery and radiotherapy appeared to be the most effective treatments, with the best results 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 among BCC subtypes.

In 2015, Wang et al published a meta-analysis of RCTs on PDT for treating BCC, both superficial and nodular. To be included in the systematic review, studies needed to include adults with 1 or more primary BCCs, randomize participants to PDT versus placebo or another treatment and report the complete clearance rate, recurrence rate, cosmetic outcomes, and/or adverse events. A total of 8 RCTs with 1583 patients, published between 2001 and 2013, met inclusion criteria. Three trials included patients with superficial BCC, 3 included patients with nodular BCC, and 1 included patients with both types of low-risk BCC. Four trials compared PDT and surgery, 2 compared PDT and cryotherapy, 1 compared PDT and pharmacologic treatment, and 1 was placebo controlled.

In meta-analysis of 7 studies, the estimated probability of complete clearance after treatment was similar in the PDT and non-PDT groups (RR=0.97, 95% CI, 0.88 to 1.06). In subgroup analyses by treatment type, PDT was associated with a significantly higher clearance rate only when compared with placebo. Surgery was associated with a significantly lower rate of recurrence compared with PDT, and there was no significant difference in recurrence rates when PDT was compared with cryotherapy and pharmacologic therapy. In meta-analyses of cosmetic outcomes at 1 year, there was a significantly higher probability of a good-to-excellent outcome with PDT than with surgery (RR=1.87; 95% CI, 1.54 to 2.26) or cryotherapy (RR=1.51; 95% CI, 1.30 to 1.76).

A 2016 meta-analysis by Zou et al identified 5 RCTs comparing PDT and surgical excision in patients with nodular BCC that had at least 3 months of follow-up. The rate of CR was significantly lower in the PDT group than in the surgical excision group at 1 year (RR=0.89; 95% CI, 0.80 to 0.99) and at 3 years (RR=0.73; 95% CI, 0.63 to 0.85); there were no significant differences in CR at 2, 4, or 5 years. The rate of recurrence was significantly higher in the PDT group than in the surgical excision group at all time points.

Representative RCTs are described next.

An industry-sponsored multicenter RCT was published in 2008 by Szeimies et al. The trial compared with 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 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 and 60% after surgery.

In 2007, Rhodes et al published 5-year follow-up of an industry-sponsored multicenter randomized study comparing MAL-PDT with surgery for nodular BCC. A total of 101 adults with previously untreated nodular BCC were randomized to receive MAL therapy or surgery. At 3 months, CR rates
did not differ between the 2 groups; however, at 12 months, CR rate had fallen from 91% to 83% in the MAL-PDT group, 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.

A 2016 noninferiority RCT by Roozeboom et al compared MAL-PDT to imiquimod cream and to fluorouracil cream in patients with superficial BCC. A total of 601 patients were randomized, 202 to MAL-PDT, 198 to imiquimod, and 201 to fluorouracil. A total of 490 (82%) patients completed the 1-year follow-up and 417 (69%) completed the 3-year follow-up. Median follow-up was 35 months. The estimated tumor-free survival rates at 3 years were 58% (95% CI, 47.8% to 66.9%) in the PDT group, 79.7% (95% CI, 71.6% to 85.7%) in the imiquimod group, and 68.2% (95% CI, 58.1% to 76.3%) in the fluorouracil group. Results of the noninferiority analysis suggested that imiquimod was superior to MAL-PDT and imiquimod was noninferior to MAL-PDT.

Section Summary: Basal Cell Carcinoma
Systematic reviews of RCTs have found that PDT does not appear to be as effective as surgery for superficial and nodular BCC. In the small number of trials available, PDT was more effective than placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery.

SQUAMOUS CELL CARCINOMA

Squamous Cell Carcinoma In Situ (Bowen Disease)
Bath-Hextall et al published a Cochrane review of interventions for cutaneous Bowen disease in 2013. Investigators identified 7 RCTs evaluating PDT; 4 of these compared 2 PDT protocols, 1 compared PDT with cryotherapy, 1 compared PDT with topical 5-fluorouracil (5-FU), and 1 compared PDT with both PDT and 5-FU. The authors did not pool study results.

The largest study (n=225) was a 3-arm trial published in 2006 by Morton et al. 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 disease. Unblinded assessment of lesion clearance found PDT to be noninferior to cryotherapy and 5-FU (93%, 86%, 83%, respectively) at 3 months and superior to cryotherapy and 5-FU (80% vs 67% vs 69%, respectively) at 12 months. Cosmetic outcome at 3 months was rated higher for PDT than the standard nonsurgical 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 with another intervention in patients with Bowen disease was published by Salim et al in 2003. Forty patients were randomly assigned to undergo either topical 5-FU or MAL therapy. Twenty-nine (88%) of 33 lesions in the PDT group cleared
completely compared with 22 (67%) of 33 lesions 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: Squamous Cell Carcinoma In Situ (Bowen Disease)**

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

**Nonmetastatic Invasive Squamous Cell Carcinoma**

In 2013, Lansbury et al published a systematic review of observational studies evaluating interventions for nonmetastatic cutaneous squamous cell carcinoma (SCC). Investigators identified 14 prospective studies evaluating PDT. Sample sizes ranged from 4 to 71 patients, and only 3 studies included more than 25 patients. These studies evaluated various PDT protocols. There was only 1 comparative study, and it compared 2 different PDT regimens. In meta-analysis, a mean of 72% of lesions had a CR to treatment (95% CI, 61.5% to 81.4%; \( I^2 = 71\% \)). Eight studies addressed recurrence rates in patients who were initial responders. In meta-analysis, pooled odds of recurrence was 26.4% (95% CI, 12.3% to 43.7%; \( I^2 = 72\% \)).

**Section Summary: Nonmetastatic Invasive Squamous Cell Carcinoma**

No RCTs evaluating PDT for treatment of nonmetastatic invasive SCC were found. There are a number of small, uncontrolled studies, and they represent insufficient evidence on which to draw conclusions about the efficacy and safety of PDT for patients with this condition.

**ACNE**

Several RCTs and a Cochrane review have been published. The Cochrane review, by Barbaric et al (2016), addressed a variety of light therapies for acne, including PDT. For studies on MAL-PDT, only data on investigator-assessed change in lesion counts were suitable for pooling. A meta-analysis of 3 studies on MAL-PDT did not find a significant difference from placebo on investigator-assessed change in inflamed lesion counts (mean difference [MD], -2.85; 95% CI, -7.51 to 1.81) or change in noninflamed lesion counts (MD = -2.01; 95% CI, -7.07 to 3.05). Reviewers concluded that there is a lack of high-quality evidence on light therapies for treating acne and low certainty in the usefulness of PDT.

In 2016, Pariser et al published a multicenter double-blind placebo-controlled, randomized trial evaluating MAL-PDT for severe facial acne. A total of 153 patients were randomized and included in the intention-to-treat analysis, 100 to MAL-PDT and 53 to a matching vehicle (ie, placebo) cream. All patients received 4 treatments, 2 weeks apart and were evaluated up to 12 weeks after the first treatment. One hundred twenty nine (84%) patients completed the study. The primary outcome (change from baseline in facial inflammatory lesion count at 12 weeks) was significantly lower in the MAL-PDT group (mean, -15.6) than the placebo group (mean, -7.8; \( p=0.006 \)). Change
in facial noninflammatory lesion count at 12 weeks did not differ significantly between groups (-11.8 vs -10.7; p=0.85). The most commonly reported adverse events were pain (n=17 [17%] in the MAL-PDT group vs 0 in the placebo group) and a skin burning cessation (n=15 [15%] in the PDT group vs 5 [9%] in the placebo group). Most adverse events were mild-to-moderate, although 12 patients in the MAL-PDT group dropped out due to treatment-related adverse events.

A randomized, single-blind, split-faced trial was published in 2010 by Orringer et al. The trial included 44 patients with facial acne. A randomly selected side of the face received ALA-PDT and the other side went untreated. Patients received up to 3 treatments at intervals of approximately 2 weeks. Twenty-nine (66%) patients completed the 16-week study. For most outcomes, there were no statistically significant differences between treated and untreated sides of the face. This included change from baseline to 16 weeks in mean number of inflammatory papules, pustules, cysts, closed comedones, or open comedones. There was a significantly greater reduction in erythematous macules on the treated (mean reduction, 5.9) than the untreated side of the face (mean reduction, 2.5; p=0.04). In addition, improvement in mean Leed’s Acne Severity Grading score was significantly greater on the treated side (-1.07) than on the untreated side of the face (-0.52; p=0.001). There were few adverse effects, which tended to be mild. A limitation of the study was the high dropout rate.

In 2013, Mei et al in China published an RCT of 41 patients with moderate-to-severe facial acne. The trial evaluated the additional value of ALA PDT in patients treated with IPL. Twenty-one patients were randomized to 4 weeks of treatment with IPL plus PDT, and 20 patients were randomized to IPL plus placebo PDT. Mean reduction in both inflammatory and noninflammatory lesions was significantly greater in the IPL plus PDT group than in the IPL-only group at the 4-, 8-, and 12-week follow-ups. For example, in the IPL plus PDT group, the mean number (SD) of noninflammatory acne lesions decreased from 31.3 (7.1) at baseline to 14.0 (6.2) at 12-week follow-up. In the IPL-only group, the mean number (SD) of noninflammatory lesions decreased from 28.2 (4.1) at baseline to 18.6 (3.1) at 12 weeks (p<0.05). An improvement of 75% to 100% in all lesions was attained by 13 patients (62%) in the IPL plus PDT group and by 3 patients (15%) in the IPL-only group. Both treatments were well tolerated, and no patient withdrew from the trial due to adverse effects of treatment. The trial did not evaluate the efficacy of PDT in the absence of IPL therapy.

In some studies, a higher rate of adverse events with PDT has been reported. For example, a 2006 study by Wiegell et al in Denmark evaluated patients 12 weeks after MAL-PDT (n=21) or a control group (n=15). 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 (33%) of 21 in the treatment group did not receive the second treatment due to pain.

Section Summary: Acne
Several RCTs and a Cochrane review have evaluated PDT for treatment of acne. The Cochrane review did not conduct meta-analyses on most outcomes. For the pooled analysis of studies comparing MAL-PDT and placebo, reviewers did not find a significant difference in investigator
assessment of lesion change. The available RCTs have not consistently found significantly better outcomes with PDT than with comparator interventions. Several trials found that PTD was associated with high rates of adverse events leading to cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions.

**OTHER DERMATOLOGIC CONDITIONS**

No controlled studies using FDA-approved photosensitizing agents for PDT in other dermatologic indications were identified. Only case series were identified, including series on PDT for hidradenitis suppurativa and PDT for interdigital mycoses. Most series had small sample sizes (eg, <25 patients). There were a few systematic reviews. For example, a 2015 systematic review by Mostafa and Tarakji of studies evaluating PDT for oral lichen planus identified 5 case reports and a 2015 systematic review by Yazdani Abyaneh et al identified 15 case series (total N=223) on PDT for actinic cheilitis. In 2011, Xiao et al in China published a large retrospective case series. A total of 642 patients with port wine stains were treated with PDT; 507 were included in the study, and the rest were excluded because they had had previous lesion treatments or had been lost to follow-up. After treatment, 26 patients (5.1%) 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: Other Dermatologic Conditions**

There is insufficient evidence that PDT improves the net health outcome in patients with these miscellaneous dermatologic conditions (eg, hidradenitis suppurativa, mycoses, port wine stains).

**SUMMARY OF EVIDENCE**

The evidence for photodynamic therapy (PDT) in individuals who have nonhyperkeratotic actinic keratoses includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses on the face or scalp compared with placebo or other active interventions. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have low-risk basal cell carcinoma (BCC) includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular BCC. In the small number of trials available, PDT was more effective than placebo. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have squamous cell carcinoma in situ includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events/cosmetic outcomes appeared to be better after
PDT. Few RCTs compare PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these other standard treatments. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have nonmetastatic invasive squamous cell carcinoma includes observational studies and a systematic review of observational studies. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, and treatment-related morbidity. Conclusions cannot be drawn from small, uncontrolled studies. RCTs are needed to determine the safety and efficacy of PDT for this condition. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in individuals who have acne includes RCTs and other controlled trials. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. The available RCTs have not consistently found significantly better outcomes with PDT compared with comparison interventions and a meta-analysis did not find significantly better results with PDT versus placebo. Several trials have found that PTD is associated with high rates of adverse events leading to cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in individuals who have noncancerous skin conditions, such as, hidradenitis suppurativa, mycoses, or port wine stains, includes case series and systematic reviews of uncontrolled series. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Canadian Dermatology Association
In 2015, the Canadian Dermatology Association published the following recommendations on dermatologic use of PDT:

- Basal cell carcinoma: PDT may be used for superficial BCC when nonsurgical treatment is desired, there are multiple carcinomas, and when cosmetic outcome is important. PDT is not appropriate for nodular BCC.
- Actinic keratosis: PDT is among the recommended treatment options for actinic keratosis, although the guidance includes the statement that cryosurgery or a surgical procedure are preferred for isolated actinic keratosis and hypertonic lesions.

National Comprehensive Cancer Network
The clinical practice guideline on basal cell skin cancers (v.1.2016) 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. Superficial therapies include topical treatment with 5-FU [5-fluorouracil] or imiquimod, photodynamic therapy (PDT) and cryotherapy.” In addition, NCCN concluded that, although the cure rate may be lower, for patients with low-risk superficial BCC where surgery or radiation is contraindicated or impractical, first-line treatment with alternative therapies such as PDT, cryotherapy, 5-FU, or imiquimod may be considered.

**British Association of Dermatologists**

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.”

**International Society for Photodynamic Therapy in Dermatology**

The International Society for Photodynamic Therapy in Dermatology (ISPTD) published consensus-based guidelines on the use of PDT for nonmelanoma skin cancer in 2005. Based on both efficacy and cosmetic outcome, ISPTD recommended PDT as a first-line therapy for actinic keratosis. The guideline authors considered ALA not to have sufficient tissue penetration for nodular BCC. 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 BCC as “a viable alternative when surgery would be inappropriate or the patient or physician wishes to maintain normal skin appearance.” The guideline concluded that PDT is at least as effective as cryotherapy or 5-FU for Bowen disease but that there is insufficient evidence to support the routine use of topical PDT for squamous cell carcinoma.

**Medicare National Coverage**

Centers for Medicare and Medicaid Services 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.”

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02647151</td>
<td>Efficacy and Safety of Treatment of Actinic Keratoses With Photodynamic Therapy Between MAL Cream and ALA Gel</td>
<td>50</td>
<td>Mar 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT02644187</td>
<td>Pain Relief During Photodynamic Therapy for Actinic Keratoses With a New Irradiation Protocol</td>
<td>30</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT02367547†</td>
<td>Superficial Basal Cell Cancer’s Photodynamic Therapy: Comparing Three Photosensitises: HAL and BF-200 ALA Versus MAL</td>
<td>99</td>
<td>Dec 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
†Denotes industry-sponsored or cosponsored trial.

**VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

**VI. References**


