



Louisiana

Dermatologic Applications of Photodynamic Therapy

Policy # 00098

Original Effective Date: 06/05/2002

Current Effective Date: 12/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider photodynamic therapy (PDT) to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered for any of the following conditions:

- Non-hyperkeratotic actinic keratosis of the face and scalp; or
- Low-risk (e.g. superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated; or
- Bowen disease (squamous cell carcinoma in situ) only when surgery and radiation are contraindicated.

When Services Are Not Covered

The use of photodynamic therapy (PDT) as a technique of skin rejuvenation, hair removal, or other cosmetic indications is **not covered**. **

When Services Are Considered Investigational

Note: Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers photodynamic therapy (PDT) for other dermatologic applications, including, but not limited to the following to be **investigational**.*

- Acne vulgaris
- High-risk basal cell carcinomas
- Hidradenitis suppurativa
- Mycoses

Based on the review of available data, the Company considers the use of photodynamic therapy (PDT) when patient selection criteria are not met to be **investigational**.*

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Background/Overview

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, these agents 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. Photodynamic therapy can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results. Photodynamic therapy 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 (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 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 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 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-FU, imiquimod, and cryotherapy. Poor cosmesis resulting from surgical procedures and skin irritation induced by topical agents can be significant problems.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. 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. FDA product code: MVF.

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^{®‡} used with the Aktelite CL128 lamp, each of which received FDA approval in July 2004. Metvixia (Galderma, SA, Switzerland; PhotoCure, Norway) consists of the topical application of MAL in contrast to ALA used in the Kerastick procedure, followed by exposure with the Aktelite 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. FDA product codes: GEX and LNK.

Centers for Medicare and Medicaid Services (CMS)

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."

Rationale/Source

The policy is updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through December 6, 2015. Key literature is described next and focuses on studies evaluating U.S. 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

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that the complete response (CR) rate for the MAL group was 89% compared with 38% in the placebo group.

A 2009 double-blind RCT conducted in Germany by Hauschild et al evaluated PDT with 5-ALA using a self-adhesive patch. 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 cm², 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.

Efficacy of PDT Compared With an 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, in 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. None of the included studies were 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 photodynamic treatment and cryotherapy in 119 subjects with actinic keratoses on their faces or scalps. 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 noncomplete 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.

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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, 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 noninferiority 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 with 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 PDT patches used in the German studies have not been cleared by FDA for use in the United States.

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 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.

Efficacy of Different PDT Protocols

Several RCTs have compared different approaches to applying PDT in the treatment of actinic keratosis. No clear evidence of superiority of 1 approach over another emerges from this body of evidence, and some of the alternative approaches, eg, daylight PDT, are not FDA-cleared.

Section Summary

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.

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Basal Cell Carcinoma

A 2007 Cochrane review evaluated surgical, destructive (including PDT), and chemical interventions for BCC. 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.

More recently, 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. In a pooled subgroup analyses by tumor type, results were similar except that the upper CI for nodular BCC just crossed 1 and was thus not statistically significant, and the upper CI for superficial BCC was just below 1 and thus was statistically significant. For nodular BCC, the RR (95% CI) was 0.93 (0.85 to 1.01) and for superficial BCC, the RR (95% CI) was 0.93 (0.88 to 0.98). Only 1 study on superficial BCC contributed data to this subgroup analysis.

When data from 6 studies were pooled, there was not a statistically significant difference in the recurrence rate at 1 year in the PDT and non-PDT groups. Surgery was associated with a significantly lower rate of recurrence compared with PDT, and there was not a 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 compared 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 2012 systematic review by Roozeboom et al focused only on superficial BCC and included both randomized and nonrandomized trials. A total of 16 studies were identified that evaluated PDT for treating BCC; 6 studies were RCTs. There was significant heterogeneity among studies ($I^2=94%$, $p<0.001$). A pooled estimate of CR after treatment with PDT in 13 studies (PDT arms only) was 79% (95% 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.

Representative RCTs are described next.

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An industry-sponsored multicenter RCT was published in 2008 by Szeimies et al. This trial compared 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 in comparison with 60% following 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.

An observational study published in 2011 by Lindberg-Larsen provides additional data on recurrence rates after treatment with PDT. The study included 90 patients with 157 lesions (n=111 superficial BCC, n=40 nodular BCC, and n=6 unknown) who 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. 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 (eg, at 12 months, recurrence rates were 28% and 13%, respectively, $p=0.008$). Although this study found higher rates of recurrence for nodular versus superficial BCC, the study was not randomized, and thus, 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. In addition, the number of nodular BCCs was relatively small and findings may not be robust.

Section Summary

Systematic reviews of RCTs have found that PDT does not appear to be as effective as surgery for superficial and nodular BCC. These systematic reviews have not found statistically significant differences in clinical response rates with PDT compared with cryotherapy for BCC, which suggests, but does not conclusively demonstrate, similar efficacy. Cosmetic outcomes have been better after PDT compared with surgery and cryotherapy. In the small number of trials available, PDT was more effective than placebo.

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Squamous Cell Carcinoma

Squamous Cell Carcinoma In Situ (Bowen Disease)

Bath-Hextall et al published a Cochrane review of interventions for cutaneous Bowen disease (BD) 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 study with the largest sample size (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 BD. 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%, 67%, 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 BD 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, as 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

Randomized controlled trials have found that PDT has similar or greater efficacy compared with cryotherapy and 5-FU for patients with BD. 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 BD; 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 SCC. The investigators identified 14 prospective studies evaluating PDT. 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% $I^2=72%$).

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Section Summary

No RCTs evaluating PDT for treatment of nonmetastatic 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-RCTs have been published. A randomized single-blind split-faced study was published in 2010 by Orringer et al and was U.S.-based. 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.

In 2012, Shaaban et al in Egypt published a nonrandomized split-faced study of 30 patients with inflammatory and nodulocystic acne. In each patient, the right side was treated with a monthly session of ALA-PDT plus IPL treatment, and the left side was treated with IPL only. From baseline to 1-month follow-up, mean (SD) count of facial acne lesions decreased from 9.55 (1.1) to 2.1 (1.68) in the combined treatment group, and from 9.8 (4.8) to 5.01 (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 et al in China published a parallel group RCT that included 41 patients with moderate to severe facial acne. The trial evaluated the additional value of ALA PDT in patients treated with 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 noninflammatory lesions was significantly greater in the IPL plus PDT group compared with 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 noninflammatory 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 noninflammatory 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 75a% to 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.

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In some studies, a higher rate of adverse events had 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 of 21 in the treatment group (33% did not receive the second treatment due to pain).

Section Summary

There are several small (ie, <50 patients) randomized and nonrandomized 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 including series on PDT for hidradenitis suppurativa and PDT for interdigital mycoses. Most series had small sample sizes (fewer than 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 systemic review by Yazdani Abyaneh et al identified 15 case series (total N=223) on PDT for actinic cheilitis. A large retrospective case series was published in 2011 by Xiao et al in China. A total of 642 patients with port-wine stains were treated with PDT; 507 were included in the study, and the remainder was excluded because they had had previous treatment for their lesions or was 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 (eg, hidradenitis suppurativa, mycoses, port wine stains).

Summary

The evidence for PDT in individuals who have nonhyperkeratotic actinic keratoses includes 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.

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The evidence for PDT in individuals who have low-risk 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. These systematic reviews have not found statistically significant differences in clinical response rates with PDT compared with cryotherapy for BCC, which suggests, but does not conclusively demonstrate, similar efficacy. Cosmetic outcomes have been better after PDT than after surgery or cryotherapy. In the small number of trials available, PDT was more effective than placebo. 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 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. Several small (ie, <50 patients) randomized and nonrandomized studies have evaluated 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 adverse events associated with PDT therapy, while others have not. A limitation of this body of evidence is that few studies have evaluated 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in individuals who have 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.

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05/16/2002 Medical Policy Committee review

06/05/2002 Managed Care Advisory Council approval

05/04/2004 Medical Director review

05/18/2004 Medical Policy Committee review. Format revision. No substance change to policy.

06/28/2004 Managed Care Advisory Council approval

06/07/2005 Medical Director review

06/21/2005 Medical Policy Committee review. Clinical criteria revision. Added coverage eligibility and investigational statement for Metvixia. Added acne, mycoses, and hidradenitis suppurativa as investigational indications for aminolevulinic acid.

07/15/2005 Managed Care Advisory Council approval

06/05/2006 Medical Director review

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06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, No change in policy statement
11/07/2007	Medical Director review
11/15/2007	Medical Policy Committee approval. Title changed and policy replaced.
12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009	Medical Policy Committee approval
12/16/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility
11/04/2010	Medical Policy Committee approval
11/16/2010	Medical Policy Implementation Committee approval. Removed the restriction of face and scalp from the criteria for treatment of non-hyperkeratotic actinic keratoses.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/23/2013	Updated coverage eligibility statement when patient selection criteria not met
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. "for other dermatologic applications, including, but not limited to the following" was added to the investigational statement.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Changes to language in policy statements: Superficial or nodular changed to Low-risk and non-superficial changed to high-risk.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2018	Coding update
Next Scheduled Review Date:	12/2018

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Code Type	Code
CPT	96567 Codes to be added eff 1/1/2018: 96573, 96574
HCPCS	J7308, J7309 Code to be added eff 1/1/2018: J7345
ICD-10 Diagnosis	A00.0 B48.1 B48.8 C44.00-C44.09 C50.011-C50.019 C84.00-C84.09 D04.0-D04.9 D06.0-D06.9 L11.8-L11.9 L57.0 L57.2 L57.4 L66.4 L70.0-L70.9 L72.0 L72.2-L72.9 L73.0 L73.2 L74.52 L74.8 L75.0-L75.1 L75.8 L82.0 L85.8 L87.1 L87.8 L90.3-L90.4 L90.8 L91.8 L92.2 L94.8 L98.5-L98.6 L99 N49.0

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- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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