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Dermatologic Applications of Photodynamic Therapy

Policy # 00098

Original Effective Date: 06/05/2002

Current Effective Date: 12/18/2013

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 to be **eligible for coverage**.

Patient Selection Criteria

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

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

When Services Are Not Covered

The use of photodynamic therapy 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 the use of photodynamic therapy as treatment for the following conditions to be **investigational**:*

- Acne vulgaris
- Non-superficial basal cell carcinomas
- Hidradenitis suppurativa
- Mycoses

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

Background/Overview

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.

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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 (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 masoprolac 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. 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 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.

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.



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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 Aktilite 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 Aktilite 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.

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 was created in 2001 and was updated regularly with searches of the MEDLINE database. The most recent literature search was for the period December 2011 through November 2012. Key literature is described below and focused on studies evaluating FDA-approved photosensitizing agents.

Actinic Keratoses

Multiple randomized controlled trials (RCTs) evaluating PDT for actinic keratoses have been published. Piacquadio and colleagues published findings in 2004 of data submitted for FDA approval of Levulan Kerastick. Two similarly designed studies randomly assigned 243 patients with 4 to 15 non-hyperkeratotic actinic keratoses on the face or scalp to receive active or placebo PDT. From 63% to 69% of patients in the active treatment group reported complete response at 8 weeks, compared to 13% to 14% in the placebo group. Patients who were not complete responders after 8 weeks had retreatment of the persistent lesions. Among these patients, 43% showed a complete response after a second treatment, compared to only 4% in the placebo group. This clinical trial has since been published in the peer-reviewed literature. In a 2003 trial, Pariser and colleagues conducted a randomized, placebo-controlled trial of 80 patients with actinic keratoses. The authors reported that the complete response rate for the 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. Eligibility criteria included Caucasian patients, age



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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). Women of child-bearing potential were excluded, as were individuals who had used treatments or had other conditions that might interfere with study treatments. 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; 4 patients who withdrew from the study were excluded. 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, a statistically significant difference favoring PDT.

Several trials have compared PDT to cryotherapy for treating actinic keratoses. 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. At a 12-week follow-up, PDT resulted in a significantly larger 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). Thus, approximately 12% more cryotherapy sessions were required to achieve comparable outcomes to PDT. 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. Subjects perceived PDT to have better efficacy and cosmetic outcome.

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. 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 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%. Cosmetic outcome was rated by a blinded investigator at each 3-month visit and categorized as excellent, good, fair, or poor. At 1 year, on a per lesion basis, 210 (53%) in the cryosurgery group, 422 (82%) in the 5-ALA patch group, and 47 (90%) in the placebo patch group were categorized as having an excellent cosmetic appearance by the Investigators

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(statistically better cosmetic appearance in the cryosurgery versus the 5-ALA groups). In addition, 1 year after treatment, 94% of the lesions in the 5-ALA group and only 68% of the lesions in the cryosurgery group were normally pigmented; this difference was statistically significant. 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 MAL alone, imiquimod alone, and the combination of the 2 treatments. Patients with non-hyperkeratotic actinic keratoses 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.

Conclusions: 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 cryotherapy. 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 would need 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. 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. 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. 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,



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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. 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.

Conclusions: 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

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. 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. After a median follow-up of 28 months, there were 21 failures (recurrent tumor) after PDT and 2 after surgical excision. A Kaplan-Meier survival analysis estimated the 3-year cumulative incidence of failure as 30.3% in the PDT group and 2.3% in the surgery group ($p<0.001$).

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. A total of 101 adults with previously untreated nodular



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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.

In 2010, Foley and colleagues reported on a pair of industry-sponsored single-blind RCTs evaluating MAL-PDT versus placebo for treating primary nodular BCC (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. Clinical response was categorized as (CR disappearance of lesion), partial response ([PR] at least 50% reduction in the longest diameter of the lesion), no response (less than 50% reduction in the longest diameter) or progression (at least 20% increase in the longest diameter). 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 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.

In 2011, Lindberg-Larsen et al. published an uncontrolled retrospective study evaluating recurrence of BCC after treatment with PDT. A total of 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

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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.

Conclusions: 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 in situ (Bowen's disease)

In 2003, Salim and colleagues published the results of a trial that randomly assigned 40 patients with Bowen's disease 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.

A 2006 multicenter randomized trial with 225 patients (from 40 hospital outpatient dermatology clinics in 11 European countries) compared MAL with cryotherapy or 5-FU for the treatment of Bowen's disease (squamous cell carcinoma in situ) with lesions on the face or scalp (23%), neck, or trunk (12%), or extremities (65%). 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.

Conclusions: 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.

Acne

Literature on the use of PDT for acne consists of several small (n=25 or fewer per group) RCTs from outside of the United States. Studies varied in the comparison intervention used and several evaluated combined treatments. Moreover, some studies reported significant adverse effects associated with PDT treatment. 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). There was a 68% reduction from baseline in inflammatory lesions in the treatment group and no change in the control group ($p=0.23$). 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).



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Several split-face studies have been conducted. A 2010 single-blind RCT, for example, 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) 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 and colleagues in Egypt conducted a split-face study that included 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 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.

Conclusions: There are several small RCTs and non-randomized controlled studies evaluating PDT for treating acne; most have been performed outside of the United States. The studies have varied in the comparison intervention used and several evaluated combined treatments. Moreover, some studies reported significant adverse effects associated with PDT treatment. There remains insufficient evidence to draw conclusions about the effect of PDT on the net health outcome in patients with 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 and one on PDT for patients with interdigital mycoses included fewer than 15 patients each. A large retrospective case series was published in 2011 by Xiao and colleagues in China. 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.

Conclusions: 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.



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Summary

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 BCC and that PDT for superficial BCC 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.

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Coding

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HCPSCS	J7308, J7309
ICD-9 Diagnosis	173.0 thru 173.9, 232.0 thru 232.9, 702.0
ICD-9 Procedure	No code

Policy History

Original Effective Date: 06/05/2002

Current Effective Date: 12/18/2013

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
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.
1/23/2013 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.

Next Scheduled Review Date: 12/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. in accordance with nationally accepted standards of medical practice;
- 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
- 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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