Dermatologic Applications of Photodynamic Therapy
Corporate Medical Policy

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Description/Summary

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 keratoses and nonmelanoma skin cancers.

There is evidence from randomized controlled trials (RCTs) that PDT is an effective treatment for selected patients with actinic keratoses of the face and scalp compared with placebo or cryotherapy. The evidence to date suggests that PDT is less effective than surgery and radiotherapy and of similar efficacy to cryotherapy for treating low-risk basal cell carcinoma (BCC) (eg, superficial and nodular). Moreover, the evidence suggests that cosmetic outcomes are better after PDT compared with surgery and cryotherapy. Evidence from RCTs suggests that, in patients with Bowen disease (BD), PDT has similar or higher efficacy compared with cryotherapy and 5-fluorouracil (5-FU), and better cosmetic outcomes. Thus, PDT may be considered medically necessary for treating nonhypertrophic actinic keratoses of the face and scalp and for treating low-risk BCC and BD when surgery and radiation are contraindicated.

There is insufficient evidence that PDT improves the net health outcome for other dermatologic conditions compared with accepted treatments, and therefore they are considered investigational.

Policy

When a service may be considered medically necessary

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

- Nonhyperkeratotic actinic keratoses of the face and scalp.
- Low-risk (eg superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated.
• Bowen disease (squamous cell carcinoma in situ) only when surgery and radiation are contraindicated.

When a service is considered investigational

Photodynamic therapy is considered investigational for other dermatologic applications, including, but not limited to, acne vulgaris, high-risk basal cell carcinomas, hidradenitis suppurativa and mycoses.

When a service is considered not medically necessary

Photodynamic therapy as a technique of skin rejuvenation, hair removal, or other cosmetic indications is considered not medically necessary.

Policy Guidelines

Surgery or radiation is the preferred treatment for low-risk basal cell cancer and Bowen disease (see Rationale 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.

Coding Information

Photodynamic therapy typically involves 2 office visits: one to apply the topical ALA and a second visit to expose the patient to blue light. The second physician office visit, performed solely to administer blue light, should not warrant a separate Evaluation and Management CPT code. Photodynamic protocols typically involve 2 treatments spaced a week apart; more than 1 treatment series may be required.

Click the links below for attachments, coding tables & instructions.

Attachment I- Code Table & Instructions

Background

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 BD, acne vulgaris, mycoses, hidradenitis suppurativa, and superficial and nodular 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 generally 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-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.

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. BD 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.

Rationale/Scientific Background

The policy was created in 2001 and was updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through December 15, 2014. 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 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 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,2 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, leaving 283 patients. The rate of complete clearance of all lesions was 67% (86/129) in the 5-ALA group, 52% (66/126) in the cryosurgery group, and 12% (5/43) in the placebo group. 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 per lesion basis. The 360 patients with at least 1 lesion cleared at 12 weeks were followed 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 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. 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 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 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.

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 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 among BCC subtypes.

More recently, in 2014, 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.

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.

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**
RCTs 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 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 a variety of different PDT protocols. There was only 1 comparative study, and this study 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%; I²=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%; I²=72%).

**Section Summary**
No RCTs evaluating PDT for treatment of nonmetastatic invasive SCC were 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 trial was published in 2010 by Orringer et al in the United States. The trial included 44 patients with facial acne. A randomly selected side of the face received the intervention (combined treatment with topical 5-ALA and 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 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 compared with the untreated side of the face (a mean reduction of 5.9 and 2.5, respectively; p=0.04). In addition, improvement in mean Leed acne severity score was significantly greater on the treated side of the face (-1.07) compared with 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 dropout 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 intense pulsed-light (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 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 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 (SD) number 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 (SD) number 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**
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 adverse effects associated with PTD 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 Dermatologic Indications**
No controlled studies using FDA-approved photosensitizing agents for PDT in other dermatologic indications were identified. Only case series were identified. Most, such as 2 studies of hidradenitis suppurativa and 1 on PDT for patients with interdigital
mycoses, included fewer than 15 patients each. 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 treatment for their lesions or were 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
There is insufficient evidence that PDT improves the net health outcome in patients with dermatologic conditions other than those discussed in previous sections of the document.

Summary of Evidence
There is evidence from randomized controlled trials (RCTs) that photodynamic therapy (PDT) is an effective treatment for selected patients with actinic keratoses of the face and scalp compared with placebo or cryotherapy. The evidence to date suggests that PDT is less effective than surgery and radiotherapy and of similar efficacy to cryotherapy for treating low-risk basal cell carcinoma (BCC) (eg, superficial and nodular). Moreover, the evidence suggests that cosmetic outcomes are better after PDT compared with surgery and cryotherapy. Evidence from randomized controlled trials RCTs suggests that, in patients with Bowen disease (BD), PDT has similar or higher efficacy compared with cryotherapy and 5-fluorouracil, and better cosmetic outcomes. Thus, PDT may be considered medically necessary for treating non-hypertonic actinic keratoses of the face and scalp, and for treating low-risk BCC and BD when surgery and radiation are contraindicated.

There is insufficient evidence that PDT improves the net health outcome for other dermatologic conditions compared with accepted treatments, and therefore they are considered investigational.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
The v1.2015 clinical practice guideline on basal cell skin cancers from the National Comprehensive Cancer Network (NCCN) states: “Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical. Superficial therapies include topical treatment with 5-FU or imiquimod, photodynamic therapy (PDT) and cryotherapy.” Moreover, the guideline describes BCC histologic subtypes that have low-risk of recurrence as nodular, superficial, and other nonaggressive growth patterns, such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus. For patients with low-risk BCCs, the guideline states, “...topical therapies such as 5-FU (5-fluorouracil), imiquimod, PDT (eg, porfimer sodium or topical amino levulinic acid) or vigorous cryotherapy may be considered even though the cure rate may be lower.”

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.

The International Society for Photodynamic Therapy in Dermatology published consensus-based guidelines on the use of PDT for nonmelanoma skin cancer in 2005. Based on both efficacy and cosmetic outcome, they recommended PDT as a first-line therapy for actinic keratosis. The guideline authors considered ALA to not have sufficient tissue penetration for nodular 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 report 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.

Reference Resources


**Document Precedence**

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer’s benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member’s contract/employer benefit plan language takes precedence.

**Audit Information**

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.

** Administrative and Contractual Guidance**

**Benefit Determination Guidance**

Prior approval is required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

An approved referral authorization for members of the New England Health Plan (NEHP) is required. A prior approval for Access Blue New England (ABNE) members is required. NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member’s health plan.
Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member’s benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member’s benefit.

Coverage varies according to the member’s group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict. If the member receives benefits through an Administrative Services only (ASO) only group, benefits may vary or not apply. To verify benefit information, please refer to the member’s employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

| 08/2016 | New policy. Adoption of BCBSA MPRM# 2.01.44. |

Health Care Procedure Coding System (HCPCS) codes related to chemotherapy drugs, drugs administered other than oral method, and enteral/parenteral formulas may be subject to National Drug Code (NDC) processing and pricing. The use of NDC on medical claims helps facilitate more accurate payment and better management of drug costs based on what was dispensed and may be required for payment. For more information on BCBSVT requirements for billing of NDC please refer to the provider portal [http://www.bcbsvt.com/provider-home](http://www.bcbsvt.com/provider-home) latest news and communications.

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by BCBSVT Medical Directors Date Approved

Joshua Plavin, MD
Senior Medical Director
Chair, Health & Payment Policy Committee

Robert Wheeler MD
Chief Medical Officer
Attachment I
Code Table & Instructions

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<tr>
<th>Code Type</th>
<th>Number</th>
<th>Brief Description</th>
<th>Policy Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96567</td>
<td>Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (e.g., lip) by activation of photosensitive drug(s), each phototherapy exposure session</td>
<td>Prior Approval Required</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J7308</td>
<td>Aminolevulinic hydrochloric acid for topical administration, 20%, single unit dosage form (354 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J7309</td>
<td>Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram</td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>L57.0</td>
<td>Actinic keratosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C44.0-C44.9</td>
<td>Other malignant neoplasm of skin code range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D04.0-D04.9</td>
<td>Carcinoma in situ of skin code range</td>
<td></td>
</tr>
</tbody>
</table>

**Type of Service**: Medical  
**Place of Service**: Office, Outpatient