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# Dermatologic Applications of Photodynamic Therapy (PDT)

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| Related Policies (if applicable) |
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## Disclaimer

**Carefully check state regulations and/or the member contract.**
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Coverage

**This medical policy does NOT address Gender Reassignment Services (Transgender Services). This medical policy IS NOT TO BE USED for Gender Reassignment Services. Refer to SUR717.001, Gender Assignment Surgery and Gender Reassignment Surgery and Related Services**

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

- Nonhyperkeratotic actinic keratoses of the face and scalp;
- Nonhyperkeratotic actinic keratoses of the upper extremities;
- Low-risk (e.g., superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated;
- Cutaneous squamous cell carcinoma in situ (Bowen disease) only when surgery and radiation are contraindicated.

Photodynamic therapy **is considered experimental, investigational and/or unproven** for other dermatologic applications, including but not limited to:

- Acne vulgaris;

- High-risk basal cell carcinomas;
- Hidradenitis suppurativa;
- Mycoses;
- Nonhyperkeratotic actinic keratoses (AK) for all other body parts (excluding the face, scalp, and upper extremities).

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

## Policy Guidelines

Surgery and radiation are the preferred treatments 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 than surgery or radiation.

Photodynamic therapy typically involves 2 office visits: 1 to apply the topical aminolevulinic acid and a second visit to expose the individual 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.

Based on characteristics of individuals enrolled in randomized controlled trials, 4 or more lesions per site (face, scalp, or upper extremities) is an appropriate threshold for use of photodynamic therapy for individuals with nonhyperkeratotic actinic keratosis.

## Description

**Photodynamic Therapy (PDT)**

Photodynamic therapy (PDT) refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Two common photosensitizing agents are 5-aminolevulinic acid (ALA) and its methyl ester, methyl aminolevulinate. When applied topically, these agents pass readily through abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. The agents ALA and methyl aminolevulinate are metabolized by underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404 to 420 nm and 635 nm) 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 (AKs).

**Regulatory Status**

In 1999, Levulan® Kerastick™, a topical preparation of ALA, in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of nonhyperkeratotic AKs of the face and scalp. In 2018, the indication was expanded to include nonhyperkeratotic AKs of the upper extremities. The product is applied in the physician's office.

FDA product code: MVF.

In 2016, the FDA approved Ameluz® (aminolevulinic acid hydrochloride) gel, 10% (BF-200 ALA; Biofrontera AG) in combination with PDT using BF-RhodoLED lamp, to be used for the lesion-directed and field-directed treatment of AKs of mild-to-moderate severity on the face and scalp. The treatment is to be administered by a healthcare provider.

ALA patch technology is available outside of the US through an agreement between Intendis (now Bayer HealthCare) and Photonamic. The ALA patch is not approved by the FDA.

Another variant of PDT for skin lesions is Metvixia® used with the Aktilite CL128 lamp, each of which received the FDA approval in 2004. Metvixia® (Galderma; Photocure) consists of the topical application of methyl aminolevulinate (in contrast to ALA used in the Kerastick procedure), followed by exposure with the Aktilite CL128 lamp, a red light source (in contrast to the blue light source in the Kerastick procedure). Broadband light sources (containing the appropriate wavelengths), intense pulsed light (FDA product code: ONF), pulsed dye lasers, and potassium-titanyl-phosphate lasers have also been used. Metvixia® is indicated for the treatment of nonhyperkeratotic AKs of the face and scalp in immunocompetent patients when used 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.

## Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable

intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The key literature is described next and focuses on studies evaluating the U.S. Food and Drug Administration (FDA) approved photosensitizing agents.

**Actinic Keratoses (AK)**

Clinical Context and Therapy Purpose

The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with nonhyperkeratotic actinic keratoses (AKs) on the face or scalp.

The following PICO was used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals with nonhyperkeratotic AKs on the face, scalp, or upper extremities. AKs are rough, scaly, or warty premalignant growths on the 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, AKs may progress to squamous cell carcinoma.

*Interventions*

The therapy being considered is PDT.

*Comparators*

The following therapies are currently being used to treat nonhyperkeratotic AKs on the face, scalp, or upper extremities: pharmacologic therapy, cryotherapy, and laser therapy. Available treatments for AKs can be divided into surgical and nonsurgical methods. Surgical treatments used to treat 1 or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodessication), and laser surgery. Nonsurgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (chemical peels), and dermabrasion. Topical treatments are generally used in individuals with multiple lesions and involve extensive areas of skin. Under some circumstances, combinations of treatments may be used.

*Outcomes*

The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity. Specific outcomes of interest include complete clearance of AKs, percentage of AKs cleared, severity of adverse events, patient-reported outcomes, and recurrence of lesions. (1) Effectiveness measurements should be measured at 2 to 4 months after treatment

to ensure that treatment-associated inflammation has resolved. Recurrence should be assessed no sooner than 6 to 12 months after therapy. Most adverse events are transient and occur during or right after treatment. Treatment location-specific incidence of and progression to squamous cell carcinoma should be reported whenever long-term follow-up is possible but may not be practical in some clinical trials.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Actinic Keratoses on the Face or Scalp

*Systematic Reviews*

Patel et al. (2014) published a systematic review of RCTs with at least 10 patients that addressed the efficacy of topical PDT compared with an alternative (i.e., non-PDT) treatment of AKs. (2) Thirteen studies (N=641) met the reviewers' inclusion criteria. Studies compared PDT with cryotherapy (n=6), 5-FU (n=2), imiquimod (n=4), and carbon dioxide laser (n=1). Seven studies used 5-aminolevulinic acid (ALA), and the other 6 used methyl aminolevulinate (MAL) as the PDT sensitizer. Most studies focused on facial or scalp lesions. No study in the review was double-blinded. In 12 of the 13 studies, the primary outcome was a measure related to the clearance rate of lesions. Data from 4 RCTs comparing PDT with 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.

Ezzedine et al. (2020) performed a systematic review and network meta-analysis of RCTs evaluating the efficacy and acceptability of interventions for AK of the face, ears, and/or scalp. (3) For the outcome of complete clearance (number of patients with 100% cleared lesions), 21 RCTs contributed to the network. The most efficacious interventions as measured by surface under the cumulative ranking curve (SUCRA) included 5-FU 5% (85%), 5-FU 4% (78%), ALA/PDT (70%), imiquimod 5% (67%), 5-FU 0.5% (63%), and ingenol mebutate (60%). Results were similar in an analysis of partial clearance (number of patients with ≥75% cleared lesions) using data from 10 RCTs. Using data from 9 RCTs, rates of withdrawal due to adverse events were most favorable, as measured by SUCRA, for 5-FU combined with salicylic acid (81%), imiquimod 2.5% (71%), 5-FU 4% (71%), 5-FU 5% (66%), and imiquimod 3.75% (55%). However, rates of withdrawal due to adverse events were not significantly different for any of these agents in comparisons with placebo.

Steeb et al. (2021) performed a systematic review and network meta-analysis of RCTs evaluating the long-term efficacy (≥12 months) of interventions for AK of the face and/or scalp. (4) Seventeen trials reporting initial and follow-up results of 15 unique RCTs (N=4252) were included. For the outcome of participant complete clearance, the most favorable RRs were with ALA/PDT (8.06; 95% CI, 2.07 to 31.37; moderate certainty in the evidence) followed by imiquimod 5% (RR, 5.98; 95% CI, 2.26 to 15.84; very low certainty in the evidence), photodynamic therapy with MAL/PDT (RR, 5.95; 95% CI, 1.21 to 29.41; low certainty in the evidence), and cryosurgery (RR, 4.67; 95% CI, 1.36 to 16.66; very low certainty in the evidence). For the outcome of lesion-specific clearance (number of cleared lesions compared with baseline), ALA/PDT had the most favorable RR (5.08; 95% CI, 2.49 to 10.33; moderate certainty in the evidence). For the outcome of participant partial clearance, network meta-analysis was not possible because of poor reporting.

*Randomized Controlled Trials*

Pariser et al. (2003) conducted a randomized, placebo-controlled trial of 80 patients with AKs. (5) Complete response (CR) rate for the MAL group was 89% and 38% in the placebo group.

Morton et al. (2006) published an industry-sponsored, 25-center, randomized, left-right comparison of single PDT and cryotherapy in 119 subjects with AKs on the face or scalp. (6) At a 12-week follow-up, PDT resulted in a higher rate of cured lesions (86.9%) than cryotherapy (76.2%). Lesions with a non-CR were treated 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 rates (85.8% vs. 82.5%, respectively). Greater skin discomfort was reported with PDT than with cryotherapy. Investigator-rated cosmetic outcomes showed no difference in the percentages 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.

A double-blind RCT conducted in Germany by Hauschild et al. (2009) evaluated PDT with ALA using a self-adhesive patch. (7) Eligibility criteria included white patients, age 18 years and older, with skin type I to IV (pale to olive complexion), and AKs on the head of mild or moderate grade, as defined by Cockerell (maximum diameter, 1.8 cm; intralesional distance, at least 1 cm). Patients were randomized to ALA 8 mg patches or identical placebo patches. Patches were square, measuring 4 $cm^2$, 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 ALA patch group and 6% (2/33) in the placebo patch group; there was a statistically significant difference favoring PDT.

Szeimies et al. (2010) reported on a phase 3 clinical trial using a stable ALA nanoemulsion formulation (BF-200 ALA) developed for PDT for AKs. (8) The multicenter, double-blind, interindividual 2 armed-trial randomized 122 patients to BF-200 ALA or placebo. The patients

had 4 to 8 mild-to-moderate AKs lesions on the face and/or bald scalp. BF-200 ALA was used in combination with 1 of 2 different light sources. The efficacy of BF-200 ALA after the first PDT treatment was evaluated at 12 weeks. For patients who were not completely cleared of AKs received a second PDT treatment, with the final evaluation 12 weeks later for all participants. The results showed PDT with BF-200 ALA was superior to PDT with a placebo in respect to patient complete clearance rate (per-protocol group, 64% vs. 11%; p<.001) and lesion complete clearance rate (per-protocol group, 81% vs. 22%) after the last PDT treatment. Statistically significant differences in the patient and lesion complete clearance rates and adverse event profiles were observed for the 2 light sources (Aktilite CL128 and PhotoDyn 750) at both time points of the assessment. The patient and lesion complete clearance rates after illumination with the Aktilite CL128 were 96% and 99%, respectively. No adverse events (discomfort, pain) were mentioned by patients related to the application of the gel prior to PDT treatment. Burning and itching were reported during or after the red light illumination. Moreover, 100% of patients treated using Aktilite CL128 had burning after the second PDT session. Of the patients treated using PhotoDyn 750, 60% reported pain during or after PDT. A limitation of the study was its lack of follow-up for patients beyond study protocols.

Szeimies et al. (2010) in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch with cryotherapy. (9) The study had the same eligibility criteria and primary outcome as the Hauschild et al. (2009) study (previously described). A total of 148 patients were randomized to a 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 with cryotherapy. The rate of complete clearance of all lesions was 67% (86/129) in the ALA group, 52% (66/126) in the cryosurgery group, and 12% (5/43) in the placebo group. The clearance rate was significantly higher in the ALA patch group than in either comparator group. Results were similar in the analysis of clearance rates on a per lesion basis. The 360 patients with at least 1 lesion cleared at 12 weeks were followed for an additional 9 months; 316 patients completed the final visit 1 year after treatment. Overall clearance rate on a lesion basis was still statistically higher in the ALA patch group than in the placebo (in both studies) and the cryosurgery (in the second study) groups. Moreover, 32% of patients in the ALA group from the first study and 50% of patients in the ALA group from the second study were still completely free from lesions by the end of the trial. The corresponding rate 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; however, no serious adverse events due to study intervention were documented.

A randomized pilot study by Serra-Guillen et al. (2012) in Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments. (10) Patients with nonhyperkeratonic AKs on the face and/or scalp were randomized 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) treatment as with group 1 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 AKs 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 higher rate of CR in the PDT plus imiquimod group compared with PDT only (p=.004). A study limitation was that the PDT-only group had a shorter follow-up, which could at least partially explain the lower rate of CR.

Dirschka et al. (2012) reported on an industry-sponsored randomized, multicenter, observer-blind, placebo-controlled, interindividual trial comparing BF-200 ALA for the treatment of AKs with MAL cream and placebo. (11) Six hundred patients with 4 to 8 mild-to-moderate AKs lesions on the face and/or bald scalp were enrolled in 26 study centers. A total of 549 patients completed the study. Early dropouts were reported, including 15 patients for unexplained reasons, 4 patients with adverse events associated with treatment, and 2 patients with protocol violations. The trial results showed PDT with BF-200 ALA was superior to placebo PDT with respect to patient complete clearance rate (78.2% vs. 17.1%; p<.001) and lesion complete clearance rate (90.4% vs. 37.1%) at 3 months after the last PDT, respectively. Superiority was demonstrated over the MAL cream for the primary endpoint of patient complete clearance (78.2% vs. 64.2%; p<.05). Significant differences in the patient and lesion complete clearance rates and severities of treatment-related adverse events were observed for the narrow- and broad-spectrum light sources. Patient clearance rates and lesion clearance rates were higher compared with MAL. Table 1 provides the data on the light source affecting the clearance rates.

**Table 1. Summary of Key RCT Results for Light Source Effects on Clearance Rates**

| **Study** | **Patients /Lesions** | **Patient Total Clearance Rate** | | **Lesion Total Clearance Rate** | |
|---|---|---|---|---|---|
| | | ***Narrow-Light Spectrum, %*** | ***Broad-Light Spectrum, %*** | ***Narrow-Light Spectrum, %*** | ***Broad-Light Spectrum, %*** |
| **Dirschka et al. (2012) (11)** | | | | | |
| One BF-200 ALA treatment w/ PDT | 248/1504 | 54.0 | 46.5 | 77.1 | 69.7 |
| One MAL treatment w/ PDT | 247/1557 | 37.0 | 35.0 | 73.0 | 59.1 |
| Two BF-200 ALA treatments w/ PDT | 123/NR | 84.8 | 71.5 | 93.6 | 86.3 |
| Two MAL treatments | 150/NR | 67.5 | 61.3 | 89.3 | 76.3 |

ALA: 5-aminolevulinic acid; BF-200 ALA: nanoemulsion-based 5-ALA formulation; MAL: methyl aminolaevulinate; NR: not reported; PDT: photodynamic therapy; RCT: randomized controlled trials.

Dirschka et al. (2013) reported on the follow-up phase of patients from 2 phase 3 studies that compared BF-200 ALA (n=329) with placebo (n=117) or MAL (n=247) for the treatment of AKs.

(12) No safety concerns were reported. Recurrence rates were similar for BF-200 ALA and MAL. The percentage of patients who achieved complete clearance with PDT and remained completely clear for at least 12 months after PDT were 47% for BF-200 ALA and 36% for MAL treatment. The authors reported that the follow-up phase data confirmed the efficacy and safety of PDT with BF-200 ALA. No p-values or CIs were reported.

Zane et al. (2014) published the results of an RCT on the treatment of multiple AKs of the face and scalp. (13) The trial compared MAL/PDT with diclofenac 3% plus hyaluronic acid gel (DHA). Two hundred patients were enrolled. At 3 months, the complete remission rate was 85.9% for patients using MAL/PDT and 51.8% for patients using DHA ($p<.001$). Incomplete responses to MAL/PDT were followed by a second treatment. At 12 months, the complete remission rate was 37% for patients treated with MAL/PDT and 7% for patients treated with DHA. Based on these results, the authors determined that MAL/PDT was "superior in comparison with DHA for the treatment of actinic keratosis." Potential weaknesses in the DHA arm were that patients self-administered the DHA gel and had a longer treatment cycle (90 days) than the MAL/PDT arm.

Reinhold et al. (2016) published results from a double-blind RTC comparing BF-200 ALA with placebo for the field-directed treatment of mild-to-moderate AKs with PDT using the BF-RhodoLED lamp. (14) After a maximum of 2 PDT treatments the results, measured 12 weeks after the last PDT, showed a patient complete clearance rate of 91% using BF-200 ALA versus 22% using a placebo ($p<.001$), and a lesion complete clearance rate of 94.3% using BF-200 ALA versus 32.9% using a placebo ($p<.001$). There were treatment adverse events in 100% of the BF-200 ALA group and in 69% of the placebo group. The adverse events were application-site events and included site pain, erythema, pruritus, scab, exfoliation, edema, and vesicles. Local skin reactions were of mild-to-moderate intensity. Application-site pain was the most common individual adverse event in both groups (96.4% for BF-200 ALA vs. 50.0% for placebo) and was rated as severe by 49% of the BF-200 ALA group and 3% of the patients treated with placebo. One of 32 patients in the placebo group and no patients in the BF-200 ALA group displayed a new lesion after PDT. Trialists indicated that this result may be the preventive effect of field-directed AKs treatment.

Karrer et al. (2021) reported findings from an RCT comparing MAL/PDT with cryosurgery in 58 patients with AK of the face. (15) Patients received either 5 full-face treatments with MAL/PDT or a single freeze-thaw cryosurgery cycle, followed by additional intervention in the case of non-cleared or newly developed AK. At 24 months of follow-up, the primary outcome, the cumulative number of new AKs after visit 1, was not significantly different between MAL/PDT and cryosurgery (mean difference, -2.5; 95% CI, -6.2 to 1.2). Overall, complete clearance of AKs was significantly greater with MAL-PDT (mean difference, 43.5%; 95% CI, -12.5 to 39.3); however, no differences were detected in grade I or II lesions.

Cortelazzi et al. (2021) reported results of an RCT evaluating the effect of imiquimod 3.75% versus MAL/PDT in patients with AK of the scalp. (16) Nine bald male patients were randomized to receive a single session of treatment on either the right or left side of the scalp and were

assessed at up to 12 months of follow-up. By degree of AK, rates of clearance for imiquimod versus MAL/PDT were 68.8% and 48.0% for degree I, 64.5% and 69.8% for degree II, and 75% and 66.7% for degree III, respectively.

Section Summary: AKs on the Face or Scalp

Evidence from meta-analyses and multiple RCTs has suggested that PDT improves the net health outcome as measured by complete clinical clearance of lesions in patients with nonhyperkeratotic AKs of the face or scalp compared with placebo or other active interventions. Study limitations for the trials comparing MAL with BF-200 ALA included results using different light sources and the use of non-FDA-approved light sources, self-reported pain assessments, and self-administered topical treatment.

Actinic Keratoses on the Upper Extremities

*Systematic Reviews*

Steeb et al. (2020) published a systematic review of RCTs that evaluated cryosurgery, ingenol mebutate, PDT, colchicine, and 5-FU for the treatment of AK in nonscalp and nonface localizations. (4) Thirteen studies (N=1380 ) met the reviewers' inclusion criteria. Studies evaluating PDT included comparisons to placebo (4 studies), cryotherapy (3 studies), 5-FU (2 studies), colchicine (1 study), and imiquimod (1 study). Direct (pairwise) comparison analyses found that PDT was significantly better than placebo in achieving complete clearance (RR, 3.87; 95% CI, 2.14 to 6.97). Ten of the studies were included in a network analysis. Compared to placebo, cryosurgery showed the highest complete clearance rates (RR, 7.73; 95% CI, 3.21 to 18.61), followed by imiquimod (RR, 7.00; 95% CI, 3.06 to 15.98), and PDT (RR, 3.87; 95% CI, 2.14 to 6.97). Cryosurgery was associated with a higher likelihood of complete clearance than PDT (RR, 2.00; 95% CI, 1.04 to 3.84) with a low certainty of evidence. Authors of the review noted caution in directly comparing topical treatments, which may be more suitable as a field-directed treatment of multiple or clustered lesions, with cryosurgery, which is preferable for single or a limited number of AKs.

*Randomized Controlled Trials*

Three placebo-controlled RCTs used ALA and PDT with blue light (Tables 2 and 3). (17-19) The largest and most recent of these, Jiang et al. (2019), was the basis for the FDA approval of Levulan Kerastick for the treatment of AKs on the upper extremities. (17) Two of these had a similar design: individual patients were randomized to active treatment or placebo, patients were re-treated at 8 weeks if any AKs remained, and outcomes were reported at 8 and 12 weeks. In both, significantly more patients had a complete clearance of all lesions after 12 weeks. The most common adverse events were stinging/burning during light treatment and erythema after light treatment. No subjects withdrew from treatment due to adverse events in Jiang et al. (2019), and 2 requested an early withdrawal in Schmieder et al. (2012). Schmieder et al. (2012) additionally randomized patients to occlusion or no occlusion on alternate extremities and found better results with occlusion. Taub et al. (2011) was a small (n=15), 4-week, intra-individual study in which patients were randomized to receive active treatment or placebo on alternate arms. (19) At 4 weeks, no patients experienced complete clearance, but the mean lesion count was significantly lower in the treatment group compared to the placebo.

Two other small RCTs compared ALA/PDT using red light to imiquimod (20) or 5-FU (21) and found similar efficacy between the active treatment groups after 6 months of follow-up (Tables 2 and 3).

Study limitations are summarized in Tables 4 and 5.

**Table 2. Characteristics of RCTs of Photodynamic Therapy for Actinic Keratoses on the Upper Extremities**

| Study; Trial | Countries | Sites | Dates | Design | Participants | Interventions | |
|---|---|---|---|---|---|---|---|
| | | | | | | ***Active*** | ***Comparator*** |
| Jiang et al. (2019) (17) NCT02137785 | U.S. | 13 | 2014-2015 | Parallel groups | 269 adults 18 or older with 4 to 15 Grade 1 or 2 AKs on one upper extremity | 20% ALA-blue light PDT N=135 | VEH-PDT N=134 |
| Schmieder et al. (2012) (18) NCT01458587 | U.S. | 3 | 2012 | Parallel groups | 70 adults 18 or older with at least 4 Grade 1 or 2 AKs on the dorsal hand/ forearm | 20% ALA-blue light PDT N=35 | VEH-PDT patients N=35 |
| Taub et al. (2011) (19) | U.S. | NR | NR | Intra-individual, randomized to alternate upper extremities | 15 adults (ages 42 to 79 years) with 4 or more AKs lesions on the dorsal sides of both hands and forearms | 20% ALA-blue light PDT | VEH-PDT |
| Sotiriou et al. (2009) (20) | Greece | 1 | NR | Intra-individual, randomized to alternate upper extremities | 30 adults with Grade 1 or 2 AKs on the dorsal hand/forearm; at least 6 comparable lesions of similar severity on both sides | 20% ALA-red light PDT | Imiquimod 5% cream |
| Kurwa et al. (1999) (21) | England | NR | NR | Intra-individual, randomized to alternate upper extremities | 17 adults (ages 53 to 79 years) with a long history of Aks affecting the forearms and hands | 20% ALA-red light PDT | 5-FU cream |

AKs: actinic keratoses; ALA: aminolevulinic acid; NR: not reported; PDT: photodynamic therapy; RCT: randomized controlled trial; VEH: vehicle (placebo); 5-FU:5-fluorouracil.

**Table 3. Results of RCTs of Photodynamic Therapy for Actinic Keratoses on the Upper Extremities**

| Study | Complete Clearance | Lesion Reduction |
|---|---|---|
| **Jiang et al. (2019) (17)** | | |
| ALA-PDT | 8 weeks: 35/135 (25.9%)<br>12 weeks:42/135 (31.1%) | |
| VEH-PDT | 8 weeks: 12/134 (9.0%)<br>12 weeks: 17/134 (12.7%) | |
| P-value | 0.0001 at 8 and 12 weeks | |
| **Schmieder et al. (2012) (18)** | | |
| ALA-PDT | 8 weeks: 8/35 (22.9%)<br>12 weeks: 12/35 (34.3%) | |
| VEH-PDT | 8 weeks: 0/35 (0%)<br>12 weeks: 1/35 (2.9%) | |
| P-value | 0.002 at 12 weeks; 8 weeks NR | |
| **Taub et al. (2011) (19)** | | Mean (SD) lesion count reduction at 4 weeks: |
| ALA-PDT | | 58.4% (22.2) |
| VEH-PDT | | 24.8% (20.6) |
| P-value | | 0.004 |
| **Sotiriou et al. (2009) (20)** | | |
| ALA-PDT | 4 weeks: 87/124 (70.16%)<br>6 months: 81/124 (65.32%);<br>95% CI, 56.9 to 73.7% | |
| Imiquimod | 4 weeks: 21/115 (18.26%)<br>6 months: 64/115 (55.65%) ;<br>95% CI, 46.6<br>to 64.7% | |
| P-value | <0.05 at 4 weeks<br>>0.05 at 6 months | |
| **Kurwa et al. (1999) (21)** | | Mean reduction in lesion area at 6 months: |
| ALA-PDT | | 73% (95% CI, 61%-84%) |
| 5-FU | | 70% (95% CI, 61% to 80%) |
| Difference | | 2% (95% CI, –10% to 14%; P = .721) |

ALA: aminolevulinic acid; CI: confidence interval; NR: not reported; PDT: photodynamic therapy; RCT: randomized controlled trial; SD: standard deviation; VEH: vehicle (placebo); 5-FU: 5-fluorouracil.

**Table 4. Study Relevance Limitations**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Jiang et al. (2019) (17) NCT02137785 | | | | | |
| Schmieder et al. (2012) (18) NCT01458587 | | | | | |
| Taub et al. (2011) (19) | | | | 1. complete clearance not reported | 1. 4 weeks |
| Sotiriou et al. (2009) (20) | | | 4. Patient applied | | |
| Kurwa et al. (1999) (21) | | | 4. Patient applied | | |

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 5. Study Design and Conduct Limitations**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Jiang et al. (2019) (17) NCT02137785 | 3. allocation concealment method not reported | 1. Outcome assessors, but not patients, | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | were blinded | | | | |
| Schmieder et al. (2012) (18) NCT01458587 | 3. allocation concealment method not reported | 1. Outcome assessors, but not patients, were blinded | | | | |
| Taub et al. (2011) (19) | 3. allocation concealment method not reported | 1. Outcome assessors, but not patients, were blinded | | | 1. small sample size (N=15), no power calculation | |
| Sotiriou et al. (2009) (20) | 3. allocation concealment method not reported | 1. Not blinded | | | 1. small sample size (N=30), no power calculation | |
| Kurwa et al. (1999) (21) | 3. allocation concealment method not reported | 1. Not blinded | | | 1. small sample size (N=17), no power calculation | |

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive limitations assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: AKs on the Upper Extremities

A systematic review of interventions for nonface and nonscalp AKs found PDT to be superior to placebo for complete clearance, but found a significant increase in complete clearance with cryotherapy versus PDT. In 2 placebo-controlled RCTs, significantly more patients had a complete clearance of AKs with ALA/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-FU and found similar efficacy between the active treatment groups after 6 months of follow-up.

**Low-Risk Basal Cell Carcinoma**

Clinical Context and Therapy Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with low-risk basal cell carcinoma (BCC).

The following PICO was used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals with low-risk BCC. Nonmelanoma skin cancers are the most common malignancies in the white population. Most often found in light-skinned individuals, BCC 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.

*Interventions*

The therapy being considered is PDT.

*Comparators*

The following therapies are currently being used to treat BCC: pharmacologic therapy, cryotherapy, surgery, and radiotherapy. 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.

*Outcomes*

The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity. Specific outcomes of interest include complete clearance rate, recurrence rate, cosmetic outcomes, and adverse events. (22) Clearance rates are assessed after the first treatment cycle. Recurrence rates should be evaluated at least 12 months from treatment. Cosmetic outcomes should be evaluated after 12 months. Most adverse events are transient and occur during or right after treatment.

Study Selection Criteria

Methodologically credible studies were selected using the using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Mpourazanis et al. (2020) compared PDT to cryotherapy for BCC in a systematic review of 19 RCTs and prospective observational trials. (23) Of these studies, only 5 RCTs were included in the quantitative analysis. For rates of complete clearance, there was no significant difference found between PDT and cryotherapy (2 studies; odds ratio [OR], 0.83; 95% CI, 0.47 to 1.49; $I^2$=0%). Similarly, no difference was found between PDT and cryotherapy for the recurrence rate (3 studies; OR, 4.99; 95% CI, 0.40 to 62.40; $I^2$=87.3%). The review did not distinguish among BCC subtypes.

Wang et al. (2017) published a systematic review of RCTs on PDT for treating BCC, both superficial and nodular types. (22) To be selected, studies had to include adults with 1 or more primary BCCs, randomize participants to PDT, placebo, or another treatment, and report the complete clearance rate, recurrence rate, cosmetic outcomes, and/or adverse events rate. Eight RCTs (N=1583), published between 2001 and 2013, met inclusion criteria. Three trials included patients with superficial BCC; 3 included patients with nodular BCC and 1 trial included patients with both types of low-risk BCC. Four trials compared PDT with surgery, 2 compared PDT with cryotherapy, 1 compared PDT with pharmacologic treatment, and 1 was placebo-controlled.

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

A meta-analysis by Zou et al. (2016) identified 5 RCTs comparing PDT with surgical excision in patients who had nodular BCC and at least 3 months of follow-up. (24) The rate of CR was significantly lower in the PDT group than in the surgical excision group at 1 year (RR, 0.89; 95% CI, 0.80 to 0.99) and at 3 years (RR, 0.73; 95% CI, 0.63 to 0.85); there were no significant differences in CR at 2, 4, or 5 years. The rate of recurrence was significantly higher in the PDT group than in the surgical excision group at all time points.

A Cochrane review by Bath-Hextall et al. (2007) evaluated surgical, destructive (including PDT), and chemical interventions for BCC. (25) Reviewers concluded that surgery and radiotherapy appeared to be the most effective treatments, with the best results obtained using surgery. In addition, they stated that cosmetic outcomes appear to be good with PDT, but additional data with long-term follow-up are needed. Cochrane reviewers did not distinguish among BCC subtypes.

Randomized Controlled Trials

A noninferiority RCT by Roozeboom et al. (2016) compared MAL/PDT with imiquimod cream and with 5-FU cream in patients with superficial BCC. (26) A total of 601 patients were randomized, 202 to MAL/PDT, 198 to imiquimod, and 201 to fluorouracil. A total of 490 (82%) patients completed the 1-year follow-up and 417 (69%) completed the 3-year follow-up. Median follow-up was 35 months. The estimated tumor-free survival rates at 3 years were 58% (95% CI, 47.8% to 66.9%) in the PDT group, 79.7% (95% CI, 71.6% to 85.7%) in the imiquimod group, and 68.2% (95% CI, 58.1% to 76.3%) in the fluorouracil group. Results of the noninferiority analysis suggested that imiquimod was superior to MAL/PDT and imiquimod was noninferior to MAL/PDT.

An industry-sponsored multicenter RCT was published by Szeimies et al. (2008). (27) This trial compared MAL/PDT with surgery for small (8 to 20 mm) superficial BCC in 196 patients. At 3 months posttreatment, 92% of lesions treated with MAL/PDT showed a clinical response, compared with 99% of lesions treated with surgery (per-protocol analysis). At a 12-month follow-up, no lesion recurrence was reported in the surgery group, while the recurrence rate was 9% in the MAL/PDT group. Approximately 10% of patients discontinued MAL/PDT due to an incomplete response or adverse event compared with 5% of patients in the surgery group. Cosmetic outcomes were rated by the investigators as good-to-excellent in 94% of lesions treated with MAL/PDT and 60% after surgery.

Rhodes et al. (2007) published a 5-year follow-up to an industry-sponsored multicenter randomized trial comparing MAL/PDT with surgery for nodular BCC. (28, 29) A total of 101 adults with previously untreated nodular BCC were randomized to MAL therapy or surgery. At 3 months, CR rates did not differ between groups; however, at 12 months, the CR rate had fallen from 91% to 83% in the MAL/PDT group, and from 98% to 96% in the surgery group. Of 97 patients in the per-protocol population, 66 (68%) were available for a 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 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 in 54% of the surgery patients.

Section Summary: Basal Cell Carcinoma

Systematic reviews of RCTs have found that PDT may not be as effective as surgery for low-risk superficial and nodular BCC. In the small number of trials available, PDT was more effective

than a placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery for low-risk BCC.

**Squamous Cell Carcinoma**

Clinical Context and Therapy Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with squamous cell carcinoma in situ (Bowen disease).

The following PICO were used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals with squamous cell carcinoma in situ. Bowen disease is a squamous cell carcinoma in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive squamous cell carcinoma. Lesions may appear on the sun-exposed or covered skin.

*Interventions*

The therapy being considered is PDT.

*Comparators*

The following therapies are currently being used to treat squamous cell carcinoma in situ: pharmacologic therapy, cryotherapy, surgery, and radiotherapy.

*Outcomes*

The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity. Specific outcomes of interest include clearance of lesions, recurrence, cosmetic outcomes, and adverse events. (30) Clearance rates are assessed after the first treatment cycle. Recurrence rates should be evaluated at least 12 months from treatment. Most adverse events are transient and occur during or right after treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Xue et al. (2022) performed a meta-analysis of 8 RCTs that compared PDT for Bowen disease. (31) Compared to other topical treatments (5-FU and cryotherapy), PDT resulted in a higher CR

rate (1.36; 95% CI, 1.01 to 1.84; p=.04; $I^2$=86%), a lower rate of recurrence (0.53; 95% CI, 0.30 to 0.95; p=.03; $I^2$=0%), and better cosmetic outcome (1.34; 95% CI, 1.15 to 1.56; p=.0002; $I^2$=0%). Another systematic review and meta-analysis (Yongpisarn et al. [2022]) of 43 studies of PDT included 1943 Bowen disease lesions and 282 cutaneous squamous cell carcinoma lesions. (32) The pooled clearance rate at 1 year was 76% for Bowen disease lesions (95% CI, 71% to 80%; $I^2$=78.9%). The authors concluded that the evidence supported use of PDT for Bowen disease with patient education about the possibility of recurrence, and that further studies are needed.

Zhong et al. (2020) performed meta-analyses using data from 12 RCTs (N=446) comparing PDT with other treatments in patients with Bowen disease. (33) For the outcome of lesion reduction reported between 1 and 12 months, PDT was associated with a significantly higher lesion reduction rate compared with control groups (OR, 2.86; 95% CI, 1.89 to 4.33). In comparisons with specific control groups, PDT was associated with significant improvements in lesion reduction compared with 5-FU (OR, 3.70; 95% CI, 2.07 to 6.62) and compared with cryotherapy (OR, 2.24; 95% CI, 1.24 to 4.04). No significant differences were observed in recurrence rates between PDT and control groups. Most domains of study quality were assessed as low or unclear risk of bias. The authors reported the potential for publication bias, and concluded PDT to be a safe and effective therapy for Bowen disease.

Bath-Hextall et al. (2013) published a Cochrane review of interventions for cutaneous Bowen disease. (30) Reviewers identified 7 RCTs evaluating PDT: 4 compared 2 PDT protocols, 1 compared PDT with cryotherapy, 1 compared PDT with topical 5-FU, and 1 compared PDT with both PDT and 5-FU. Reviewers did not pool study results.

*Randomized Controlled Trials*

The largest study (N=225 patients) was a 3-arm trial published by Morton et al. (2006). (34) This multicenter trial was conducted in 11 European countries. A total of 225 patients were randomized to MAL/PDT, cryotherapy, or 5-FU for treatment of Bowen disease. Unblinded assessment of lesion clearance found PDT to be noninferior to cryotherapy and 5-FU (93% vs. 86% vs. 83%, respectively) at 3 months and superior to cryotherapy and 5-FU (80% vs. 67% vs. 69%, respectively) at 12 months. Cosmetic outcomes at 3 months were rated higher for PDT than for standard nonsurgical treatments by both investigators and blinded evaluators, with investigators rating cosmetic outcomes as good or excellent in 94% of patients treated with MAL/PDT, 66% of patients treated with cryotherapy, and 76% of those treated with 5-FU.

Another representative trial comparing PDT with another intervention in patients with Bowen disease was published by Salim et al. (2003). (35) Forty patients were randomized to topical 5-FU or MAL therapy. Twenty-nine (88%) of 33 lesions in the PDT group cleared completely compared with 22 (67%) of 33 lesions in the 5-FU group. In the 5-FU group, severe eczematous reactions developed around 7 lesions, ulceration of 3, and erosions of 2. No such reactions were noted in the PDT group.

<u>Section Summary: Squamous Cell Carcinoma In Situ (Bowen Disease)</u>

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

**Nonmetastatic Invasive Squamous Cell Carcinoma**

Clinical Context and Therapy Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with nonmetastatic invasive squamous cell carcinoma.

The following PICO was used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals with nonmetastatic invasive squamous cell carcinoma.

*Interventions*

The therapy being considered is PDT.

*Comparators*

The following therapies are currently being used to treat nonmetastatic invasive squamous cell carcinoma: cryotherapy, surgery, and radiotherapy.

*Outcomes*

The general outcomes of interest are overall survival, symptoms, change in disease status, QOL, surgery, and radiotherapy. Specific outcomes of interest include recurrence, initial response to treatment, cosmetic appearance, and death due to disease. (36) Recurrence can be assessed during follow-up from 1 month to 10 years after treatment.

Study Selection Criteria

Methodologically credible studies were selected using the principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Lansbury et al. (2013) published a systematic review of prospective and retrospective studies evaluating interventions for nonmetastatic cutaneous squamous cell carcinoma. (36) Reviewers

identified 14 prospective studies evaluating PDT. Sample sizes ranged from 4 to 71 patients, with only 3 studies including more than 25 patients. The 14 studies evaluated various PDT protocols. Only 1 was comparative, and it assessed 2 PDT regimens. In a meta-analysis, a mean of 72% of lesions had a CR to treatment (95% CI, 61.5% to 81.4%; $I^2$=71%). Eight studies addressed recurrence rates in patients who were initial responders. In a meta-analysis, the pooled odds of recurrence were 26.4% (95% CI, 12.3% to 43.7%; $I^2$=72%).

Section Summary: Nonmetastatic Invasive Squamous Cell Carcinoma

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

**Acne**

Clinical Context and Therapy Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with acne.

The following PICO was used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals with acne.

*Interventions*

The therapy being considered is PDT.

*Comparators*

The following therapies are currently being used to treat PDT: pharmacologic therapy (e.g., benzoyl peroxide, salicylic acid, topical or systemic retinoids, topical or systemic antibiotics, hormonal agents) and other physical modalities (e.g., laser or light therapy, chemical peels).

*Outcomes*

The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity. Specific outcomes of interest most commonly evaluated in clinical trials include patients' global assessment of improvement, investigators' assessment in change of lesion count, and adverse effects. (37) Evaluation of efficacy should ideally take place after at least 8 weeks of treatment, though shorter-term data (4 to 8 weeks) may indicate early improvement.

The duration of follow-up would be based on the extent of lesions and 4, 8, and 12 weeks would be appropriate.

Study Selection Criteria

Methodologically credible studies were selected using the principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review by Wu et al. (2021) performed a meta-analysis using data from 13 RCTs (N=422) that compared red light PDT with placebo, pharmacotherapy, or other sources of light in the treatment of acne. (38) For the outcome of inflammatory lesions, red light did not differ significantly at any point in time up to 12 weeks compared with other conventional treatment methods (weighted mean difference, 0.701; 95% CI, -0.809 to 2.212). Similar results were reported for the outcome of non-inflammatory lesions (weighted mean difference, -0.527; 95% CI, -3.055 to 2.001). Most domains of study quality were assessed as low or unclear risk of bias. The authors concluded that further study is needed comparing red light PDT with traditional therapies.

A Cochrane review by Barbaric et al. (2016) addressed a variety of light therapies for acne, including PDT. (37) For studies on MAL/PDT, only data on the investigator-assessed change in lesion counts were suitable for pooling. A meta-analysis of 3 studies on MAL/PDT did not find a significant difference from placebo on investigator-assessed change in inflamed lesion counts (mean difference, -2.85; 95% CI, -7.51 to 1.81) or change in noninflamed lesion counts (mean difference, -2.01; 95% CI, -7.07 to 3.05). Reviewers concluded there is a lack of high-quality evidence on light therapies for treating acne and a low certainty in the usefulness of PDT.

Randomized Controlled Trials

Tables 6 and 7 summarize the characteristics and results of relevant RCTs.

**Table 6. Summary of Key RCT Characteristics**

| **Study** | **Countries** | **Sites** | **Participants** | **Interventions** | |
|---|---|---|---|---|---|
| | | | | ***Active*** | ***Comparator*** |
| Wojewoda et al. (2021) (39) | Sweden | 1 | 36 patients with mild to severe acne, split-faced | MAL-PDT (either 2 or 4 treatments) | Placebo (either 2 or 4 treatments) |
| Nicklas et al. (2018) (40) | Chile | 1 | 46 patients with moderate inflammatory facial acne | ALA-PDT | Doxycycline plus adapalene gel |

| | | | | | |
|---|---|---|---|---|---|
| Xu et al. (2017) (41) | China | 1 | 95 patients with moderate-to-severe facial acne | Minocycline hydrochloride capsule plus PDT | Minocycline hydrochloride capsule without PDT |
| Pariser et al. (2016) (42) | U.S. | 5 | 153 patients with severe facial acne | MAL-PDT | Placebo cream |
| Orringer et al. (2010) (43) | U.S. | 1 | 44 patients with facial acne, split-faced | ALA-PDT | No treatment |

ALA: aminolevulinic acid; MAL: methyl aminolevulinate; PDT: photodynamic therapy; RCT: randomized controlled trial.

**Table 7. Summary of Key RCT Results**

| Study | Mean Reduction in Facial Inflammatory Lesion Count | Adverse Events (%) |
|---|---|---|
| **Wojewoda et al. (2021) (39)** | | |
| MAL/PDT | Week 20:<br>2 treatments: -74%<br>4 treatments: -85% | • Erythema (20)<br>• Hyperpigmentation (7)<br>• Ulceration (2)<br>• Scarring (2) |
| Placebo | Week 20:<br>2 treatments: -57%<br>4 treatments: -83% | • Erythema (9)<br>• Hyperpigmentation (8)<br>• Ulceration (1)<br>• Scarring (1) |
| p-value | Week 20:<br>2 treatments: .08<br>4 treatments: .44 | |
| **Nicklas et al. (2018) (40)** | | |
| ALA-PDT | -12.0 (median) | |
| Doxycycline plus adapalene gel | | |
| p-value | 0.038 | |
| **Xu et al. (2017) (41)** | | |
| Minocycline hydrochloride capsule plus PDT | -74.4% | • Pain (16.7)<br>• Burning sensation (14.6)<br>• Dizziness (6.3)<br>• Headache (4.2)<br>• Erythema (8.3)<br>• Hyperpigmentation (2.1) |
| Minocycline hydrochloride capsule without PDT | -53.3% | • Dizziness (8.5)<br>• Headache (6.4) |
| p-value | 0.001 | |

| | | |
|---|---|---|
| **Pariser et al. (2016) (42)** | | |
| MAL-PDT | -15.6 | • Pain (17) |
| Placebo | -7.8 | |
| p-value | 0.006 | |
| **Orringer et al. (2010) (43)** | | |
| MAL-PDT | -5.9 | • Mild peeling (4.5)<br>• Hyperpigmentation (4.5)<br>• A small blister (2.3) |
| No treatment | -2.5 | |
| p-value | 0.04 | |

ALA: aminolevulinic acid; MAL: methyl aminolevulinate; PDT: photodynamic therapy; RCT: randomized controlled trial.

The purpose of limitations tables (see Tables 8 and 9) is to display notable limitations identified in each study.

**Table 8. Study Relevance Limitations**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Wojewoda et al. (2021) (39) | | | | | |
| Nicklas et al. (2018) (40) | | | | | 1. Short follow-up |
| Xu et al. (2017) (41) | | | | 4. No consensus on quantitative evaluation of acne severity | 1. Short follow-up |
| Pariser et al. (2016) (42) | | | | | |
| Orringer et al. (2010) (43) | | | | | |

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 9. Study Design and Conduct Limitations**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Wojewoda et al. (2021) (39) | | | | 1. 48% of randomized participants did not complete trial | 2. Power not calculated for primary outcome; prespecified sample size not met | |
| Nicklas et al. (2018) (40) | | | | | | |
| Xu et al. (2017) (41) | | | | | 1. Sample size calculations not performed | |
| Pariser et al. (2016) (42) | | | | 1. 16% of participants did not complete trial | | |
| Orringer et al. (2010) (43) | | | | 1. 34% of participants did not complete trial | 1. Sample size calculations not performed | |

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Wojewoda et al. (2021) performed a double-blind RCT comparing MAL/PDT with placebo in patients with facial acne. (39) The trial randomized 36 patients to MAL/PDT or placebo, each given in either 2 or 4 treatments. After 20 weeks, the number of inflammatory lesions decreased by 74% and 85% with 2 and 4 treatments of MAL/PDT, respectively. However, there were no significant differences in relative change of inflammatory or non-inflammatory lesions in comparisons with the placebo group. No severe adverse effects were reported in either group. Trial limitations included a high rate of attrition and small sample size.

Nicklas et al. (2018) conducted an RCT involving 46 patients (age range, 18 to 30 years; 26 male, 20 female) with moderate inflammatory facial acne. (40) In the trial, 23 patients received 2 sessions of PDT plus topical ALA, while the other 23 patients received treatments of doxycycline plus adapalene gel. Two blinded dermatologists evaluated all patients at baseline and at 6 and 12 weeks after the start of treatment to count the inflammatory and noninflammatory facial lesions. The PDT group had a significantly higher median percent reduction in noninflammatory lesion count (p=.013) and total lesions (p=.038) at 6 weeks. Similar results were found at 12 weeks (p=.020 for noninflammatory lesions; p=.026 for total lesions). No severe side effects were observed for either therapy. Trial limitations included a small sample size and a short follow-up.

Xu et al. (2017) conducted an RCT involving 95 patients (age range, 15 to 35 years; 41 male, 54 female) to compare the efficacy of minocycline plus PDT with minocycline alone in treating moderate-to-severe acne. (41) In the trial, all patients took a daily minocycline hydrochloride capsule for 4 weeks, and 48 patients also received PDT once a week for 4 weeks. Both groups were evaluated before the study and at 2, 4, 6, and 8 weeks after the first treatment. The PDT group reported a greater mean percentage reduction in lesion counts from baseline than the minocycline alone group (-74.4% vs. -53.3%; p<.001) as well as a greater reduction in noninflammatory lesions (-61.7% vs. -42.4%; p<.05). Adverse events were mild and manageable. Limitations included a short follow-up and the lack of broad consensus on quantitative evaluation of acne severity.

Pariser et al. (2016) published a multicenter double-blind placebo-controlled, randomized trial evaluating MAL/PDT for severe facial acne. (42) A total of 153 patients were randomized and included in the intention-to-treat analysis. All patients received 4 treatments, 2 weeks apart, and were evaluated up to 12 weeks after the first treatment. In total, 84% of patients completed the trial. Mean change from baseline in facial inflammatory lesion count at 12 weeks was significantly lower in the MAL/PDT group than the placebo group (-15.6 and -7.8; p=.006, respectively). Change in facial noninflammatory lesion count at 12 weeks did not differ significantly between groups (-11.8 vs. -10.7; p=.85). The most commonly reported adverse

events were pain (n=17 [17%] in the MAL/PDT group vs. 0 in the placebo group) and a skin burning cessation (n=15 [15%] in the PDT group vs. 5 [9%] in the placebo group). Most adverse events were mild-to-moderate, although 12 patients in the MAL/PDT group dropped out due to treatment-related adverse events.

In a randomized, single-blind, split-faced trial, Orringer et al. (2010) evaluated the efficacy of ALA/PDT in 44 patients with facial acne. (43) For most outcomes, there were no statistically significant differences between the treated and untreated sides of the face. This included a 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 (mean reduction, 5.9) than the untreated side of the face (mean reduction, 2.5; p=.04). There were few adverse events, which tended to be mild. A trial limitation was the high dropout rate of 34%.

Other studies have reported higher rates of adverse events with PDT. For example, a study by Wiegell et al. (2006) evaluated patients 12 weeks after MAL/PDT (n=21) or a control group (n=15). (44) There was a 68% reduction from baseline in inflammatory lesions in the treatment group and no change in the control group (p=.023). However, all patients experienced moderate-to-severe pain after the treatment, and 7 (33%) of 21 in the treatment group did not receive the second treatment due to pain.

Section Summary: Acne

Several RCTs and systematic reviews have evaluated PDT for the treatment of acne. Neither review found significant improvements in lesion count with PDT compared with other therapies, and both reviews concluded there is a lack of high-quality evidence on light therapies for treating acne. The available RCTs have not consistently found significantly better outcomes with PDT than with comparator interventions. Several trials found that PDT was associated with high rates of adverse events leading to the cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions.

**Other Noncancerous Dermatologic Conditions**

Clinical Context and Therapy Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with noncancerous dermatologic skin conditions (e.g., hidradenitis suppurativa, mycoses, port-wine stain).

The following PICO were used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals with noncancerous dermatologic skin conditions, including hidradenitis suppurativa, mycoses, and port-wine stain.

*Interventions*

The therapy being considered is PDT.

*Comparators*
The following therapies are currently being used to treat noncancerous dermatologic skin conditions: pharmacologic therapy, cryotherapy, and laser therapy.

*Outcomes*
The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity.

Duration of follow-up would be based on the type and extent of lesions and would typically occur in weeks to months after treatment.

Study Selection Criteria
Methodologically credible studies were selected using the principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Reshetylo et al. (2022) published a systematic review of PDT for treatment of hidradenitis suppurativa. (45) All of the 18 included studies had a high risk of bias and there was heterogeneity among studies that limited the overall analysis. The authors concluded that there might be clinical benefit with ALA/PDT with blue light, MAL/PDT with red light, and ALA with intralesional diode, but further high-quality studies are needed.

Yang et al. (2022) conducted a systematic review of 19 publications (N=292) with PDT for actinic cheilitis. (46) Clinical trials, observational studies, and case series were considered but all of the included studies were uncontrolled cohorts and case series. Rates of complete clinical response were 80% with ALA/PDT, 76.74% with daylight PDT, and 65.14% with traditional PDT. The highest rates of painlessness were reported in patients who received daylight PDT. Local phototoxicity (moderate to severe) occurred most frequently in the traditional PDT group (47.78%) and least frequently in the daylight PDT group (0%). Limitations of the study included lack of control populations, small sample sizes (range, 2 to 43), inclusion of only red light for traditional PDT, differences in follow-up times, and outcome assessment by unblinded investigators. The authors stated that the evidence was of low quality and insufficient to base a recommendation for any particular treatment.

Shen et al. (2020) published a systematic review of clinical trials and case series evaluating PDT, with a focus on the photosensitizers used, for superficial fungal infections. (47) Thirty-four studies were identified for inclusion, including 13 clinical trials and 20 cases (N=440 [n=336 for

PDT participants only]). None of the clinical trials were blinded. The follow-up times of the studies varied from no follow-up to 2 years. Quantitative analyses were not performed. The majority of the included studies (n=18) evaluated PDT for onychomycosis. Seven different photosensitizers were evaluated for onychomycosis, ALA (3 studies), MAL (6 studies), porphyrin (1 study), methylene blue (5 studies), rose Bengal (1 study), curcumin (1 study), and aluminum phthalocyanine chloride nanoemulsions (1 study). Treatment with methylene blue had complete cure rates ranging from 70% to 80% (2 trials); whereas mycological cure rates for ALA and MAL ranged from 17% to 57% (2 trials) and 32% (1 trial), respectively. The most common adverse events reported in the included studies were pain/burning/stinging sensation (n=147/323 [45.5%]), erythema (n=66/177 [37.3%]), blistering (n=14/150 [9.3%]), edema (n=48/170 [28.2%]), and hyper-/hypopigmentation (n=10/140 [7.1%]).

Randomized Controlled Trials

Wu et al. (2018) conducted a prospective, multicenter RCT involving 100 patients (age range, 16 to 50 years) to measure the efficacy of different dose levels of hemoporfin with PDT in treating a port-wine stain. (48) In the trial, 40 patients received hemoporfin 2.5 mg/kg intravenously, 40 received hemoporfin 5 mg/kg intravenously, and 20 received a saline placebo. Ten minutes after infusion, all patients received PDT. After an evaluation at week 8, 75% of the high-dose group reported improvements in skin lesions compared with 40% of the low-dose group and 15% of the placebo group. Adverse events were mild and resolved within a week. Limitations included a short follow-up and a small sample size.

Case Series

No controlled studies using FDA-approved photosensitizing agents for PDT in other dermatologic conditions were identified for conditions other than a port-wine stain and onychomycosis. Only case series were identified, including series on PDT for hidradenitis suppurativa (49, 50) and PDT for interdigital mycoses. (51) Most series were small (e.g., <25 patients). There are a few systematic reviews. For example, a systematic review by Mostafa and Tarakji (2015) evaluated PDT for oral lichen planus identified 5 case reports, (52) and a systematic review by Yazdani Abyaneh et al. (2015) identified 15 case series (N=223 patients) on PDT for actinic cheilitis. (53) Xiao et al. (2011) in China published a large retrospective case series. (54) A total of 642 patients with port-wine stains were treated with PDT; 507 were included in analyses, and the rest were excluded because they had previous lesion treatments or were lost to follow-up. After treatment, 26 (5.1%) 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. Similarly, Chun-Hua et al. (2021) reported a retrospective review of 439 children with port-wine stains treated with PDT. (55) An effective response (>20% fading) occurred in 95.2% of patients, and 74.3% experienced almost complete resolution and great improvement (≥60% fading). Zhang et al. (2022) also evaluated a series of 107 children who received PDT for port-wine stains that were resistant to pulsed dye laser. (56) Good-to-excellent improvement was achieved in 32.7% of 107 patients who received a single session of treatment and in 50.8% of patients who received 2 sessions of treatment. These uncontrolled studies are insufficient to draw conclusions about the effect of PDT on health outcomes in patients with port-wine stains.

Section Summary: Other Noncancerous Dermatologic Conditions

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

**Summary of Evidence**

For individuals who have nonhyperkeratotic actinic keratoses (AKs) on the face or scalp who receive photodynamic therapy (PDT), the evidence includes meta-analyses and randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, quality of life (QOL), and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome as measured by complete clinical clearance of lesions in patients with nonhyperkeratotic AKs on the face or scalp compared with placebo or other active interventions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have nonhyperkeratotic AKs on the upper extremities who receive PDT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. A systematic review of interventions for nonface and nonscalp AKs found PDT to be superior to placebo for complete clearance but found a significant increase in complete clearance with cryotherapy versus PDT. In 2 placebo-controlled RCTs, significantly more patients had a complete clearance of AKs with 5-aminolevulinic acid (ALA)/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-fluorouracil (5-FU) and found similar efficacy between the active treatment groups after 6 months of follow-up The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have squamous cell carcinoma in situ who receive PDT, the evidence includes meta-analyses and RCTs. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. Meta-analyses and RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-FU. Additionally, adverse events and cosmetic outcomes appear to be better after PDT. Few RCTs have compared PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these other standard treatments. Current guidance from the National Comprehensive

Cancer Network notes that topical modalities, including PDT, may have lower cure rates than with surgical treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have nonmetastatic invasive squamous cell carcinoma who receive PDT, the evidence includes observational studies and a systematic review of observational studies. The relevant outcomes are overall survival, symptoms, change in disease status, QOL, 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 that the technology results in an improvement in the net health outcome.

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

For individuals who have noncancerous dermatologic skin conditions (e.g., hidradenitis suppurativa, mycoses, port-wine stain) who receive PDT, the evidence includes case series, systematic reviews of uncontrolled series, and an RCT for port-wine stain. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. RCTs are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Practice Guidelines And Position Statements**

American Academy of Dermatology

The American Academy of Dermatology has guidelines addressing use of photodynamic therapy (PDT) in actinic keratosis (AK), basal cell carcinoma, and acne:

- Actinic keratosis (2021): PDT is included in the following recommendations for patients with AK: (57)
  - 5-aminolevulinic acid (ALA)-red light PDT is conditionally recommended (low quality of evidence)
  - ALA-daylight PDT is conditionally recommended as less painful than but equally effective as ALA-red light PDT (moderate quality of evidence)
  - ALA-blue light PDT is conditionally recommended (moderate quality of evidence)
  - ALA-red light PDT is conditionally recommended over cryosurgery alone (low quality of evidence)
- Basal cell carcinoma (2018): Use of topical therapies, including PDT, is most appropriate for low-risk basal cell carcinoma when surgery is impractical or declined by the patient. (58)

Discussions of the relative effectiveness of topical therapies should be discussed with the patient. The guideline further notes that "Cure rates after surgical excision are 10% to 20% higher than those for topical therapies, including PDT, with excision associated with recurrence rates of less than 5%. Surgical excision may also be less painful and better tolerated."

- Acne (2016, update expected in 2023): More studies are needed on the use of PDT or other laser/light devices. (59) PDT has the most evidence among laser/light devices for treating acne, but "additional studies are needed to determine the optimal photosensitizer, incubation time, and light source."

National Comprehensive Cancer Network (NCCN)

- For treatment of precancers (diffuse actinic keratoses, field cancerization, and cutaneous squamous cell carcinoma prophylaxis), the NCCN (squamous cell skin cancer, v.1.2024) made the following recommendations: "Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) (preferred) with or without calcipotriol (calcipotriene), topical imiquimod, topical tirbanibulin, photodynamic therapy (e.g., aminolevulinic acid, porfimer sodium), and curettage and electrodesiccation. For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies may be considered." (60)
- For squamous cell skin cancers, the NCCN (squamous cell skin cancer, v.1.2024) made the following recommendations: “In patients with CSCC [cutaneous squamous cell carcinoma] in situ (Bowen disease), therapies such as topical 5-FU, topical imiquimod, photodynamic therapy (e.g., ALA, porfimer sodium), may be considered, although cure rates are approximately 10% lower than for surgical treatment modalities.” (60)
- For basal cell skin cancer, the NCCN (v.3.2024) made the following recommendations: “In patients with superficial BCC [basal cell carcinoma], therapies such as topical imiquimod, topical 5-fluorouracil (5-FU), or photodynamic therapy (PDT) may be considered, although cure rates are approximately 10% lower than for surgical treatment modalities.” (61)

United States and Canadian Hidradenitis Suppurativa Foundations

A joint guideline from the United States and Canadian Hidradenitis Suppurativa Foundations (2019) provides guidance on diagnosis and complementary and procedural management of hidradenitis suppurativa. (62) The guideline recommends PDT at a level C (based on consensus, opinion, case studies, or disease-oriented evidence). The authors state that PDT has a limited role in managing hidradenitis suppurativa, mainly due to a lack of large, well-controlled studies.

Medicare National Coverage

The Centers for Medicare & Medicaid Services’ 2001 coverage policy on the treatment of AKs noted:

“Various options exist on treating AKs [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 AKs include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy...

Medicare covers the destruction of AKs without restrictions based on lesion or patient characteristics." (63)

**Ongoing And Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 10.

**Table 10. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT03909646 | Surgical Excision Versus Photodynamic Therapy and Topical 5-fluorouracil in Treatment of Bowen's Disease: a Multicenter Randomized Controlled Trial | 250 | Dec 2025 |
| NCT03642535 | Aminolevulinic Acid-photodynamic Therapy for Facial Actinic Keratosis Treatment and Prevention: A Long-term (3 Years) Follow-up of Prospective, Randomized, Multicenter-clinical Trial | 300 | Jun 2025 |
| NCT02367547[a] | Superficial Basal Cell Cancer's Photodynamic Therapy: Comparing Three Photosensitises: Hexylaminolevulinate and Aminolevulinic Acid Nano Emulsion Versus Methylaminolevulinate | 117 | Dec 2025 |
| NCT03573401[a] | A Randomized, Double-Blind, Vehicle-controlled Multicenter Phase III Study to Evaluate the Safety and Efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the Treatment of Superficial Basal Cell Carcinoma (sBCC) With Photodynamic Therapy (PDT) | 186 | Feb 2029 |
| NCT05662202[a] | Study to Evaluate the Safety, Tolerability and Efficacy of BF-200 ALA (Ameluz®) in the Field-directed Treatment of Actinic Keratosis (AK) | 165 | Apr 2025 |

| | | | |
|---|---|---|---|
| | on the Extremities and Neck/Trunk With Photodynamic Therapy (PDT) Using a RhodoLED Lamp | | |
| ***Unpublished*** | | | |
| NCT05522036 | Clinical Evaluation of a Short Illumination Duration (35 Minutes) When Performing Photodynamic Therapy of Actinic Keratosis Using the Dermaris® | 25 | Jun 2023 (completed) |
| NCT05359419 | Safety and Efficacy of Photodynamic Therapy With Aminolevulinic Acid 10% Topical Gel Activated by Red Light Versus Aminolevulinic Acid 20% Topical Solution Activated by Blue Light for the Treatment of Actinic Keratosis on the Upper Extremities: A Blinded Randomized Study | 20 | Dec 2023 (unknown status) |
| NCT05245045 | Efficacy and Safety of STBF Photodynamic Therapy for Moderate and Severe Acne Vulgaris | 20 | Feb 2023 (unknown status) |
| NCT04167982 | Efficacy and Safety of Painless 5-aminolevulinic Acid Photodynamic Therapy for the Treatment of Moderate and Severe Acne Vulgaris – A Multicenter, Randomized Controlled Clinical Trial | 234 | Nov 2022 (unknown status) |

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

| | |
|---|---|
| **CPT Codes** | 96567, 96573, 96574 |
| **HCPCS Codes** | J7308, J7309, J7345 |

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

## References


1. Reynolds KA, Schlessinger DI, Vasic J, et al. Core Outcome Set for Actinic Keratosis Clinical Trials. JAMA Dermatol. Mar 01 2020; 156(3):326-333. PMID 31939999
2. Patel G, Armstrong AW, Eisen DB. Efficacy of photodynamic therapy vs. other interventions in randomized clinical trials for the treatment of actinic keratoses: a systematic review and meta-analysis. JAMA Dermatol. Dec 2014; 150(12):1281-1288. PMID 25162181
3. Ezzedine K, Painchault C, Brignone M. Systematic Literature Review and Network Meta-analysis of the Efficacy and Acceptability of Interventions in Actinic Keratoses. Acta Derm Venereol. Jan 04 2021; 101(1):adv00358. PMID 33170301
4. Steeb T, Wessely A, Schmitz L, et al. Interventions for Actinic Keratosis in Nonscalp and Nonface Localizations: Results from a Systematic Review with Network Meta-Analysis. J Invest Dermatol. Feb 2021; 141(2):345-354.e8. PMID 32645365
5. Pariser DM, Lowe NJ, Stewart DM, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. J Am Acad Dermatol. Feb 2003; 48(2):227-232. PMID 12582393
6. Morton C, Campbell S, Gupta G, et al. Intraindividual, right-left comparison of topical methyl aminolaevulinate- photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. Br J Dermatol. Nov 2006; 155(5):1029-1036. PMID 17034536
7. Hauschild A, Stockfleth E, Popp G, et al. Optimization of photodynamic therapy with a novel self-adhesive 5- aminolaevulinic acid patch: results of two randomized controlled phase III studies. Br J Dermatol. May 2009; 160(5):1066-1074. PMID 19222455
8. Szeimies RM, Radny P, Sebastian M, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. Br J Dermatol. Aug 2010; 163(2):386-394. PMID 20518784
9. Szeimies RM, Stockfleth E, Popp G, et al. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. Br J Dermatol. Feb 1 2010; 162(2):410-414. PMID 19804593
10. Serra-Guillen C, Nagore E, Hueso L, et al. A randomized pilot comparative study of topical methyl aminolevulinate photodynamic therapy versus imiquimod 5% versus sequential application of both therapies in immunocompetent patients with actinic keratosis: clinical and histologic outcomes. J Am Acad Dermatol. Apr 2012; 66(4):e131-137. PMID 22226430
11. Dirschka T, Radny P, Dominicus R, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. Br J Dermatol. Jan 2012; 166(1):137-146. PMID 21910711
12. Dirschka T, Radny P, Dominicus R, et al. Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis. Br J Dermatol. Apr 2013; 168(4):825-836. PMID 23252768
13. Zane C, Facchinetti E, Rossi MT, et al. A randomized clinical trial of photodynamic therapy with methyl aminolaevulinate vs. diclofenac 3% plus hyaluronic acid gel for the treatment of

multiple actinic keratoses of the face and scalp. Br J Dermatol. May 2014; 170(5):1143-1150. PMID 24506666
14. Reinhold U, Dirschka T, Ostendorf R, et al. A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) vs. placebo in the field-directed treatment of mild-to- moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED® lamp. Br J Dermatol. Oct 2016; 175(4):696-705. PMID 26921093
15. Karrer S, Szeimies RM, Philipp-Dormston WG, et al. Repetitive Daylight Photodynamic Therapy versus Cryosurgery for Prevention of Actinic Keratoses in Photodamaged Facial Skin: A Prospective, Randomized Controlled Multicentre Two-armed Study. Acta Derm Venereol. Jan 04 2021; 101(1):adv00355. PMID 33313936
16. Cortelazzi C, Odorici G, Castagnetti E, et al. Comparative study of imiquimod 3.75% vs. photodynamic therapy for actinic keratosis of the scalp. Photodermatol Photoimmunol Photomed. Sep 2021; 37(5):404-409. PMID 33566432
17. Brian Jiang SI, Kempers S, Rich P, et al. A Randomized, Vehicle-Controlled Phase 3 Study of Aminolevulinic Acid Photodynamic Therapy for the Treatment of Actinic Keratoses on the Upper Extremities. Dermatol Surg. Jan 2019; 45(7):890-897. PMID 30640777
18. Schmieder GJ, Huang EY, Jarratt M. A multicenter, randomized, vehicle-controlled phase 2 study of blue light photodynamic therapy with aminolevulinic acid HCl 20% topical solution for the treatment of actinic keratoses on the upper extremities: the effect of occlusion during the drug incubation period. J Drugs Dermatol. Dec 2012; 11(12):1483-1489. PMID 23377520
19. Taub AF, Garretson CB. A randomized, blinded, bilateral intraindividual, vehicle-controlled trial of the use of photodynamic therapy with 5-aminolevulinic acid and blue light for the treatment of actinic keratoses of the upper extremities. J Drugs Dermatol. Sep 2011; 10(9):1049-1056. PMID 22052276
20. Sotiriou E, Apalla Z, Maliamani F, et al. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. J Eur Acad Dermatol Venereol. Sep 2009; 23(9):1061-1065. PMID 19470041
21. Kurwa HA, Yong-Gee SA, Seed PT, et al. A randomized paired comparison of photodynamic therapy and topical 5- fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol. Sep 1999; 41(3 Pt 1):414-418. PMID 10459115
22. Wang H, Xu Y, Shi J, et al. Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis. Photodermatol Photoimmunol Photomed. Jan 2015; 31(1):44-53. PMID 25377432
23. Mpourazanis G, Mpourazanis P, Stogiannidis G, et al. The effectiveness of photodynamic therapy and cryotherapy on patients with basal cell carcinoma: A systematic review and meta-analysis. Dermatol Ther. Nov 2020; 33(6):e13881. PMID 32558087
24. Zou Y, Zhao Y, Yu J, et al. Photodynamic therapy versus surgical excision to basal cell carcinoma: meta- analysis. J Cosmet Dermatol. Dec 2016; 15(4):374-382. PMID 27363535
25. Bath-Hextall FJ, Perkins W, Bong J, et al. Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev. Jan 24 2007; (1):CD003412. PMID 17253489

26. Roozeboom MH, Arits AH, Mosterd K, et al. Three-year follow-up results of photodynamic therapy vs. imiquimod vs. fluorouracil for treatment of superficial basal cell carcinoma: a single-blind, noninferiority, randomized controlled trial. J Invest Dermatol. Aug 2016; 136(8):1568-1574. PMID 27113429
27. Szeimies RM, Ibbotson S, Murrell DF, et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. J Eur Acad Dermatol Venereol. Nov 2008; 22(11):1302-1311. PMID 18624836
28. Rhodes LE, de Rie M, Enstrom Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs. surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol. Jan 2004; 140(1):17-23. PMID 14732655
29. Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs. surgery for nodular basal cell carcinoma. Arch Dermatol. Sep 2007; 143(9):1131-1136. PMID 17875873
30. Bath-Hextall FJ, Matin RN, Wilkinson D, et al. Interventions for cutaneous Bowen's disease. Cochrane Database Syst Rev. Jun 24 2013; 2013(6):CD007281. PMID 23794286
31. Xue WL, Ruan JQ, Liu HY, et al. Efficacy of Photodynamic Therapy for the Treatment of Bowen's Disease: A Meta-Analysis of Randomized Controlled Trials. Dermatology. 2022; 238(3):542-550. PMID 34657035
32. Yongpisarn T, Rigo R, Minkis K. Durable Clearance Rate of Photodynamic Therapy for Bowen Disease and Cutaneous Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. Dermatol Surg. Apr 01 2022; 48(4):395-400. PMID 35143444
33. Zhong S, Zhang R, Mei X, et al. Efficacy of photodynamic therapy for the treatment of Bowen's disease: An updated systematic review and meta-analysis of randomized controlled trials. Photodiagnosis Photodyn Ther. Dec 2020; 32:102037. PMID 33011394
34. Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or Fluorouracil for treatment of squamous cell carcinoma in situ: Results of a multicenter randomized trial. Arch Dermatol. Jun 2006; 142(6):729-735. PMID 16785375
35. Salim A, Leman JA, McColl JH, et al. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol. Mar 2003; 148(3):539-543. PMID 12653747
36. Lansbury L, Bath-Hextall F, Perkins W, et al. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ. Nov 04 2013; 347:f6153. PMID 24191270
37. Barbaric J, Abbott R, Posadzki P, et al. Light therapies for acne. Cochrane Database Syst Rev. Sep 27 2016; 9(9):CD007917. PMID 27670126
38. Wu Y, Deng Y, Huang P. Application of red light therapy for moderate-to-severe acne vulgaris: A systematic review and meta-analysis. J Cosmet Dermatol. Nov 2021; 20(11):3498-3508. PMID 34363730
39. Wojewoda K, Gillstedt M, Tovi J, et al. Optimizing treatment of acne with photodynamic therapy (PDT) to achieve long-term remission and reduce side effects. A prospective randomized controlled trial. J Photochem Photobiol B. Oct 2021; 223:112299. PMID 34500216

40. Nicklas C, Rubio R, Crdenas C et al. Comparison of efficacy of aminolaevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris-A simple, blind, randomized, and controlled trial. Photodermatol Photoimmunol Photomed. Jan 2019; 35(1):3-10. PMID 29993146.
41. Xu X, Zheng Y, Zhao Z et al. Efficacy of photodynamic therapy combined with minocycline for treatment of moderate to severe facial acne vulgaris and influence on quality of life. Medicine (Baltimore). Dec 2017; 96(51):e9366. PMID 29390528
42. Pariser DM, Eichenfield LF, Bukhalo M, et al. Photodynamic therapy with methyl aminolaevulinate 80 mg g(-1) for severe facial acne vulgaris: a randomized vehicle-controlled study. Br J Dermatol. Apr 2016; 174(4):770-777. PMID 26663215
43. Orringer JS, Sachs DL, Bailey E, et al. Photodynamic therapy for acne vulgaris: a randomized, controlled, split- face clinical trial of topical aminolevulinic acid and pulsed dye laser therapy. J Cosmet Dermatol. Mar 2010; 9(1):28-34. PMID 20367670
44. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. Br J Dermatol. May 2006; 154(5):969-976. PMID 16634903
45. Reshetylo S, Narla S, Bakker C, et al. Systematic review of photodynamic therapy for the treatment of hidradenitis suppurativa. Photodermatol Photoimmunol Photomed. Jan 2023; 39(1):39-50. PMID 35713108
46. Yang Y, Shen S, Wang P, et al. Efficacy of photodynamic therapy in actinic cheilitis: A systematic review. Photodiagnosis Photodyn Ther. Jun 2022; 38:102782. PMID 35218940
47. Shen JJ, Jemec GBE, Arendrup MC, et al. Photodynamic therapy treatment of superficial fungal infections: A systematic review. Photodiagnosis Photodyn Ther. Sep 2020; 31:101774. PMID 32339671
48. Wu Q, Tu P, Zhou G, et al. A dose-finding study for hemoporfin in photodynamic therapy for port-wine stain: A multicenter randomized double-blind phase IIb trial. Photodermatol Photoimmunol Photomed. Sep 2018; 34(5):314-321. PMID 29533491
49. Gold M, Bridges TM, Bradshaw VL, et al. ALA-PDT and blue light therapy for hidradenitis suppurativa. J Drugs Dermatol. 2004; 3(1 Suppl):S32-35. PMID 14964759
50. Schweiger ES, Riddle CC, Aires DJ. Treatment of hidradenitis suppurativa by photodynamic therapy with aminolevulinic acid: preliminary results. J Drugs Dermatol. Apr 2011; 10(4):381-386. PMID 21455548
51. Calzavara-Pinton PG, Venturini M, Capezzera R, et al. Photodynamic therapy of interdigital mycoses of the feet with topical application of 5-aminolevulinic acid. Photodermatol Photoimmunol Photomed. Jun 2004; 20(3):144-147. PMID 15144392
52. Mostafa D, Tarakji B. Photodynamic therapy in treatment of oral lichen planus. J Clin Med Res. Jun 2015; 7(6):393-399. PMID 25883701
53. Yazdani Abyaneh MA, Falto-Aizpurua L, Griffith RD, et al. Photodynamic therapy for actinic cheilitis: a systematic review. Dermatol Surg. Feb 2015; 41(2):189-198. PMID 25627629
54. Xiao Q, Li Q, Yuan KH, et al. Photodynamic therapy of port-wine stains: long-term efficacy and complication in Chinese patients. J Dermatol. Dec 2011; 38(12):1146-1152. PMID 22032688

55. Chun-Hua T, Li-Qiang G, Hua W, et al. Efficacy and safety of hemoporfin photodynamic therapy for port-wine stains in paediatric patients: A retrospective study of 439 cases at a single centre. Photodiagnosis Photodyn Ther. Dec 2021; 36:102568. PMID 34614424
56. Zhang LC, Yang J, Huang YB, et al. Efficacy of hemoporfin photodynamic therapy for pulsed dye laser-resistant facial port-wine stains in 107 children: A retrospective study. Indian J Dermatol Venereol Leprol. Mar-Apr 2022; 88(2):275. PMID 34672476
57. Eisen DB, Asgari MM, Bennett DD, et al. Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol. Oct 2021; 85(4):e209-e233. PMID 33820677
58. Kim JYS, Kozlow JH, Mittal B, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol. Mar 2018; 78(3):540-559. PMID 29331385
59. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. May 2016; 74(5):945-973.e33. PMID 26897386
60. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer. Version 1.2024. Available at: <https://www.nccn.org> (accessed November 11, 2024).
61. National Comprehensive Cancer Network (NCCN). NCCN Practice Guidelines in Oncology: Basal Cell Skin Cancer. Version 3.2024. Available at <https://www.nccn.org> (accessed November 11, 2024).
62. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management. J Am Acad Dermatol. Jul 2019; 81(1):76-90. PMID 30872156
63. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Treatment of Actinic Keratosis (250.4). 2011. Available at <https://www.cms.gov> (accessed October 12, 2023).

## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

## Policy History/Revision

| Date | Description of Change |
|---|---|
| 12/15/2024 | Document updated with literature review. Coverage unchanged.<br>Added/updated the following references: 31, 32, 45, 46, and 60-62. |
| 12/01/2023 | Reviewed. No changes. |

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|---|---|
| 04/15/2022 | Document updated with literature review. Coverage unchanged. Added references 1, 3, 4, 15-16, 23, 31, 36, 37, 43, 51-55; others updated. |
| 07/01/2021 | Reviewed. No changes. |
| 09/01/2020 | Document updated with literature review. The following changes were made in the medically necessary Coverage statement for photodynamic therapy 1) Added nonhyperkeratotic actinic keratoses (AK) of the upper extremities; 2) Added "cutaneous" to the state " Cutaneous squamous cell carcinoma in situ (Bowen disease) only when surgery and radiation are contraindicated; 3) Added "and upper extremities" to state "actinic keratoses (AK) for all other body parts (excluding the face, scalp, and upper extremities)" is considered experimental, investigational and/or unproven. 4) Expanded NOTE 1 to include: "Based on characteristics of patients enrolled in randomized controlled trials, 4 or more lesions per site (face, scalp, or upper extremities) is an appropriate threshold for use of PDT for patients with nonhyperkeratotic actinic keratosis". Added references: 16, 18-20, 33, 34, 38. |
| 06/15/2019 | Reviewed. No change(s). |
| 04/15/2018 | Document updated with literature review. Coverage unchanged. |
| 12/01/2017 | Document updated with literature review. The following was added to the experimental, investigational and /or unproven coverage statement: Non-hyperkeratotic actinic keratoses (AK) for all other body parts (excluding the face and scalp). Added to Coverage: NOTE: Photodynamic typically involves 2 treatments spaced a week apart; more than 1 treatment series may be required. Title changed from: Photodynamic Therapy (PDT) for the Treatment of Actinic Keratoses (AK) and Other Skin Lesions. |
| 04/15/2017 | Reviewed. No changes. |
| 06/15/2016 | Document updated with literature review. The following was added to coverage: 1) "low risk" to identify risk level for basal cell carcinoma and 2) "nodular" included as an example of basal skin cancer. |
| 07/15/2015 | Document updated with literature review. Coverage unchanged. |
| 07/01/2014 | Reviewed. No changes. |
| 02/01/2013 | Document updated with literature review. Coverage unchanged. |
| 10/15/2010 | Document updated with literature review. Changed coverage statements: deleted requirement of ten or more lesions to be to be medically necessary for non-hyperkeratotic actinic keratoses, deleted type of light and method of treatment, only PDT is reviewed. |
| 08/15/2010 | Document updated with literature review. Changed coverage statements: deleted requirement of ten or more lesions to be to be medically necessary for non-hyperkeratotic actinic keratoses, deleted type of light and method of treatment, only PDT is reviewed. |
| 09/01/2008 | Revised/updated entire document |
| 09/15/2006 | Coverage Revised. |
| 03/01/2006 | New medical document |