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## Medical Policy



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(See policy history boxes for previous effective dates)

### **Title: Photodynamic Therapy for Dermatologic Applications**

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#### **Description/Background**

##### **PHOTODYNAMIC THERAPY**

Photodynamic therapy (PDT) refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Two common photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester, methyl aminolevulinate (MAL). When applied topically, these agents pass readily through abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. 5-ALA and MAL are metabolized by underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404 to 420 nm and 635 nm, respectively) generates reactive oxygen species that are cytotoxic, ultimately destroying the lesion. PDT can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results. PDT with topical ALA has been investigated primarily as a treatment of actinic keratoses (AKs).

##### **Applications**

It has also been investigated as a treatment of other superficial dermatologic lesions, such as Bowen disease, acne vulgaris, mycoses, hidradenitis suppurativa, and superficial and nodular basal cell carcinoma (BCC). Potential cosmetic indications include skin rejuvenation and hair removal.

Actinic keratoses are rough, scaly, or warty premalignant growths on sun-exposed skin that are very common in older people with fair complexions, with a prevalence of greater than 80% in fair-skinned people older than 60 years of age. In some cases, actinic keratosis may progress to squamous cell carcinoma (SCC). Available treatments for actinic keratoses can be divided into surgical and nonsurgical methods. Surgical treatments used to treat 1 or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodesiccation), and laser surgery. Nonsurgical treatments include cryotherapy, topical

chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (chemical peels), and dermabrasion. Topical treatments are generally used in patients with multiple lesions and involve extensive areas of skin. Under some circumstances, combinations treatments may be used.

Nonmelanoma skin cancers are the most common malignancies in the white population. BCC is most often found in light-skinned people and is the most common of the cutaneous malignancies. Although BCC tumors rarely metastasize, they can be locally invasive if left untreated, leading to significant local destruction and disfigurement. The most prevalent forms of BCC are nodular BCC and superficial BCC. Bowen disease is an SCC in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive SCC. Lesions may appear on sun-exposed or covered skin. Excision surgery is the preferred treatment for smaller nonmelanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-FU, imiquimod, and cryotherapy. Poor cosmesis resulting from surgical procedures and skin irritation induced by topical agents can be significant problems.

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## Regulatory Status

In 1999, Levulan® Kerastick™, a topical preparation of aminolevulinic acid (ALA), in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, was approved by the U.S. Food and Drug Administration (FDA) for the following indication: “The Levulan Kerastick for topical solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of nonhyperkeratotic actinic keratoses of the face and scalp.” The product is applied in the physician’s office. FDA product code: MVF.

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 actinic keratoses of mild-to-moderate severity on the face and scalp. The treatment is to be administered by a healthcare provider.

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

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

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## Medical Policy Statement

The safety and effectiveness of photodynamic therapy for dermatologic applications have been established. It may be considered a useful therapeutic option when indicated.

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## Inclusionary and Exclusionary Guidelines

Photodynamic therapy is considered established as a treatment of:

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

Photodynamic therapy is considered experimental/investigational for other dermatologic, including but not limited to, acne vulgaris, high-risk basal cell carcinomas, Hidradenitis Suppurativa, and mycoses.

When photodynamic therapy is used as a cosmetic procedure (e.g., as a technique of skin rejuvenation or hair removal) it is not a covered benefit.

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### Established codes:

96567	96573	96574	J3396
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### Other codes (investigational, not medically necessary, etc.):

N/A

*Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*

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## Rationale

Evidence reviews 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, 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 a technology, two 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 U.S. Food and Drug Administration (FDA)-approved photosensitizing agents.

## **ACTINIC KERATOSES**

### **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 on the face or scalp.

The following **PICOs** were used to select literature to inform this review.

### **Populations**

The relevant population of interest are individuals with nonhyperkeratotic actinic keratoses on the face or scalp. Actinic keratoses 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, actinic keratosis may progress to squamous cell carcinoma.

### **Interventions**

The therapy being considered is photodynamic therapy.

Patients with nonhyperkeratotic AKs on the face, scalp, or upper extremities are actively managed by dermatologists and oncologists in an outpatient setting.

### **Comparators**

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

## Outcomes

The general outcomes of interest are symptoms, change in disease status, quality of life, and treatment-related morbidity. Specific outcomes of interest include complete clearance of actinic keratoses, percentage of actinic keratoses cleared, severity of adverse events, patient reported outcomes, and recurrence of lesions.<sup>1</sup> 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

In 2014, Patel et al reviewed RCTs with at least 10 patients that addressed the efficacy of topical PDT compared with an alternative (i.e., non-PDT) treatment of actinic keratosis.<sup>2</sup> Thirteen studies (total N=641 participants) met the reviewers' inclusion criteria. Studies compared PDT with cryotherapy (n=6), fluorouracil (n=2), imiquimod (n=4), and carbon dioxide laser (n=1). Seven studies used ALA and the other 6 used MAL as the PDT sensitizer. Most studies focused on 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 and cryotherapy were suitable for meta-analysis. The pooled lesion response rate 3 months after treatment was significantly higher with PDT than with cryotherapy (pooled relative risk [RR], 1.14, 95% confidence interval [CI], 1.11 to 1.18). Due to heterogeneity among the interventions, other data were not pooled.

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.<sup>3</sup> 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 ( $\geq 12$  months) of interventions for AK of the face and/or scalp.<sup>4</sup> 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 MALvPDT (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**

In 2003, Pariser et al conducted a randomized, placebo-controlled trial of 80 patients with actinic keratoses.<sup>5</sup> The authors reported that the complete response (CR) rate for the methyl aminolevulinate (MAL) group was 89% and 38% in the placebo group.

In 2006, Morton et al published an industry-sponsored, 25-center, randomized, left-right comparison of single PDT and cryotherapy in 119 subjects with actinic keratoses on the face or scalp.<sup>6</sup> At 12-week follow-up, PDT resulted in a significantly higher rate of cured lesions (86.9%) than cryotherapy (76.2%). Lesions with a non-CR were retreated after 12 weeks; a total of 108 (14.9%) of 725 lesions received a second PDT session; 191 (26.8%) of 714 lesions required a second cryotherapy treatment. At 24 weeks, groups showed equivalent clearance (85.8% vs. 82.5%, respectively). Greater skin discomfort was reported with PDT than with cryotherapy. Investigator-rated cosmetic outcomes showed no difference in the percentage of subjects with poor cosmetic outcomes (0.3% vs. 0.5%, respectively), with more subjects rated as having excellent outcomes at 24 weeks after PDT (77.2% vs. 49.7%, respectively). With PDT, 22.5% had cosmetic ratings of fair or good compared with 49.9% for cryotherapy.

A 2009 double-blind RCT conducted in Germany by Hauschild et al evaluated photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) using a self-adhesive patch.<sup>7</sup> Eligibility criteria included white patients, age 18 years and older, with skin type I to IV (pale to olive complexion), and actinic keratoses on the head of mild or moderate grade, as defined by Cockerell (maximum diameter, 1.8 cm; interlesional distance, at least 1 cm). Patients were randomized to 5-ALA patches containing 5-ALA 8 mg or identical placebo patches. Patches were square, measuring 4 cm<sup>2</sup>, and patients received 3 to 8 of them, depending on the number of study lesions. The primary efficacy outcome was the complete clinical clearance rate 12 weeks after PDT. A total of 99 of 103 randomized patients were included in the primary efficacy analysis. Complete clinical clearance rate on a per patient basis (all lesions cleared) was 62% (41/66) in the 5-ALA patch group and 6% (2/33) in the placebo patch group; there was a statistically significant difference favoring PDT.

In 2010, Szeimies et al reported on a Phase 3 clinical trial using a stable 5-aminolaevulinic acid nanoemulsion formulation (BF-200 ALA) developed for PDT for actinic keratosis.<sup>8</sup> 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 actinic keratosis 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 actinic keratoses 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 placebo in respect to patient complete clearance rate (per-protocol group, 64% vs. 11%;  $p<0.001$ ) 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 (Aktelite® CL128 and PhotoDyn® 750) at both time points of the assessment. The patient and lesion complete clearance rates after illumination with the Aktelite CL128 were 96% and 99%, respectively. No adverse events (discomfort, pain) were mentioned by patients related to 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 Aktelite® 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.

In 2010, Szeimies et al in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch to cryotherapy.<sup>9</sup> The study had the same eligibility criteria and primary outcome as the Hauschild study<sup>2</sup> (previously described). A total of 148 patients were randomized to a 5-ALA patch group, 49 to a placebo group, and 149 to a cryotherapy group. The study used a test of noninferiority of PDT versus cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT and cryotherapy. The rate of complete clearance of all lesions was 67% (86/129) in the 5-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 5-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 completed the final visit 1 year after treatment. Overall clearance rate on a lesion basis was still statistically higher in the 5-ALA patch group than in the placebo (in both studies) or the cryosurgery (in the second study) groups. Thirty-two percent of patients in the 5-ALA group from the first study and 50% of patients in the 5-ALA group from the second study were still completely free from lesions. The corresponding 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, but no serious adverse effects due to study intervention were documented.

A 2012 randomized pilot study by Serra-Guillen et al from Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments.<sup>10</sup> Patients with nonhyperkeratotic actinic keratoses 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) PDT, as above, followed by 4 weeks of imiquimod cream ( $n=32$ ). Follow-up occurred 1 month after PDT (group 1) or 1 month after the end of treatment with imiquimod (groups 2 and 3). The primary outcome measure (complete clinical response) was defined as the total absence of actinic keratoses by visual evaluation and palpation. Complete clinical response was achieved by 4 (10%) of patients in group 1, 9 (27%) of patients in group 2, and 12 (37.5%) of patients in group 3. There was a statistically significantly higher rate of CR in the PDT plus imiquimod group compared with PDT only ( $p=0.004$ ). A limitation of the study was that the PDT-only group had shorter follow-up, which could at least partially explain the lower rate of CR.

In 2012, Dirschka et al reported on an industry-sponsored randomized, multicenter, observer-blind, placebo-controlled, interindividual trial comparing BF-200 ALA for the treatment of actinic keratosis with methyl-5-aminolevulinate (MAL) cream and placebo.<sup>11</sup> Six hundred patients with 4-to-8 mild-to-moderate actinic keratosis lesions on the face and/or bald scalp were enrolled in 26 study centers. Five hundred forty-nine 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%;  $p<0.001$ ) 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%;  $p<0.05$ ). 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 Result for Light Source Effects on Clearance Rates**

Study	Patients/Lesions	Patient Total Clearance Rate		Lesion Total Clearance Rate	
		<i>Narrow-Light Spectrum, %</i>	<i>Broad-Light Spectrum, %</i>	<i>Narrow-Light Spectrum, %</i>	<i>Broad-Light Spectrum, %</i>
Dirschka et al (2012)					
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; BP-200 ALA: nanoemulsion-based 5-ALA formulation; MAL: methyl-5-aminolevulinate; PDT: photodynamic therapy.

In 2013 Dirschka 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 actinic keratosis.<sup>12</sup> No safety concerns were reported. Recurrence rates were similar for BF-200 ALA and MAL. The percentage of patients who achieve complete clearance with PDT and remained completely clear for at least 12 months after PDT were 47% for BF-200 ALA (both studies) 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 confidence intervals were reported.

In 2014, Zane et al published results of an RCT on the treatment of multiple actinic keratoses of the face and scalp.<sup>13</sup> 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 ( $p < 0.001$ ). 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 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.

In 2016, Reinhold et al published results from a double-blind RTC comparing BF-200 ALA with placebo for the field-directed treatment of mild-to-moderate actinic keratoses with PDT using the BF-RhodoLED lamp.<sup>14</sup> 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 vs. 22% using placebo ( $p < 0.001$ ), and a lesion complete clearance rate of 94.3% using BF-200 ALA vs. 32.9% using placebo ( $p < 0.001$ ). 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 a 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 actinic keratosis treatment.

Karrer et al (2021) reported findings from an RCT comparing MAL-PDT with cryosurgery in 58 patients with AK of the face.<sup>15</sup> 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.<sup>16</sup> 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: Actinic Keratoses 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.<sup>4</sup> Thirteen studies (N=1380 participants) met the reviewers' inclusion criteria. Studies evaluating PDT included comparisons to placebo (n=4), cryotherapy (n=3), 5-FU (n=2), colchicine (n=1), and imiquimod (n=1). 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).<sup>17-19</sup> 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.<sup>17</sup> 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 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.<sup>19</sup> 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<sup>20</sup> or 5-FU<sup>21</sup> and found similar efficacy between the active treatment groups after 6 months of follow-up (Tables 2 and 3).

**Table 2. Characteristics of RCTs of PDT for AKs on the Upper Extremities**

Study; Trial	Countries	Sites	Dates	Design	Participants	Interventions	
						Active	Comparator
Jiang et al (2019) NCT02137785	U.S.	13	2014-2015	Parallel groups	269 adults 18 or older with 4 to 15 Grade 1 or 2 AKs on 1 upper extremity	20% ALA-blue light PDT N=135	VEH /PDT N=134

Schmieder et al (2012) 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)	U.S.	NR	NR	Intra-individual, randomized to alternate upper extremities	15 adults (ages 42 to 79 years) with 4 or more AK lesions on the dorsal sides of both hands and forearms	20% ALA-blue light PDT	VEH /PDT
Sotiriou et al (2009)	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)	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

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

**Table 3. Results of RCTs of PDT for AKs on the Upper Extremities**

Study	Complete Clearance	Lesion Reduction
Jiang et al (2019)		
ALA /PDT	8 weeks: 35/135 (25.9%) 12 weeks:42/135 (31.1%)	
VEH /PDT	8 weeks: 12/134 (9.0%) 12 weeks: 17/134 (12.7%)	
P-value	.0001 at 8 and 12 weeks	
Schmieder et al (2012)		
ALA /PDT	8 weeks: 8/35 (22.9%) 12 weeks: 12/35 (34.3%)	

VEH /PDT	8 weeks: 0/35 (0%) 12 weeks: 1/35 (2.9%)	
P-value	.002 at 12 weeks; 8 weeks NR	
Taub et al (2011)		Mean (SD) lesion count reduction at 4 weeks
ALA /PDT		58.4% (22.2)
VEH /PDT		24.8% (20.6)
P-value		.004
Sotiriou et al (2009)		
ALA /PDT	4 weeks: 87/124 (70.16%) 6 months: 81/124 (65.32%); 95% CI, 56.9 to 73.7%	
Imiquimod	4 weeks: 21/115 (18.26%) 6 months: 64/115 (55.65%); 95% CI, 46.6 to 64.7%	
p-value	<.05 at 4 weeks >.05 at 6 months	
Kurwa et al (1999)		Mean reduction in lesion area at 6 months:
ALA /PDT		73% (95% CI, 61 to 84%).
5-FU		70% (95% CI, 61 to 80%)
Difference		2% (95% CI, -10 to 14%; p=.721)

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

**Table 4. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Jiang et al (2019) NCT02137785					
Schmieder et al (2012) NCT01458587					
Taub et al (2011)				1. complete clearance not reported	1. 4 weeks
Sotiriou et al (2009)			4. Patient applied		
Kurwa et al (1999)			4. Patient applied		

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

<sup>a</sup> 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.

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

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered

effectively.

<sup>d</sup> 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. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Jiang et al (2019) NCT02137785	3. allocation concealment method not reported	1. Outcome assessors, but not patients, were blinded				
Schmieder et al (2012) NCT01458587	3. allocation concealment method not reported	1. Outcome assessors, but not patients, were blinded				
Taub et al (2011)	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)	3. allocation concealment method not reported	1. Not blinded			1. small sample size (N=30), no power calculation	
Kurwa et al (1999)	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 review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> 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).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> 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: Actinic Keratoses 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 BCC.

The following **PICOs** were used to select literature to inform this review.

### **Populations**

The relevant population of interest are 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. Patients with low-risk BCC are actively managed by dermatologists and oncologists in an outpatient setting.

### **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, quality of life, and treatment-related morbidity. Specific outcomes of interest include complete clearance rate, recurrence rate, cosmetic outcomes, and adverse events.<sup>19</sup> 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 principles outlined for indication 1.

### **Systematic Reviews**

Mpourazanis et al (2020) compared PDT to cryotherapy for BCC in a systemic review of 19 RCTs and prospective observational trials.<sup>23</sup> 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; 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.

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

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

A 2016 meta-analysis by Zou et al identified 5 RCTs comparing PDT and surgical excision in patients with nodular BCC that had at least 3 months of follow-up.<sup>24</sup> 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 2007 Cochrane review evaluated surgical, destructive (including PDT), and chemical interventions for basal cell carcinoma (BCC).<sup>25</sup> Reviewers concluded that surgery and radiotherapy appeared to be the most effective treatments, with the best results obtained with surgery. In addition, they stated that cosmetic outcomes appear to be good with PDT, but additional data with long-term follow-up are needed. Cochrane reviewers did not distinguish among BCC subtypes.

### **Randomized Controlled Trials**

A 2016 noninferiority RCT by Roozeboom et al compared MAL-PDT to imiquimod cream and to fluorouracil cream in patients with superficial BCC.<sup>26</sup> 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 in 2008 by Szeimies et al.<sup>27</sup> This trial compared MAL-PDT to surgery for small (8-20 mm) superficial BCC in 196 patients. At 3 months after treatment, 92% of lesions treated with MAL-PDT showed clinical response, compared with 99% of lesions treated with surgery (per protocol analysis). At 12-month follow-

up, no 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.

In 2007, Rhodes et al published 5-year follow-up to an industry-sponsored multicenter randomized trial comparing MAL-PDT with surgery for nodular BCC.<sup>28,29</sup> 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 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 placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery.

## **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 **PICOs** were used to select literature to inform this review.

### **Populations**

The relevant population of interest are 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, quality of life, and treatment-related morbidity. Specific outcomes of interest include clearance of lesions, recurrence, cosmetic outcomes, and adverse events.<sup>27</sup> 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 principles outlined for indication 1.

### **Systematic Reviews**

Xue et al (2022) performed a meta-analysis of 8 RCTs that compared PDT for Bowen disease.<sup>31</sup> Compared to other topical treatments (5-FU and cryotherapy), PDT resulted in a higher complete response 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.<sup>32</sup> 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.<sup>33</sup> 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 published a Cochrane review of interventions for cutaneous Bowen disease in 2013.<sup>30</sup> Reviewers identified 7 RCTs evaluating PDT: 4 compared 2 PDT protocols, 1 compared PDT with cryotherapy, 1 compared PDT with topical 5-fluorouracil (5-FU), and 1 compared PDT with both PDT and 5-FU. Reviewers did not pool study results.

### **Randomized Controlled Trials**

The largest study ( $N=225$  patients) was a 3-arm trial published in 2006 by Morton et al.<sup>34</sup> 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 in 2003.<sup>35</sup> 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.

### **Section Summary: Squamous Cell Carcinoma In Situ (Bowen Disease)**

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 **PICOs** were used to select literature to inform this review.

### **Populations**

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

Individuals with squamous cell carcinoma in situ are actively managed by dermatologists and oncologists in an outpatient setting.

### **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, quality of life, surgery, and radiotherapy. Specific outcomes of interest include recurrence, initial response to treatment, cosmetic appearance, and death due to disease.<sup>30</sup> Recurrence can be assessed during follow-up from one month to 10 years after treatment.

### **Study Selection Criteria**

Methodologically credible studies were selected using the principles outlined for indication 1.

### **Systematic Reviews**

In 2013, Lansbury et al published a systematic review of observational studies evaluating interventions for nonmetastatic cutaneous squamous cell carcinoma (SCC).<sup>36</sup> Reviewers identified 14 prospective studies evaluating PDT. Sample sizes ranged from 4 to 71 patients, with only 3 studies included more than 25 patients. These studies evaluated various PDT protocols. There was only 1 comparative study, and it compared 2 different PDT regimens. In meta-analysis, a mean of 72% of lesions had a CR to treatment (95% CI, 61.5% to 81.4%;

$I^2=71\%$ ). Eight studies addressed recurrence rates in patients who were initial responders. In meta-analysis, the pooled odds of recurrence was 26.4% (95% CI, 12.3% to 43.7%;  $I^2=72\%$ ).

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

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

## **ACNE**

### **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 **PICOs** were used to select literature to inform this review.

### **Populations**

The relevant population of interest are 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, quality of life, 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.<sup>31</sup> 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.

### **Study Selection Criteria**

Methodologically credible studies were selected using the principles outlined for indication 1.

### **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.<sup>38</sup> 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.

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

## Randomized Controlled Trials

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

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

Study	Countries	Sites	Participants	Interventions	
				Active	Comparator
Zhang et al (2023)	China	3	152 patients aged 18 to 40 years with moderate to severe acne	ALA/PDT	Isotretinoin 0.5 mg/kg daily (total dose of 90mg/kg)
Wojewoda et al (2021)	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)	Chile	1	46 patients with moderate inflammatory facial acne	ALA /PDT	Doxycycline plus adapalene gel
Xu et al (2017)	China	1	95 patients with moderate-to-severe facial acne	Minocycline hydrochloride capsule plus PDT	Minocycline hydrochloride capsule without PDT
Pariser et al (2016)	U.S.	5	153 patients with severe facial acne	MAL /PDT	Placebo cream
Orringer et al (2010)	U.S.	1	44 patients with facial acne, split-faced	ALA /PDT	No treatment

ALA: aminolevulinic acid; MAL-PDT: 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 (%)
Zhang et al (2023)		
ALA/PDT		<ul style="list-style-type: none"> <li>Erythema (79)</li> <li>Hyperpigmentation (65)</li> <li>Pain (66)</li> <li>Dryness (77)</li> </ul>
Isotretinoin		<ul style="list-style-type: none"> <li>Oral dryness (93)</li> <li>Increased liver enzymes (3)</li> <li>Increased lipids (21)</li> <li>Dryness (91)</li> </ul>
Wojewoda et al (2021)		

MAL /PDT	Week 20: 2 treatments: -74% 4 treatments: -85%	<ul style="list-style-type: none"> <li>Erythema (20)</li> <li>Hyperpigmentation (7)</li> <li>Ulceration (2)</li> <li>Scarring (2)</li> </ul>
Placebo	Week 20: 2 treatments: -57% 4 treatments: -83%	<ul style="list-style-type: none"> <li>Erythema (9)</li> <li>Hyperpigmentation (8)</li> <li>Ulceration (1)</li> <li>Scarring (1)</li> </ul>
p-value	Week 20: 2 treatments:.08 4 treatments:.44	
Nicklas et al (2018)		
ALA /PDT	-12.0 (median)	
Doxycycline plus adapalene gel		
p-value	.038	
Xu et al (2017)		
Minocycline hydrochloride capsule plus PDT	-74.4%	<ul style="list-style-type: none"> <li>Pain (16.7)</li> <li>Burning sensation (14.6)</li> <li>Dizziness (6.3)</li> <li>Headache (4.2)</li> <li>Erythema (8.3)</li> <li>Hyperpigmentation (2.1)</li> </ul>
Minocycline hydrochloride capsule without PDT	-53.3%	<ul style="list-style-type: none"> <li>Dizziness (8.5)</li> <li>Headache (6.4)</li> </ul>
p-value	.001	
Pariser et al (2016)		
MAL /PDT	-15.6	<ul style="list-style-type: none"> <li>Pain (17)</li> </ul>
Placebo	-7.8	
p-value	.006	
Orringer et al (2010)		
MAL /PDT	-5.9	<ul style="list-style-type: none"> <li>Mild peeling (4.5)</li> <li>Hyperpigmentation (4.5)</li> <li>A small blister (2.3)</li> </ul>
No treatment	-2.5	
p-value	.04	

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

The purpose of gaps tables (see Tables 8 and 9) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

**Table 8. Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Zhang et al (2023)		2. Modified photodynamic therapy	2. Isotretinoin dose at lower end of range	1. Number of acne lesions not reported	
Wojewoda et al (2021)					
Nicklas et al (2018)					1. Short follow-up
Xu et al (2017)				4. No consensus on quantitative evaluation of acne severity	1. Short follow-up
Pariser et al (2016)					
Orringer et al (2010)					

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

<sup>a</sup> 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.

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

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

<sup>d</sup> 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. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Zhang et al (2023)		1. Patient blinding unreported		1. 52% of isotretinoin completed; 80% of photodynamic therapy completed	1. Sample size calculations not performed	3. Confidence interval not reported
Wojewoda et al (2021)				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)						
Xu et al (2017)					1. Sample size calculations not performed	
Pariser et al (2016)				1. 16% of participants did not complete trial		

Orringer et al (2010)				1. 34% of participants did not complete trial	1. Sample size calculations not performed	
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The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> 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).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> 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.

Zhang et al (2023) conducted an investigator-blind comparison of ALA/PDT with isotretinoin in 152 patients.<sup>39</sup> A modified PDT method with reduced incubation time and increased light dose was used. The primary outcome was the overall effective rate (i.e., the percent of patients with a clearance rate of 75% or more). Effective rates at 1 month were higher in the ALA/PDT group than in the isotretinoin group (66.23% vs. 13.33% by intention-to-treat analysis and 67.74% vs. 10.26% by per-protocol analysis; both  $p < .001$ ). Time to achieve 50% lesion improvement was lower with ALA/PDT (median, 1 week vs. 8 weeks). The majority of patients experienced anticipated adverse events, but most were mild. The trial is limited by a very high dropout rate ( $n=36$ ) in the isotretinoin group as well as limited demographic heterogeneity with the inclusion of only 3 sites, all located in China.

Wojewoda et al (2021) performed a double-blind RCT comparing MAL-PDT with placebo in patients with facial acne.<sup>40</sup> 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, 18-30 years; 26 male, 20 female) with moderate inflammatory facial acne.<sup>41</sup> In the trial, 23 patients received 2 sessions of PDT plus topical aminolevulinic acid, 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 ( $p=0.013$ ) and total lesions ( $p=0.038$ ) at 6 weeks. Similar results were found at 12 weeks ( $p=0.02$ ) for noninflammatory lesions;  $p=0.026$  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, 15-35 years; 41 male, 54 female) to compare the efficacy of minocycline plus PDT with minocycline alone in treating moderate-to-severe acne.<sup>42</sup> 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 two, four, six, and eight weeks after 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%;  $p<0.001$ ) as well as a greater reduction in noninflammatory lesions (-61.7% vs -42.4%;  $p<0.05$ ). Adverse events were mild and manageable. Limitations included a short follow-up and the lack of broad consensus on quantitative evaluation of acne severity.

In 2016, Pariser et al published a multicenter double-blind placebo-controlled, randomized trial evaluating MAL-PDT for severe facial acne.<sup>43</sup> A total of 153 patients were randomized and included in the intention-to-treat analysis, 100 to MAL-PDT and 53 to a matching vehicle (i.e., placebo) cream. All patients received 4 treatments, 2 weeks apart and were evaluated up to 12 weeks after the first treatment. One hundred twenty nine (84%) patients completed the study. The primary outcome (change from baseline in facial inflammatory lesion count at 12 weeks) was significantly lower in the MAL-PDT group (mean, -15.6) than the placebo group (mean, -7.8;  $p=0.006$ ). Change in facial noninflammatory lesion count at 12 weeks did not differ significantly between groups (-11.8 vs. -10.7;  $p=0.85$ ). The most commonly reported adverse events were pain ( $n=17$  [17%] in the MAL-PDT group vs. 0 in the placebo group) and a skin burning sensation ( $n=15$  [15%] in the PDT group vs. 5 [9%] in the placebo group). Most adverse events were mild- to-moderate, although 12 patients in the MAL-PDT group dropped out due to treatment-related adverse events.

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

In some studies, higher rates of adverse events with PDT have been reported. For example, a 2006 study by Wiegell et al in Denmark evaluated patients 12 weeks after MAL-PDT ( $n=21$ ) or a control group ( $n=15$ ).<sup>45</sup> There was a 68% reduction from baseline in inflammatory lesions in the treatment group and no change in the control group ( $p=0.023$ ). However, all patients experienced moderate-to-severe pain after treatment and 7 (33%) of 21 in the treatment group did not receive the second treatment due to pain.

### **Section Summary: Acne**

Several RCTs and 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 **PICOs** were used to select literature to inform this review.

### **Populations**

The relevant population of interest are 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, quality of life, and treatment-related morbidity.

### **Study Selection Criteria**

Methodologically credible studies were selected using the principles outlined for indication 1.

### **Systematic Reviews**

Reshetylo et al (2022) published a systematic review of PDT for treatment of hidradenitis suppurativa.<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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, 16-50 years) to measure the efficacy of different dose levels of hemoporfin with PDT in treating port wine stain.<sup>48</sup> 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 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. Only case series were identified, including series on PDT for hidradenitis suppurative<sup>49,50</sup> and PDT for interdigital mycoses.<sup>51</sup> Most series were small (e.g., <25 patients). There are a few systematic reviews. For example, a 2015 systematic review by Mostafa and Tarakji of studies evaluating PDT for oral lichen planus identified 5 case reports<sup>52</sup> and a 2015 systematic review by Yazdani Abyaneh et al identified 15 case series (total N=223 patients) on PDT for actinic cheilitis.<sup>53</sup> In 2011, Xiao et al in China published a large retrospective case series.<sup>54</sup> 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 had previous lesion treatments or were lost to follow-up. After treatment, 26 patients (5.1%) were considered to have complete clearing, 48 (9.5%) had significant (<75% to <100%) clearing, and 77 (15.2%) had moderate (<50% to <75%) clearing. This single uncontrolled study is insufficient to draw conclusions about the effect of PDT on health outcomes in patients with port wine stains.

### **Section Summary: Other Noncancerous Dermatologic Conditions**

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

### **SUMMARY OF EVIDENCE**

For individuals who have nonhyperkeratotic actinic keratoses on the face or scalp who receive photodynamic therapy (PDT), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses on the face or scalp compared

with placebo or other active interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have low-risk basal cell carcinoma (BCC) who receive PDT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, 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 two 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-fluorouracil 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 a meaningful improvement in the net health outcome.

For individuals who have squamous cell carcinoma in situ who receive PDT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events/cosmetic outcomes 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 a meaningful improvement in the net health outcome.

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

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

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

## SUPPLEMENTAL INFORMATION

### PRACTICE GUIDELINES AND POSITION STATEMENTS

#### American Academy of Dermatology

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

- Actinic keratosis (2021): PDT is included in the following recommendations for patients with AK:<sup>58</sup>
  - 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.<sup>59</sup> 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 (2024): PDT is one of several physical modalities to have insufficient evidence to develop a recommendation.<sup>60</sup>

#### 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.<sup>63</sup> 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.

#### National Comprehensive Cancer Network

The NCCN has published clinical practice guidelines on basal cell skin cancers and squamous cell skin cancers.

For squamous cell skin cancers, the NCCN (squamous cell skin cancer, v.1.2024) made the following recommendations: "In patients with SCC [squamous cell carcinoma] in situ (Bowen's disease) alternative, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (e.g., ALA, porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities."<sup>61</sup>

For basal cell skin cancer, NCCN (v.3.2024) made the following recommendations: "In patients with low-risk, superficial basal cell skin cancer, where surgery and radiation are contraindicated or impractical, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (e.g., aminolevulinic acid ALA., porfimer sodium), or vigorous

cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities.”<sup>62</sup>

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 10.

**Table 10. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
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 <sup>a</sup>	Superficial Basal Cell Cancer's Photodynamic Therapy: Comparing Three Photosensitises: Hexylaminolevulinate and Aminolevulinic Acid Nano Emulsion Versus Methylaminolevulinate	117	Dec 2025
NCT03573401 <sup>a</sup>	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 2027
NCT05662202 <sup>a</sup>	Study to Evaluate the Safety, Tolerability and Efficacy of BF-200 ALA (Ameluz®) in the Field-directed Treatment of Actinic Keratosis (AK) on the Extremities and Neck/Trunk With Photodynamic Therapy (PDT) Using a RhodoLED Lamp	165	Apr 2025
<b>Unpublished</b>			
NCT05522036	Clinical Evaluation of a Short Illumination Duration (35 Minutes) When Performing Photodynamic Therapy of Actinic Keratosis Using the Dermaris ®	25	Jun 2023
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
NCT05245045	Efficacy and Safety of STBF Photodynamic Therapy for Moderate and Severe Acne Vulgaris	20	Feb 2023
NCT04167982	Efficacy and Safety of Painless 5-aminolevulinic Acid Photodynamic Therapy for the Treatment of Moderate and Severe Acne Vulgaris-- A Multi-center, Randomized Controlled Clinical Trial	234	Nov 2022

NCT: national clinical trial

<sup>a</sup> Denotes industry-sponsored or cosponsored trial

## Government Regulations

## National:

### National Coverage Determination (NCD) for Treatment of Actinic Keratosis (250.4). Effective 11/26/01<sup>58</sup>

#### Item/Service Description

Actinic Keratosis (AKs), also known as solar keratoses, are common, sun-induced skin lesions that are confined to the epidermis and have the potential to become a skin cancer.

Various options exist for treating AKs. Clinicians should select an appropriate treatment based on the patient's medical history, the lesion's characteristics, and on the patient's preference for a specific treatment. Commonly performed treatments for AKs include cryosurgery with liquid nitrogen, topical drug therapy, and curettage. Less commonly performed treatments for AK include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy. An alternative approach to treating AKs is to observe the lesions over time and remove them only if they exhibit specific clinical features suggesting possible transformation to invasive squamous cell carcinoma.

#### Indications and Limitations of Coverage

Effective for services performed on and after November 26, 2001, Medicare covers the destruction of actinic keratoses without restrictions based on lesion or patient characteristics.

## Local:

Code 96567 is listed with a non-facility fee in the WPS physician fee schedule. Codes 96573 and 96574 also show fee schedules.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

Photodynamic Therapy for Choroidal Neovascularization

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/18	2/20/18	2/20/18	Joint policy established
5/1/19	2/19/19		Routine policy maintenance, added references #28, 29, and 33. No change in policy status.
5/1/21	2/16/21		Added “Nonhyperkeratotic actinic keratoses of the extremities” to MPS, updated rationale, added references.
5/1/22	2/15/22		Updated rationale, added references # 15, 16, 31 and 36. No change in policy status.
5/1/23	2/21/23		Updated rationale section, added references 3,4,31,45,46 and 62. No change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
5/1/25	2/18/25		Routine policy maintenance, added reference #39. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1<sup>st</sup> Qtr. 2026

### Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

**BLUE CARE NETWORK BENEFIT COVERAGE**  
**POLICY: PHOTODYNAMIC THERAPY FOR DERMATOLOGIC APPLICATIONS**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Covered per policy
<b>BCNA (Medicare Advantage)</b>	See government section
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT – HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.