Photodynamic therapy may be considered medically necessary as a treatment of any of the following:
- Nonhyperkeratotic actinic keratoses of the face and scalp
- 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 not medically necessary as a technique of any of the following:
- Altering normal structures of the body in order to improve appearance
- Hair removal
- Skin rejuvenation

Photodynamic therapy is considered investigational for other dermatologic applications, including, but not limited to:
- Acne vulgaris
- High-risk basal cell carcinomas
- Hidradenitis suppurativa
- Mycoses

Surgery and radiation are the preferred treatments for low-risk basal cell cancer and Bowen disease (see Rationale section). If photodynamic therapy is selected for these indications because of contraindications to surgery or radiation, patients and physicians need to be aware that it may have a lower cure rate than surgery or radiation.

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

Coding
There is a CPT code specific to photodynamic therapy to treat lesions of the skin and adjacent mucosa:
- 96567: Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day

The following HCPCS J code describes 5-aminolevulinic acid:
- J7308: Aminolevulinic acid HCl for topical administration, 20%, single unit dosage form (354 mg)

The following HCPCS J code describes Metvixia®:
- J7309: Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 g
Description

Photodynamic therapy (PDT) refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Photosensitizing agents, administered orally or intravenously, have been used in nondermatologic applications and are being proposed for use with dermatologic conditions such as actinic keratoses and nonmelanoma skin cancers.

Related Policies

- Light Therapy for Psoriasis
- Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus
- Photodynamic Therapy for Choroidal Neovascularization

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 1999, Levulan® Kerastick™, a topical preparation of ALA, in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of nonhyperkeratotic 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 health care provider.

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

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

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. The agents 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) 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.

Applications
Photodynamic therapy 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). Moreover, there are some potential cosmetic indications, including skin rejuvenation and hair removal.

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. 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 electrodessication), and laser surgery. Nonsurgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or imiquimod 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.

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. 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. 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.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the 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**

**Photodynamic Therapy**

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

A 2009 double-blind RCT conducted in Germany by Hauschild et al evaluated photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) using a self-adhesive patch. Eligibility criteria included 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; intralesional distance, at least 1 cm). Patients were randomized to 5-ALA patches at 8 mg or identical placebo patches. Patches were square, measuring 4 cm², and patients received 3 to 8 of them, depending on the number of study lesions. The primary efficacy outcome was the complete clinical clearance rate 12 weeks after PDT. A total of 99 of 103 randomized patients were included in the primary efficacy analysis. Complete clinical clearance rate on a per patient basis (all lesions cleared) was 62% (41/66) in the 5-ALA patch group and 6% (2/33) in the placebo patch group; there was a statistically significant difference favoring PDT.

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. The multicenter, double-blind, interindividual 2 arned-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 (Aktilite CL128 and PhotoDyn 750) at both time points of the assessment. The patient and lesion complete clearance rates after illumination with the Aktilite CL128 were 96% and 99%, respectively. No adverse events (discomfort, pain) were mentioned by patients related to application of the gel prior to PDT treatment. Burning and itching were reported during or after the red light illumination. Moreover, 100% of patients treated using Aktilite CL128 had burning after the second PDT session. Of the patients treated using PhotoDyn 750, 60% reported pain during or after PDT. A limitation of the study was its lack of follow-up for patients beyond study protocols.

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 MAL cream and placebo. 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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patients/Lesions</th>
<th>Patient Total Clearance Rate</th>
<th>Lesion Total Clearance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Narrow-Light Spectrum, %</td>
<td>Broad-Light Spectrum, %</td>
</tr>
<tr>
<td>Dirschka et al (2012)⁴</td>
<td></td>
<td>54.0</td>
<td>46.5</td>
</tr>
<tr>
<td>One BF-200 ALA treatment w/ PDT</td>
<td>248/1504</td>
<td>54.0</td>
<td>46.5</td>
</tr>
<tr>
<td>One MAL treatment w/ PDT</td>
<td>247/1557</td>
<td>37.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Two BF-200 ALA treatments w/ PDT</td>
<td>123/NR</td>
<td>84.8</td>
<td>71.5</td>
</tr>
<tr>
<td>Two MAL treatments</td>
<td>150/NR</td>
<td>67.5</td>
<td>61.3</td>
</tr>
</tbody>
</table>

ALA: 5-aminolevulinic acid; BF-200 ALA: nanoemulsion-based 5-ALA formulation; MAL: methyl aminolaevulinate; NR: not reported; 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.⁵ 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 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, 3 RCTs compared different light sources for PDT in the treatment of actinic keratosis. One trial used 5-ALA,⁶ the second trial used MAL cream,⁷ and the third reported on the use of MAL and BF-200 ALA using daylight-mediated PDT.⁸ There was no clear evidence of the superiority of the differing light sources over another. Some of the alternative approaches (e.g., daylight PDT) have not been cleared by the FDA.

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.⁹ 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. Triallists indicated that this result may be the preventive effect of field-directed actinic keratosis treatment.
In 2017, Yazdanyar et al published results from a clinical trial on pain during topical PDT, which compared MAL (Metvix) with 5-ALA (Ameluz).\textsuperscript{10} Patients with mild-to-moderate actinic keratoses on forehead and scalp were treated with MAL-PDT and ALA-PDT on 2 similar areas of forehead and scalp. Fourteen patients completed the MAL-PDT and ALA-PDT treatments. The pattern of pain intensity was similar for both groups. Both treatments were painful, which gradually intensified during the first minute of treatment, reaching a maximum within the first 5 minutes. The pain eased immediately after the PDT treatment. The authors reported no significant difference in pain intensity between MAL-PDT and ALA-PDT, during the treatment (\(p=1.0\)) and 30 minutes after the treatment (\(p=0.19\)). Pain was the only outcome reported in this trial. Trial limitations included the lack of blinding by the nurse who administered the treatment and patient perception (because both sides were painful, the patients could not distinguish between small differences in pain intensity).

**PDT vs an Alternative Intervention**

**Systematic Reviews**

A number of published RCTs have compared PDT with other therapies, and a systematic review of these studies has been published. 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 keratoses.\textsuperscript{11} Thirteen studies (total N=641 participants) met the reviewers’ inclusion criteria. Studies compared PDT with cryotherapy (\(n=6\)), 5-fluorouracil (5-FU; \(n=2\)), 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 with cryotherapy were suitable for meta-analysis. The pooled lesion response rate 3 months after treatment was significantly higher with PDT than with cryotherapy (pooled relative risk [RR], 1.14, 95% confidence interval [CI], 1.11 to 1.18). Due to heterogeneity among the interventions, other data were not pooled.

**Randomized Controlled Trials**

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.\textsuperscript{12} 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 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 rates (85.8% vs 82.5%, respectively). Greater skin discomfort was reported with PDT than with cryotherapy. Investigator-rated cosmetic outcomes showed no difference in the percentages of subjects with poor cosmetic outcomes (0.3% vs 0.5%, respectively), with more subjects rated as having excellent outcomes at 24 weeks after PDT (77.2% vs 49.7%, respectively). With PDT, 22.5% had cosmetic ratings of fair or good compared with 49.9% for cryotherapy.

In 2010, Szeimies et al in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch with cryotherapy.\textsuperscript{13} The study had the same eligibility criteria and primary outcome as the Hauschild study (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 vs cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT with cryotherapy. The rate of complete clearance of all lesions was 67% (86/129) in the 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 patients 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) and the cryosurgery (in the second study) groups. Moreover, 32% 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 by the end of the
A 2012 randomized pilot study from Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments. Patients with nonhyperkeratotic actinic keratoses on the face and/or scalp were randomized to 1 of 3 groups: (1) 1 session of PDT with MAL (n=40); (2) self-administered imiquimod 5% cream for 4 weeks (n=33); or (3) treatment as with group 1 followed by 4 weeks of imiquimod cream (n=32). Follow-up occurred 1 month after PDT (group 1) or 1 month after the end of treatment with imiquimod (groups 2 and 3). The primary outcome measure (complete clinical response) was defined as the total absence of 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 study limitation was that the PDT-only group had shorter follow-up, which could at least partially explain the lower rate of CR.

In 2014, Zane et al published results of an RCT on the treatment of multiple actinic keratoses of the face and scalp. 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 with 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.

Section Summary: Actinic Keratoses on the Face or Scalp
Evidence from multiple RCTs has suggested that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses 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 differing light sources and the use of non-FDA approved light sources, self-reported pain assessments, and self-administered topical treatment. There is insufficient evidence to suggest that any PDT protocol is superior to another.

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

In 2015, Wang et al published a systematic review of RCTs on PDT for treating BCC, both superficial and nodular types. To be selected, studies had to include adults with one or more primary BCCs, randomize participants to PDT, placebo, or another treatment, and report the complete clearance rate, recurrence rate, cosmetic outcomes, and/or adverse events rate. Eight RCTs (total N=1583 patients), published between 2001 and 2013, met inclusion criteria. Three trials included patients with superficial BCC; three included patients with nodular BCC, and one included patients with both types of low-risk BCC. Four trials compared PDT with surgery, two compared PDT with cryotherapy, one compared PDT with pharmacologic treatment, and one was placebo-controlled.
In a meta-analysis of 7 studies, the estimated probability of complete clearance after treatment was similar in the PDT and the non-PDT groups (RR=0.97; 95% CI, 0.88 to 1.06). In subgroup analyses by treatment type, PDT was associated with a significantly higher clearance rate only compared with 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 with surgical excision in patients who had nodular BCC and at least 3 months of follow-up.18 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.

**Randomized Controlled Trials**

An industry-sponsored multicenter RCT was published in 2008 by Szeimies et al.19 This trial compared MAL-PDT with surgery for small (8-20 mm) superficial BCC in 196 patients. At 3 months post 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.20,21 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 vs 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.

A 2016 noninferiority RCT by Roozeboom et al compared MAL-PDT with imiquimod cream and with fluorouracil cream in patients with superficial BCC.22 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.

**Section Summary: Basal Cell Carcinoma**

Systematic reviews of RCTs have found that PDT may not be as effective as surgery for 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
Squamous Cell Carcinoma In Situ (Bowen Disease)
Bath-Hextall et al published a Cochrane review of interventions for cutaneous Bowen disease in 2013. Reviewers identified 7 RCTs evaluating PDT: 4 compared 2 PDT protocols, 1 compared PDT with cryotherapy, 1 compared PDT with topical 5-FU, and 1 compared PDT with both PDT and 5-FU. Reviewers did not pool study results.

The largest study (N=225 patients) was a 3-arm trial published in 2006 by Morton et al. 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. 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)
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
In 2013, Lansbury et al published a systematic review of observational studies evaluating interventions for nonmetastatic cutaneous squamous cell carcinoma. Reviewers identified 14 prospective studies evaluating PDT. Sample sizes ranged from 4 to 71 patients, with only 3 studies including more than 25 patients. The 14 studies evaluated various PDT protocols. Only one was comparative, and it assessed 2 PDT regimens. In a meta-analysis, a mean of 72% of lesions had a CR to treatment (95% CI, 61.5% to 81.4%; \( P = 0.001 \)). 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%; \( P = 0.001 \)).

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

Acne
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. 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 a low certainty in the usefulness of PDT.
In 2016, Pariser et al published a multicenter double-blind placebo-controlled, randomized trial evaluating MAL-PDT for severe facial acne. 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 trial. 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 skin burning cessation (n=15 [15%] in the PDT group vs 5 [9%] in the placebo group). Most adverse events were mild-to-moderate, although 12 patients in the MAL-PDT group dropped out due to treatment-related adverse events.

A randomized, single-blind, split-faced trial was published in 2010 by Orringer et al. 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 the mean number of inflammatory papules, pustules, cysts, closed comedones, or open comedones. There was a significantly greater reduction in erythematous macules on the treated (mean reduction, 5.9) than the untreated side of the face (mean reduction, 2.5; p=0.04). In addition, improvement in mean Leed’s 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 events, which tended to be mild. A trial limitation was the high dropout rate.

In 2013, Mei et al in China published an RCT of 41 patients with moderate-to-severe facial acne. The trial evaluated the additive value of ALA-PDT in patients treated with intense pulsating light (IPL). Twenty-one patients were randomized to 4 weeks of IPL plus PDT, and 20 patients were randomized to IPL plus placebo PDT. Mean reductions in both inflammatory and noninflammatory lesions were significantly greater in the IPL plus PDT group than in the IPL-only group at the 4-, 8-, and 12-week follow-ups. For example, in the IPL plus PDT group, the mean (SD) number of noninflammatory acne lesions decreased from 31.3 (7.1) at baseline to 14.0 (6.2) at 12-week follow-up. In the IPL-only group, the mean (SD) number of noninflammatory lesions decreased from 28.2 (4.1) at baseline to 18.6 (3.1) at 12 weeks (p<0.05). An improvement of 75% to 100% in all lesions was attained by 13 (62%) patients in the IPL plus PDT group and by 3 (15%) patients in the IPL-only group. Both treatments were well tolerated, and no one withdrew from the trial due to treatment adverse events. The trial did not evaluate the efficacy of PDT (the focus of this evidence review) in the absence of IPL therapy.

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

Section Summary: Acne
Several RCTs and a Cochrane review have evaluated PDT for treatment of acne. The review did not conduct meta-analyses on most outcomes. For the pooled analysis of studies comparing MAL-PDT and placebo, reviewers did not find a significant difference in investigator assessment of lesion change. 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

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 suppurativa and PDT for interdigital mycoses. Most series were small (e.g., <25 patients). There are a few systematic reviews. For example, a 2015 systematic review by Mostafa and Tarakji evaluated PDT for oral lichen planus identified 5 case reports, and a 2015 systematic review by Yazdani Abyaneh et al identified 15 case series (total N=223 patients) on PDT for actinic cheilitis. In 2011, Xiao et al in China published a large retrospective case series. A total of 642 patients with port wine stains were treated with PDT; 507 were included in analyses, and the rest were excluded because they had had previous lesion treatments or were lost to follow-up. After treatment, 26 (5.1%) patients were considered to have complete clearing, 48 (9.5%) had significant (<75% to <100%) clearing, and 77 (15.2%) had moderate (<50% to <75%) clearing. 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., hidradenitis suppurativa, mycoses, port wine stains).

Summary of Evidence

For individuals who have nonhyperkeratotic actinic keratoses on the face or scalp who receive PDT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses on the face or scalp compared with placebo or other active interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have low-risk basal cell carcinoma who receive PDT, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular basal cell carcinoma. 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. 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 and cosmetic outcomes appear to be better after PDT. Few RCTs have compared PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these other standard treatments. 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 other 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 the cessation of treatment. Trials have 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 dermatologic skin conditions (e.g., hidradenitis suppurativa, mycoses, port wine stain) who receive PDT, the evidence includes case series and systematic reviews of uncontrolled series. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

Canadian Dermatology Association
In 2015, the Canadian Dermatology Association published the following recommendations on the dermatologic use of photodynamic therapy (PDT):

- **Basal cell carcinoma (BCC):** PDT may be used for superficial BCC when nonsurgical treatment is desired, there are multiple carcinomas, and when cosmetic outcome is important. PDT is not appropriate for nodular BCC.38
- **Actinic keratosis:** PDT is among the recommended treatment options for actinic keratosis, although the guidance includes the statement that cryosurgery or a surgical procedure are preferred for isolated actinic keratosis and hypertonic lesions.39

National Comprehensive Cancer Network
National Comprehensive Cancer Network (NCCN) guidelines on basal cell skin cancers (v.1.2018) state40:

- Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical. Superficial therapies include topical treatment with 5-FU [5-fluorouracil] or imiquimod, photodynamic therapy (PDT) and cryotherapy.
- “Multiple randomized trials and a meta-analysis including 4 of these trials have shown that rates of excellent or good cosmetic outcomes were higher with PDT versus surgery, even though surgery was superior to PDT in terms of efficacy (complete clearance, 1-year and 5-year recurrence rates).”
- “Currently, PDT is being utilized at some NCCN Member Institutions for premalignant or superficial low-risk lesions on any location on the body, although response rates may be higher on the face and scalp.”

NCCN guidelines on squamous cell skin cancers (v.2.2018) state41:

- Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical. Superficial therapies include topical treatment with 5-FU [5-fluorouracil] or imiquimod, photodynamic therapy (PDT) and cryotherapy.
- “Results from randomized trials in patients with SCC [squamous cell carcinoma] in situ suggest that 5-FU may be associated with lower risk of adverse events compared with PDT or cryotherapy, but due to inconsistent results across trials it is unclear whether risk of toxicity differs between cryotherapy and PDT.”
- “Currently, PDT is being utilized at some NCCN Member Institutions for premalignant or superficial low-risk lesions on any location on the body, although response rates may be higher on the face and scalp.”

British Association of Dermatologists
In 2008, the British Association of Dermatologists published guidelines stating the following on PDT:
“Multicentre randomized controlled studies now demonstrate high efficacy of topical photodynamic therapy (PDT) for actinic keratoses, Bowen’s disease (BD) and superficial basal cell carcinoma (BCC), and efficacy in thin nodular BCC, while confirming the superiority of cosmetic outcome over standard therapies. Long-term follow-up studies are also now available, indicating that PDT has recurrence rates equivalent to other standard therapies in BD and superficial BCC, but with lower sustained efficacy than surgery in nodular BCC. In contrast, current evidence does not support the use of topical PDT for squamous cell carcinoma. There is an accumulating evidence base for the use of PDT in acne, while detailed study of an optimized protocol is still required.”

As of November 2017, the Association’s online guideline page indicates that update is in progress on topical PDT.

In 2017 the Association also published evidenced-based guidelines on actinic keratosis. Guidelines pertinent for this evidence review indicate a range of light sources can be used for PDT for a field change of lesions. Based on well-conducted meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias, the Association gave a strong recommendation for PDT using photosensitizing agents that include 5-aminolevulinic acid (5-ALA), BF-200 ALA, and the methyl ester of 5-ALA, 5-MAL, and BF-200 ALA. The Association also recommended pain management during treatment with cold air analgesia or nerve blocks.

International Society for Photodynamic Therapy in Dermatology
In 2012 the International Society for Photodynamic Therapy in Dermatology (ISPTD) published consensus-based guidelines on PDT for skin field cancerization. Field cancerization describes the presence of tissue chronically exposed to a carcinogen. In the dermatology setting, this defines the occurrence of several nonmelanoma skin cancers, its precursors, actinic keratosis and dysplastic keratinocytes in areas exposed to the sun. The number of lesions and size of the area influence treatment decisions. Based on high clinical response rates, cosmetic outcomes and patient preference ISPTD recommended:

- PDT for nonmelanoma skin cancer and its precursors.
- Treatment plans to include follow-up checks for recurrences or treatment failures after a short period, particularly for large treatment areas.
  - Follow-up visits would be scheduled after 3 months, but shorter intervals may be necessary.
  - Retreatment with PDT can be performed for the follow-up visit for recurrences or newly developed lesions.
- PDT combined with 5-FU or imiquimod is another option.
- In cases of a recurrence following a second PDT, a skin biopsy may be required to rule out an invasive squamous cell carcinoma.
- PDT as a suitable therapeutic option for patients with multiple actinic keratoses and a diagnosis of field cancerization.

Further, ISPTD published consensus-based guidelines on the use of PDT for nonmelanoma skin cancer in 2005. Based on both efficacy and cosmetic outcomes, ISPTD recommended PDT as a first-line therapy for actinic keratosis. ISPTD considered aminolevulinic acid not to have sufficient tissue penetration for nodular BCC. Based on 2 randomized controlled trials and 3 open-label studies, it was concluded that methyl aminolaevulinate PDT could be effective for nodular BCC lesions less than 2 mm in depth (if debulked). The guidelines recommended PDT for superficial BCC as “a viable alternative when surgery would be inappropriate, or the patient or physician wishes to maintain normal skin appearance.” Moreover, the guidelines concluded that PDT is at least as effective as cryotherapy or 5-fluorouracil for Bowen disease but that there is insufficient evidence to support the routine use of topical PDT for squamous cell carcinoma.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
The Centers for Medicare & Medicaid Services’ 2011 coverage policy on treatment of actinic keratosis noted:
“Various options exist on treating AKs [actinic keratosis]. Clinicians should select an appropriate treatment based on the patient’s history, the lesion’s characteristics, and the patient’s preference for specific treatment…. Less commonly performed treatments for AK include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy.... Medicare covers the destruction of actinic keratosis without restrictions based on lesion or patient characteristics.”

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02647151</td>
<td>Efficacy and Safety of Treatment of Actinic Keratoses With Photodynamic Therapy Between MAL Cream and ALA Gel</td>
<td>50</td>
<td>Mar 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT02685592</td>
<td>Photodynamic Therapy for Lentigo Maligna Using 5-aminolevulinic Acid Nanoemulsion as a Light Sensitizing Cream (LM PDT)</td>
<td>15</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02144077</td>
<td>Safety and Efficacy Study for the Treatment of Non-Aggressive Basal Cell Carcinoma With Photodynamic Therapy</td>
<td>281</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>NCT02367547a</td>
<td>Superficial Basal Cell Cancer's Photodynamic Therapy: Comparing Three Photosensitises: Hexylaminolevulinate and Aminolevulinic Acid Nano Emulsion Versus Methylaminolevulinate</td>
<td>99</td>
<td>Dec 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References


10. Yazdanyar S, Zarchi K, Jemec GBE. Pain during topical photodynamic therapy - comparing methyl aminolevulinate (Metvix(R)) to aminolaevulinic acid (Ameluz(R)); an intra-individual clinical study. Photodiagnosis Photodyn Ther. Aug 02 2017. PMID 28780136


2.01.44 Dermatologic Applications of Photodynamic Therapy

Page 16 of 19


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Current treatment plan
  - Previous treatment plan and response
  - Reasons for request of alternate treatment outside of surgery or radiation (i.e. contraindications for surgery/radiation)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>96567</td>
<td>Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day <em>(Code revision effective 1/1/2018)</em></td>
</tr>
<tr>
<td></td>
<td>96573</td>
<td>Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s)</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>provided by a physician or other qualified health care professional, per day <em>Code effective 1/1/2018</em></td>
</tr>
<tr>
<td></td>
<td>96574</td>
<td>Debridement of premalignant hyperkeratotic lesion(s) (i.e., targeted curettage, abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day <em>Code effective 1/1/2018</em></td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>J7308</td>
<td>Aminolevulinic acid HCl for topical administration, 20%, single unit dosage form (354 mg)</td>
</tr>
<tr>
<td></td>
<td>J7309</td>
<td>Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 g</td>
</tr>
<tr>
<td></td>
<td>J7345</td>
<td>Aminolevulinic acid HCl for topical administration, 10% gel, 10 mg per day <em>Code effective 1/1/2018</em></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>6A600ZZ</td>
<td>Phototherapy of Skin, Single</td>
</tr>
<tr>
<td></td>
<td>6A601ZZ</td>
<td>Phototherapy of Skin, Multiple</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/01/2001</td>
<td>Add to Medicine Section</td>
<td>Policy adopted by Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2002</td>
<td>Coding change</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>10/15/2007</td>
<td>Revised policy to include additional lesions</td>
<td>Literature review update: adopted BCBSA Medical policy w/more specific criteria/definitions of treatments and number of lesions</td>
</tr>
<tr>
<td>07/01/2011</td>
<td>Policy Revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/30/2015</td>
<td>Policy title change from Photodynamic Therapy for the Treatment of Actinic Keratoses and Other Skin Lesions</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td></td>
<td>Coding update</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance
with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.