I. POLICY

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

- Non-hyperkeratotic 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’s disease (squamous cell carcinoma in situ) only when surgery and radiation are contraindicated.

Photodynamic therapy is considered investigational for other dermatologic applications, including, but not limited to, acne vulgaris, non-superficial basal cell carcinomas, hidradenitis suppurativa, or mycoses. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

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

Policy Guidelines

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

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to Novitas Solutions Local Coverage Determination (LCD) L34938 Removal of Benign or Premalignant Skin Lesions.

**Refer to FEP Medical Policy Manual MP-2.01.44 Dermatologic Applications of Photodynamic Therapy. The FEP Medical Policy Manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

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. 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 electrodessication), and laser surgery. Nonsurgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (chemical peels), and dermabrasion. Topical treatments are generally used in 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.

**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 approval 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.

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 Aktilite 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 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.
IV. RATIONALE

The most recent literature search was for the period through October 26, 2016. Key literature is described below and focused on studies evaluating U.S. Food and Drug Administration (FDA) – approved photosensitizing agents.

ACTINIC KERATOSES

Efficacy of Photodynamic Therapy Compared With Placebo
Several randomized controlled trials (RCTs) have been published. For example, in 2003, Pariser et al conducted a randomized, placebo-controlled trial of 80 patients with actinic keratoses. The authors reported that the complete response (CR) rate for the methyl aminolevulinate (MAL) group was 89% 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; 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 cm², and patients received 3 to 8 of them, depending on the number of study lesions. The primary efficacy outcome was the complete clinical clearance rate 12 weeks after PDT. A total of 99 of 103 randomized patients were included in the primary efficacy analysis. Complete clinical clearance rate on a per patient basis (all lesions cleared) was 62% (41/66) in the 5-ALA patch group and 6% (2/33) in the placebo patch group; there was a statistically significant difference favoring PDT.

Efficacy of PDT Compared With an Alternative Intervention
A number of published RCTs 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 keratosis. 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.

Representative RCTs are described next.
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
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.

In 2010, Szeimies et al in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch to cryotherapy. The study had the same eligibility criteria and primary outcome as the Hauschild 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 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 from Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments. Patients with nonhyperkeratonic 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.
**Efficacy of Different PDT Protocols**

Several RCTs have compared different approaches to applying PDT in the treatment of actinic keratoses.\(^7\)\(^-\)\(^10\) No clear evidence of the superiority of 1 approach over another emerges from this evidence, and some of the alternative approaches (e.g., daylight PDT) are not FDA-cleared.

**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. There is insufficient evidence that any PDT protocol is superior to another.

**BASAL CELL CARCINOMA**

A 2007 Cochrane review evaluated surgical, destructive (including PDT), and chemical interventions for basal cell carcinoma (BCC).\(^11\) 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.

In 2015, Wang et al published a systematic review of RCTs on PDT for treating BCC, both superficial and nodular.\(^12\) 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.\(^13\) 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.

Representative RCTs are described next.
An industry-sponsored multicenter RCT was published in 2008 by Szeimies et al. 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. 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.

A 2016 noninferiority RCT by Roozeboom et al compared MAL-PDT to imiquimod cream and to fluorouracil cream in patients with superficial BCC. 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-fluorouracil (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 (SCC). 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
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 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 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 noninflamatory 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 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 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 effects, which tended to be mild. A limitation of the study 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 IPL. Twenty-one patients were randomized to 4 weeks 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 in the absence of IPL therapy.
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). 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 Cochrane 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 PTD was 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.

OTHER 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 of studies evaluating 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 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 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 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 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 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. 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. 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 PTD 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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

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

For individuals who have low-risk basal cell carcinoma (BCC) who receive PDT, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, 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 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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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 PTD 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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Canadian Dermatology Association
In 2015, the Canadian Dermatology Association published the following recommendations on 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.33

• 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.34

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) guidelines on basal cell skin cancers (v.1.2017) state: “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.” In addition, NCCN concluded that, although the cure rate may be lower, for patients with low-risk superficial BCC where surgery or radiation is contraindicated or impractical, first-line treatment with alternative therapies such as PDT, cryotherapy, 5-FU, or imiquimod may be considered.35

**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.”36

**International Society for Photodynamic Therapy in Dermatology**

The International Society for Photodynamic Therapy in Dermatology (ISPTD) published consensus-based guidelines on the use of PDT for nonmelanoma skin cancer in 2005. Based on both efficacy and cosmetic outcome, 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 and 3 open-label studies, it was concluded that methyl aminolevulinate 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.” The guidelines also 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.37
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
Centers for Medicare and Medicaid Services coverage policy on treatment of actinic keratosis dated November 26, 2001, 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 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>Ongoing</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>
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<tr>
<td>NCT02644187</td>
<td>Pain Relief During Photodynamic Therapy for Actinic Keratoses With a New Irradiation Protocol</td>
<td>30</td>
<td>Dec 2016</td>
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<tr>
<td>NCT02367547</td>
<td>Superficial Basal Cell Cancer’s Photodynamic Therapy: Comparing Three Photosensitises: HAL and BF-200 ALA Versus MAL</td>
<td>99</td>
<td>Dec 2022</td>
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</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

V. DEFINITIONS

CHEMOSURGERY is the destruction of tissue by the use of chemical compounds.

CRYOSURGERY is the use of extremely cold probes to destroy unwanted, cancerous, or infected tissue.

ELECTRODESSICATION is the destruction of cells by application of electrical energy similar to, but to a lesser intensity than, electrocoagulation.

HYPERKERATOSIS refers to hypertrophy of the corneous layer of the skin.
VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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<th>CPT Codes®</th>
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<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J7308</td>
<td>Aminolevulinic acid HCl for topical administration, 20%, single unit dosage form (354 mg)</td>
</tr>
<tr>
<td>J7309</td>
<td>Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>C44.01</td>
<td>Basal cell carcinoma of skin of lip</td>
</tr>
<tr>
<td>C44.112</td>
<td>Basal cell carcinoma of skin of right eyelid, including canthus</td>
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</table>
IX. REFERENCES


Other sources
### MEDICAL POLICY

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>DERMATOLOGIC APPLICATIONS OF PHOTODYNAMIC THERAPY</th>
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<td>MP- 4.018</td>
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## X. POLICY HISTORY

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- 7/30/10 Administrative change. Added clarification of red light therapy.
- CAC 4/26/11 Consensus review.
- **CAC 2/28/12** Adopt BCBSA. Policy title revised to “Dermatologic Applications of Photodynamic Therapy and now is specific to photodynamic therapy for treatment of dermatologic conditions. Surgical excision, chemosurgical destruction, cryosurgery, curettage, and electrodesiccation for treatment of actinic keratosis have been removed from the policy with this change. FEP variation revised.
- **CAC 3/26/13** Consensus review. References updated but no changes to the policy statements. Codes reviewed.
- **CAC 1/28/14** Consensus review. Rationale section added. No change to policy statements. References updated.
- **CAC 1/27/15** Consensus review. References and rationale updated. No changes to the policy statements.
- **CAC 1/26/16** Consensus review. No change to policy statements. References and rationale reviewed. Changed LCD number from L27527 to L34938 due to Novitas update to ICD 10. Coding reviewed.
- **Admin update 1/1/17:** Product variation section reformatted.
- **CAC 3/28/17** Consensus review. In medically necessary statement, superficial basal cell carcinoma changed to low-risk (i.e., superficial or nodular) basal cell carcinoma. In investigational statement, non-superficial basal cell carcinoma changed to high-risk basal cell carcinoma. No change to intent of statements. References and rationale updated. Coding Reviewed.

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