Cigna Medical Coverage Policy

Subject: Photodynamic Therapy for Dermatologic and Ocular Conditions

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Coverage Policy

Dermatologic Conditions
Cigna covers photodynamic therapy (PDT) using an appropriate light source with a topical photosensitizer (i.e., 5-aminolevulinic acid [5-ALA], methyl aminolevulinate [MAL]) as medically necessary for the treatment of nonhyperkeratotic actinic keratoses (AK).

Cigna covers photodynamic therapy (PDT) using an appropriate light source with a topical photosensitizer (i.e., 5-aminolevulinic acid [5-ALA], methyl aminolevulinate [MAL]) as medically necessary for the treatment of EITHER of the following conditions after failure, contraindication, or intolerance of standard medical/surgical care:

- superficial basal cell carcinoma
- Bowen’s disease

Cigna does not cover photodynamic therapy (PDT) for the treatment of ANY of the following dermatologic conditions because such therapy is considered experimental, investigational or unproven for these indications (this list may not be all-inclusive):

- acne vulgaris
- hyperkeratotic actinic keratoses
- nodular basal cell carcinoma
- psoriasis
- squamous cell carcinoma
Cigna does not cover photodynamic therapy (PDT) for the treatment of ANY of the following indications as it is considered cosmetic in nature and not medically necessary (this list may not be all-inclusive):

- photoaging (i.e., photodamage or dermatoheliosis)
- sebaceous gland hyperplasia
- hirsutism

Ocular Conditions
Cigna covers photodynamic therapy (PDT) with verteporfin (Visudyne®) for the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) (i.e., the classic lesion comprises ≥ 50% of the entire lesion) due to ANY of the following conditions:

- wet age-related macular degeneration (AMD)
- pathological myopia
- presumed ocular histoplasmosis

Cigna does not cover PDT with verteporfin (Visudyne®) for the treatment of any other ocular condition because it is considered experimental, investigational or unproven.

General Background
Photodynamic therapy (PDT), also referred to as photoradiation or photosensitizing therapy, is a two-step drug and light therapy procedure used to induce selective damage to defined tissue. In the first step, the photosensitizer is administered by one of several routes (e.g., topical, oral, intravenous) and is allowed to be absorbed by the targeted cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. PDT is used clinically to treat a wide arrange of conditions including dermatologic and ocular conditions.

Dermatologic Conditions
For the treatment of various skin conditions, the PDT process starts with the application of a topical photosensitizer like the heme precursor 5-aminolevulinic acid (5-ALA) or its methyl ester, methyl aminolevulinate (MAL). Due to its low lipophilicity, ALA diffuses slowly through the cell membrane, therefore requiring that a large amount of ALA be applied to the diseased tissue. MAL is proposed to increase the diffusion rate and enter diseased tissue more rapidly and deeper, enhancing the production of protoporphyrin IX (PpIX), a potent photosensitizer, in the cells (Gold and Nestor, 2006; Angell-Petersen, et al., 2005). After a 3- to 48-hour application interval, the lesion is exposed to the appropriate light source. The medication, which has passed through the abnormal keratin overlying the lesion, is metabolized by the underlying cells and causes damage to the treated cells upon light exposure. Topical PDT has been introduced as a method of selectively destroying cells without harming surrounding normal tissue. The diseased cells have a tendency to accumulate more of the agent than normal tissue. The photosensitizer does not penetrate thicker lesions effectively and thus is not efficiently converted to PpIX. There are two light sources, blue light and red light. Red lights generally have a deeper level of penetration. Standard therapeutic wavelengths, fluence rates and intensity rates for light therapy for PDT have not yet been established.

U.S. Food and Drug Administration (FDA)
Levulan® Kerastick® (DUSA Pharmaceuticals, Inc., Valhalla, NY) for Topical Solution 20% (aminolevulinic acid hydrochloride [HCl]), along with the light source BLU-U® Blue Light Photodynamic Therapy Illuminator (DUSA Pharmaceuticals, Inc., Valhalla, NY) was approved by the FDA premarket approval process (PMA) in 1999. The combination therapy was approved for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp. Levulan is administered in one to two treatment sessions.

Topical Metvixia™ (methyl aminolevulinate) cream 16.8% in conjunction with the red light device CureLight Broadband Model CureLight 01 (PhotoCure ASA, Oslo, Norway) (PhotoCure ASA, Oslo, Norway) was approved by the FDA in July 2004. The approval was later updated to allow the use of the PhotoCure Aktilite® CL128 red
light device. Metvixia is indicated for the treatment of “thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation in the physician’s office when other therapies are considered medically less appropriate”. Two treatment sessions should be administered one week apart and multiple lesions may be treated in the same session not to exceed more than one gram of Metvixia cream in a session (FDA, 2008).

**Actinic Keratosis (AK)**
AK, or solar keratosis, is a pre-cancerous condition that develops from overexposure to the sun and appears as small, reddish or natural colored rough, scaly spots that occur on the face, ears, and back of the hands. AK represents early epithelial transformation and may evolve into squamous cell carcinoma. Treatment options include topical agents such as fluorouracil or imiquimod, cryosurgery, electrodessication and curettage, dermabrasion, shave excision and carbon dioxide laser. PDT is also an established treatment modality for the treatment of nonhyperkeratotic AK. The method of treatment of AK is dependent upon location, type, and size of the lesion and whether it is a primary or recurrent lesion. PDT is not effective for the treatment of hyperkeratotic lesions. There is ineffective penetration of the photosensitizer in the thicker lesions and the consequent lack of conversion to PpIX.

**Literature Review - Aminolevulinic Acid (ALA):** The evidence in systematic reviews and randomized controlled trials (Hadley, et al., 2012; Fayter, et al., 2010; Ritter, et al., 2010; Sotiriou, et al., 2009; Tschen, 2006; Piaccquadio, et al., 2004; Jeffes, et al., 2001; Kurwa, et al., 1999) supports the treatment of nonhyperkeratotic AKs with ALA-PDT and blue light, especially for head and neck lesions, and is generally well-tolerated.

**Literature Review - Methyl Aminolevulinate (MAL):** The safety and effectiveness of MAL-PDT for the treatment of nonhyperkeratotic AK lesions is supported by the evidence in systematic reviews and randomized controlled trials (Fayter, et al., 2010; Kaufmann, et al., 2008; Pariser, et al., 2008; Wennberg, et al., 2008; Morton, et al., Nov, 2006; Freeman, et al., 2003; Pariser, et al., 2003). Lesions were located on the face, scalp, neck, trunk and extremities. Overall, better outcomes and fewer adverse events were reported with MAL-PDT compared to treatment with cryotherapy.

**Professional Societies/Organizations:** In their guidelines for topical PDT, the British Association of Dermatologists (Morton, et al., 2008) stated that PDT “is an effective therapy for thin and moderate thickness AK, with superiority to cryotherapy depending on protocol. Efficacy is relatively poorer for acral lesions, but PDT may still offer therapeutic benefit”. Although showing lower efficacy in immunocompetent individuals, PDT may be a useful therapy in the treatment of epidermal dysplasia in organ transplant recipients. The BAD’s guidelines (de Berker, et al., 2007) on the management of AK stated that PDT was effective in 91% of clinical trials in which PDT was compared to cryotherapy. PDT may be “particularly good” in the treatment of superficial, multiple, and confluent AKs at sites of poor healing. PDT is probably best reserved for the treatment of extensive AKs not controlled with the other therapies.

Photodynamic guidelines developed in 2007 by the International Society for Photodynamic Therapy in Dermatology stated that PDT is “highly effective” for the treatment of AK, offering the advantage of “excellent cosmetic outcome” (Braathen, et al., 2007).

The National Comprehensive Cancer Network® (NCCN®) (2014) stated that AK should be treated aggressively upon diagnosis. If left untreated AK can progress to invasive squamous cell carcinoma (SCC) with the potential for metastasis. NCCN listed PDT as an established superficial treatment option, stating that MAL PDT was found to be as effective as cryotherapy.

The National Cancer Institute’s (2013) discussion of treatment options for AK includes: topical agents (e.g., 5-FU, Imiquimod cream, trichloroacetic acid), cryosurgery, curettage, dermabrasion, shave excision, and PDT.

**Basal Cell Carcinoma (BCC)**
BCC is the most common type of skin cancer in humans. There are several different clinical presentations of BCC, but the most common are superficial BCC and nodular BCC. Superficial BCC lesions appear as a scaly patch or pin/red papule with a threadlike border, most often on the trunk, and are typically slow growing and noninvasive. The hallmark of nodular BCC is a waxy, translucent or pearly appearance with telangiectatic vessels. It appears as a nodular or nodular ulcerative lesion with raised borders looking like a sore that often bleeds, heals and recurs again. The type of treatment provided will depend upon the characteristics of the
tumor. The first line treatment is typically surgical excision which has the highest success rates. Other traditional treatment options include topical creams such as fluorouracil or imiquimod, cryosurgery, radiation therapy, electrochemotherapy and curettage (NCCN, 2014; NCI, 2013; Bath-Hextall, et al. 2007). PDT is an established treatment option for superficial basal cell carcinoma.

**Literature Review:** Systematic reviews and randomized controlled trials have reported up to a 97% complete response rate following PDT. Recurrence rates varied based on the lesion characteristics. Recurrence rates as low as 6% in small lesions have been reported. PDT is an established method of therapy for superficial BCC that is unresponsive to conventional treatment methods or in cases when traditional therapies are contraindicated or not tolerated (Fayter, et al., 2010; Ramsey and Sewell, 2010; Szeimies, et al., 2008; Telfer, et al., 2008; Szeimies, 2007; Angell-Petersen, et al., 2006).

However, the evidence in the published peer-reviewed literature and professional societies do not support PDT for the treatment of nodular BCC. Nodular BCC studies have demonstrated various short-term response rates (59–92%) and recurrence rates (5–44%). Various protocols (e.g., formulations, concentrations, light sources, penetration enhancers, ALA application time vs. light application) have been used. Several studies have included extemporaneously prepared ALA. There is a lack of long-term results regarding the efficacy of PDT for the treatment of nodular BCC (Rao, 2012; Braathen, et al., 2007; Szeimies, et al., 2007).

Fayter et al. (2010) conducted a systematic review of randomized and nonrandomized clinical trials investigating PDT for the treatment of various cancerous and precancerous conditions. The review of 88 studies included two randomized controlled trial (n=131 patients) comparing PDT to placebo, three randomized controlled trials comparing PDT to surgical excision (n=283 patients, 331 lesions) and one randomized controlled trial comparing ALA-PDT to MAL-PDT (n=39 patients, 43 lesions) for the treatment of nodular BCC. The studies suggested that PDT was superior to placebo but less effective than surgical excision. Cosmetic outcomes were more favorable following PDT. Due to the small patient populations and the poor quality of the studies, PDT could not be recommended as a treatment option for this condition.

Foley et al. (2009) reported on two multicenter randomized controlled trials comparing MAL-PDT (n=66 patients, 75 lesions) to placebo-PDT (n=65 patients, 79 lesions) for the treatment of nodular BCC. One study was conducted in the United States (n=65 patients, 79 lesions) and one in Australia (n=66 patients, 81 lesions). Both studies used the same design and procedures. Of the 64 MAL-treated patients with information available, 48 had received at least one form of previous therapy. All patients initially received two PDT sessions separated by a one-week interval. Follow-ups occurred at three and six months. Partial response lesions were retreated at three months and followed up at six and nine months. Lesions with no response or progression at three months and lesions with an incomplete response at six months after a second treatment were excised. Overall, histologically verified lesion complete response rates were “superior” following MAL-PDT compared to placebo PDT (73% vs. 27%, respectively). Lesion complete response rates for MAL-PDT and placebo-PDT were 78% vs. 33% in the United States study and 68% vs.19% in the Australian study, respectively. Cosmetic outcomes were rated as “good to excellent” in 98% of the evaluable, completely responding MAL-treated lesions. Facial lesions and smaller lesions responded better. Twenty lesions in the MAL group did not show a complete response rate. More adverse events were reported in the MAL group compared to the placebo group (91% vs. 66%, respectively). Limitations of the study include the small patient population and short-term follow-up.

In a randomized controlled trial, Mosterd et al. (2008) compared the efficacy of ALA-PDT to surgical excision (SE) of nodular basal cell carcinoma (nBCC) (n=149 patients/173 lesions). PDT patients, previously untreated, underwent tumor debulking three weeks prior to PDT and were illuminated twice on the same day, 60 minutes apart during the PDT treatment. Mean follow-up was 28 months (range 0-57 months). Three months following treatment, 94% of the ALA-PDT group had completely resolved compared to 98% of the SE group (p=0.27). There were two failures in the SE group and 21 in the PDT group. Intention-to-treat analyses on a three-year analysis reported that the cumulative incidence of failure for SE was 2.3% compared to 30.3% for PDT (p<0.001). The study showed that PDT is inferior to surgical excision in the treatment of nodular basal cell carcinoma.

Smaicler et al. (2008) prospectively studied the ability of PDT-ALA alone, Erbium (Er):YAG laser alone and PDT plus Er:YAG to ablate nBCC tumors in the head and neck regions. Subjects (n=286) had recurring nodular BCC refractory to previous interventions (i.e., surgical excision, cryotherapy, laser ablation). Follow-up occurred at three, six and 12 months. Each patient was treated with all three methods. The lesions treated with PDT/Er:YAG
were treated first with Er:YAG to reduce the tumor depth making the tumor more responsive to PDT. At the three-month follow-up, percentages without recurrence were 99.1% for PDT only, 98.39% for Er:YAG only and 100% for the PDT/ErYAG group. At the end of a year, the percentage of patients without recurrence following PDT only was 94.85%, 91.75% for Er:YAG, and 98.97% for PDT/Er:YAG. Combined therapy was significantly more effective than PDT alone (p<0.01). Recurrence occurred more quickly following Er:YAG and a noticeable fall was noted in effectiveness between month 6 and 12 (98.11% to 94.85%) following PDT only. There was significantly better healing following Er:Yag compared to PDT (p<0.01), and at 12 months, patient preference was for Er:YAG only (67.5%). Based on the results of this study the authors did not recommend the use of PDT only as a treatment modality for nodular BCC.

Bath-Hextall et al. (2007) conducted a Cochrane review of 27 randomized controlled trials, 18 published studies and nine abstracts related to the treatment of for nodular and superficial BCC with imiquimod (n=9), intralesional interferon (n=4), BEC-5 cream (n=1), fluorouracil (n=2), surgery (n=3), radiotherapy (n=2), cryotherapy (n=4), and PDT (n=8). The authors noted that surgery revealed the lowest failure rates with radiotherapy and surgery appearing to be the most effective treatment modalities. PDT yielded better cosmetic outcomes than surgery, but there were high failure rates with PDT compared to surgery, radiotherapy and cryotherapy. The majority of studies included only low-risk BCC, and there is a need for long-term follow-up data regarding the effectiveness of PDT. Overall, there has been "very little good quality research on the efficacy of treatment modalities" for BCC. Few treatments have been compared to surgery.

Rhodes et al. (2007) conducted a multicenter, prospective, randomized controlled trial to assess the recurrence rate of primary nodular BCC lesions following treatment with MAL-PDT (n=50 patients/53 lesions) compared to simple excisional surgery (n=47 patients/52 lesions). At the end of three months, 49 PDT-treated lesions (46 patients) and 52 surgically-treated lesions (47 patients) demonstrated complete response and were enrolled for a five-year follow-up. The MAL-group experienced two recurrent lesions compared to one recurrent lesion in the surgical group between years two and three. Thirty-one MAL-treated patients and 35 surgically-treated patients were available for the five-year follow-up. The five-year MAL recurrence rate was 14% compared to 4% for the surgical group. The five-year estimated sustained complete response rate was 76% for the MAL group compared to 96% for the surgical group (p=0.01). Cosmesis was better in the PDT group (87% vs. 54%) (p=0.007).

Kuijpers et al. (2006) compared the effectiveness of PDT with 5-ALA (n=22) to PDT with MAL (n=21) for the treatment of nodular BCC. Patients were randomly assigned, and results were reported at eight weeks following therapy. The authors reported no differences in the outcomes and stated that ALA and MAL were equally recommended. Rhodes et al. (2004) conducted a multicenter, randomized, prospective trial to compare MAL-PDT with standard excision surgery for nodular BCC (n=97 patients/105 lesions). Complete response rates did not differ significantly between the two groups. At 12 months, tumor-free rates were higher in the surgery group (96%) than in the MAL-PDT group (83%). At 24 months, five lesions recurred after MAL-PDT and only one after surgery.

Professional Societies/Organizations: The National Comprehensive Cancer Network® (NCCN®) (2014) stated that PDT may be a treatment option in patients with low-risk, superficial basal cell skin cancer, where surgery or radiation is contraindicated or impractical, even though the cure rate may be lower. NCCN noted that PDT is being used at NCCN institutions for superficial low-risk lesion on any part of the body but response rates may be higher for lesions on the face and scalp.

The National Cancer Institute (NCI) (2013) stated that treatment options for BCC include “excision, radiation therapy, cryosurgery, electrodesiccation and curettage, photodynamic or laser-beam light exposure, and topical therapies. NCI stated that PDT is used in the management of a wide range of “superficial epithelial tumors”. PDT has been reported to have high initial complete response rates and better cosmesis, but high regrowth rates.

**Bowen’s Disease**

Bowen’s disease, a superficial type of squamous cell carcinoma (SCC) that has not yet spread (i.e., SCC in situ), is considered the earliest form of SCC. It appears as a persistent red-brown, scaly patch which may resemble psoriasis or eczema. If untreated, it can invade deeper structures. Topical therapy, surgically excision,
cryotherapy, and liquid nitrogen are treatment options for Bowen’s disease. PDT is an established treatment alternative for individuals who fail, cannot tolerate, or are not a candidate for conventional therapies.

**Literature Review:** The evidence reported in systematic reviews and randomized controlled trials have concluded that PDT is an effective treatment modality for Bowen’s disease (Calin, et al., 2011; Fayter, et al., 2010; Morton, et al., 2006; Salim, et al., 2003).

**Professional Societies/Organizations:** The National Comprehensive Cancer Network® (NCCN®) (2014) stated that PDT may be a treatment option “in patients with low-risk, shallow cancers such as squamous cell carcinoma in situ (Bowen’s disease), where surgery or radiation is contraindicated or impractical, even though the cure rate may be lower”.

Based on a randomized controlled trial (n=229), the National Cancer Institute (NCI) (2013) reported that high complete response rates are achievable with PDT for the management of SCC in situ (Bowen disease) and that cosmetic results are good with PDT.

**Other Dermatologic Indications**
There are numerous other proposed indications for the use of PDT in dermatologic conditions including but not limited to: acne vulgaris, squamous cell carcinoma, warts, and psoriasis. Studies have included small heterogeneous patient populations and mixed outcomes. Some studies reported intolerance to PDT due to pain, no improvement in the condition, and/or in some cases worsening of the condition. PDT is not an established treatment modality for these other conditions, and the evidence in the published peer-reviewed literature does not support the safety and effectiveness of its use.

**Acne Vulgaris:** Acne vulgaris is a chronic, inflammatory disease of the pilosebaceous follicles characterized by the formation of open and closed comedones (i.e., whiteheads and blackheads), erythematous papules and pustules, pseudocysts and nodules. Treatment for this condition includes topical medications, systemic therapy with antibiotics, retinoids and hormonal medications, and/or in severe cases surgical intervention. There is insufficient evidence supporting the safety and efficacy of PDT for the treatment of acne vulgaris.

A limited number of studies with small patient populations and short-term follow-up have reported various clinical improvements of acne lesions after treatment with PDT. Orringer et al. (2010) conducted a randomized controlled split-face trial (n=44) and compared the effects of 5-ALA PDT to no therapy for the treatment of acne vulgaris. The patients received up to three treatment sessions at 2-week intervals. Clinical evaluations included live lesion counts and global grading with a modified Leeds acne severity scale. Follow-ups occurred every two weeks for 16 weeks, and counts of papules, pustules, cysts, open comedones, closed comedones, and erythematous macules were recorded. At week ten, there was a statistically significant decrease in mean inflammatory papule count in the treated skin (p=0.01), but the effect was transient with no improvement at week 16. With one exception, compared to baseline there were no significant changes in lesion counts of any subtype in the treated and untreated skin (p>0.05). There was a significant improvement in the treated skin compared to the untreated skin in the mean Leeds scores (p=0.01). Eight (18%) patients were considered responders (i.e., 25% decrease in lesion count) and inflammatory lesions responded better than noninflammatory lesions. Few adverse events were reported. Based on the results of the study, the authors concluded that an improvement in acne with their PDT regimen was “modest and inconsistent”.

A systematic review of the literature “to assess the effects of optical treatments for acne vulgaris” by Haedersdal et al. (2008a) included five randomized controlled trials that usedALA- or MAL-PDT (n=114) for the treatment of acne vulgaris. Outcomes included: significantly better results with two treatments of MAL-PDT compared to no treatment (p=0.005) and placebo-PDT (p=0.0006); three ALA-PDT treatments for back acne were significantly better than no treatment; efficacy and pain scores were comparable with ALA-PDT and MAL-PDT; and ALA-PDT resulted in more severe erythema, pustular eruptions and epidermal exfoliation.

Yeung et al. (2007) conducted a randomized controlled trial (n=30) to compare the effects of intense pulsed light (IPL) to IPL plus MAL-PDT for the treatment of skin types IV or V with more than 10 moderate acne lesions. The untreated side of the face served as the control. Twenty-five percent of subjects withdrew due to intolerance to MAL. A mean significant improvement in the inflammatory lesions was not observed with either treatment compared to the control group, but there was a significant improvement in noninflammatory lesions with both therapies 12 weeks following treatment.
Horfelt et al. (2006) conducted a randomized controlled trial comparing MAL-PDT to placebo in 30 patients with moderate inflammatory facial acne. Treatments were randomized to either side of each patient’s face. Based on results at 10-weeks’ follow-up, the authors reported significant improvement with MAL and suggested that further studies be conducted. Wiegell and Wulf (April 2006) conducted a randomized trial using MAL compared to ALA for the treatment of inflammatory acne. At twelve weeks, there was no significant difference in the response of the lesions. However, they reported more prolonged and severe adverse effects with ALA-PDT. Another randomized trial by Wiegell and Wulf (May 2006) compared patients treated with MAL (n=19) to patients who received no treatment (n=12). A 68% reduction was noted in inflammatory lesions in the MAL group at 12 weeks compared to no improvement in the group that received no treatment.

Squamous Cell Carcinoma (SCC): SCC, the second most common form of skin cancer, is often nodular and erythematous and may include keratin plugs, horns or ulceration. Surgical removal and Mohs’ micrographic surgery are indicated over other treatment methods because of the metastatic potential of these lesions. It is not unusual for repeat treatment to be necessary in order to completely eradicate the affected tissue. PDT is not an established treatment modality for SCC.

Morton et al. (2006) conducted a randomized trial comparing outcomes of the treatment of squamous cell carcinoma with MAL-PDT to cryotherapy and to topical fluorouracil. The trial included 40 patients from 11 European centers. At 12 months, results from MAL-PDT were “superior” to cryotherapy and better than fluorouracil. A 2006 randomized controlled trial on PDT and SCC was performed on 40 organ transplant recipients to determine the preventive effect of PDT on SCC. After one year, no statistically significant difference was found in the occurrence of SCC in the treated versus the untreated arm (de Graaf, et al., 2006).

Psoriasis: Psoriasis is a chronic, systemic inflammatory disease affecting multiple systems, including the skin. It is characterized by scaly, erythematous patches, papules and plaques. Depending on the severity of the disease, treatment may include topical creams, biologic agents, phototherapy, and/or photochemotherapy. There is insufficient evidence in the published peer-reviewed literature to support the effectiveness of PDT for the treatment of psoriasis. In a randomized controlled trial (n=12) comparing various dosages, Schleyer et al. (2006) reported that ALA PDT was not an appropriate treatment for psoriasis because of the disappointing clinical efficacy.

The 2010 American Academy of Dermatology guidelines on the management of psoriasis do not include PDT as a treatment option for this condition.

Warts: Warts are benign tumors involving the skin and epithelial tissues. They are classified by their clinical features (e.g., flat, filiform) and by the location (e.g., genital, plantar). Treatment depends on the type and location of the wart.

Evidence in the published peer-reviewed literature does not support the effectiveness of PDT for the treatment of warts. In a randomized controlled trial, Liang et al. (2009) evaluated the safety and efficacy of ALA-PDT (n=67) to CO2 laser therapy (control group) (n=23) for the treatment of condylomata acuminata (CA). The number of warts per patient was 1.84 ± 0.82. Follow-up for patients (n=87) with complete clearance lasted for 12 weeks. In the ALA group, 95.93% of patients achieved complete clearance compared to 100% in the control group. A total of 75 warts (60.98%) achieved clearance after one PDT treatment, 25 warts (20.32%) after two treatment cycles, 18 warts (14.63%) after three treatment cycles and five warts (4.07%) did not clear. At the 12-weeks follow-up, a statistically significant recurrence rate was reported (p<0.05) with six recurrences occurred in the ALA group compared to four in the control group. The adverse reaction rate in the control group (100%) was significantly higher than the adverse reaction rate in the ALA group (8.82%) (p<0.05). Limitations of the study include the small patient population and short-term follow-up.

Kwok et al. (2012) conducted a systematic review of randomized controlled trials (n=85 studies) to evaluated the efficacy of local treatment, including PDT for the treatment of non-genital warts. Five randomized controlled trials evaluated PDT. Due to the methodological heterogeneity of the studies pooling of the data was not possible. There was insufficient evidence to support PDT for the treatment of warts.
In a systematic review of the literature on topical treatments for cutaneous warts that included five PDT randomized controlled trials, Gibbs and Harvey (2006) concluded that the benefits and risks of the use of PDT for the treatment of warts remained to be determined.

**Photoaging and Photodamage (Dematoheliosis):** Photoaging, also called photodamage or dematoheliosis, refers to chronic cosmetic changes that occur over the course of time as the result of repeated exposure to the sun. This may include wrinkles, roughness, dark spots, leathery course skin, and telangiectasia which are untoward cosmetic changes. Photoaging is a benign condition; treatment is aimed at improving appearance and therefore, would not be considered medically necessary.

**Sebaceous Gland Hyperplasia:** Sebaceous glands are located in the skin, attached to hair follicles and produce an oily substance called sebum. They are found mainly on the face, neck, back and chest. Sebaceous gland hyperplasia appears as small white or yellow lesions or papules. A decrease in cellular turnover results in the accumulation of sebocytes within the sebaceous gland, causing an enlargement of the gland. Sebaceous gland hyperplasia is a benign condition and does not require treatment (Hogan, 2012).

**Hirsutism:** Hirsutism, hypertrichosis or excess hair, is the presence of coarse, dark hair where it does not typically grow (e.g., lip, chin, chest), especially in women. The goal of treatment using interventions such as PDT is cosmetic in nature and as such, would not be considered medically necessary.

**Additional Dermatologic Conditions:** PDT has also been proposed for the treatment of a variety of additional dermatologic conditions other than those described above. These conditions include: actinic cheilitis; chondrodermatitis nodularis chronica helicis, cutaneous sarcoïdosis, fungal conditions (e.g., Candida albicans, chromoblastomycosis, superficial [cutaneous] mycosis, dermatophytes [ringworm]), hidradenitis suppurativa, keloids, leishmaniosis, lichen planus, lichen sclerosus, Malassezia fungoides, melanoma, mycosis fungoides (cutaneous T-cell lymphoma), scleroderma and verrucous epidermal nevus (also called linear epidermal nevus). Studies are primarily in the form of case reports or case series and retrospective reviews with small patient populations (n=4–40) and short-term follow-ups (e.g., 3 months) (Agostinis, et al., 2011; Gould, et al., 2011; Schweiger, et al., 2011; Issa and Manela-Azulay, 2010; Neil, et al., 2010; Olejek, et al., 2010; Sim, et al., 2010; Sotiriou, et al., 2010; Zhao and He, 2010; Morton, et al., 2008). There is insufficient evidence in the published peer-reviewed scientific literature to support PDT for the treatment of these conditions.

In a systematic review of the literature, Qiao et al. (2010) evaluated the safety and efficacy of PDT for superficial mycoses. Seven studies using ALA-PDT included patients (n=63) with interdigital mycoses, tinea cruris, tinea pedis, onychomycosis, or pityriasis versicolor. Cure rates ranged from 36.6–80% with limited persistent healing. Limitations of the studies included small patient populations, short-term follow-up (e.g., 8 weeks to 24 months) and the use of various treatment regimens. The authors concluded that “the therapeutic effect of PDT for treating tinea pedis, tinea cruris and onychomycosis is unsatisfactory”.

**Ocular Conditions**
PDT for the treatment of ocular conditions includes an intravenous injection of a photosensitizing dye (i.e., verteporfin/Visudyne®) which is activated in the vessels by a low-energy laser. The dye then binds with low-density lipoproteins generating reactive oxygen species that accumulate in neovascular and neoplastic tissue. This accumulation leads to the destruction of the vascular endothelial tissue resulting in platelet aggregation and vessel thrombosis. Although the vessels typically close shortly after treatment, they can become reperfused within the next three months. Studies have documented the safety and effectiveness of repeat verteporfin treatments every three months when leakage is seen on follow-up fluorescein angiography (Chan, et al., 2005; Atebara and Thall, 2004).

PDT with verteporfin is an established treatment option for classic subfoveal choroidal neovascularization (CNV) due to wet age-related macular degeneration (AMD), pathological myopia, or presumed ocular histoplasmosis. CNV involves the growth of immature blood vessels from the choroid (i.e., choroidal CNV) that leak blood and fluid creating lesions under the central part of the retina below the fovea (i.e., subfoveal). Classic lesions are clearly delineated on fluorescein angiography and leak fluorescein evenly. Predominantly classic lesions occupy ≥ 50% of the lesion baseline (Wormald, et al., 2007; Verteporfin Roundtable Participants, 2005).

**U.S. Food and Drug Administration (FDA)**
Visudyne therapy is approved by the FDA premarket approval (PMA) process as a two-step combination drug and device treatment. The FDA approved verteporfin for intravitreal injection with PMA approval of the Ceralas™ laser and Ceralink slit lamp adapter (QLT, Inc., Vancouver, British Columbia, Canada) “for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.” Other approved laser systems include the Coherent Opal Photoactivator™ Laser Console and LaserLink Adapter (Lumenis, Inc., Santa Clara, CA) and the Zeiss VISULAS 690s® laser and VISULINK PDT adapter (Carl Zeiss, Inc., Thornwood, NY) (FDA, 2001; FDA, 2005).

Age-Related Macular Degeneration
There are two types of AMD, “dry” and “wet.” Dry, atrophic, or non-neovascular AMD is characterized by small yellow lipid debris deposits (i.e., drusens) beneath the retina. Wet, exudative, or neovascular AMD is characterized by choroidal neovascularization (CNV), the growth of abnormal blood vessel from the choroid. The abnormal blood vessels can leak blood and fluid causing damage to the eye, including loss of vision. The three lesion types associated with wet AMD are classic, occult, and minimally classic or mixed (Wormald, et al., 2007; Verteporfin Roundtable Participants, 2005).

Treatment for AMD depends on the stage of the disease and the type of AMD. Early AMD exhibiting no clinical signs may be observed without medical or surgical intervention. Antioxidant vitamins and mineral supplements are used for the treatment of intermediate and advanced AMD. For advanced conditions an intravitreal injection of pegaptanib (Macugen), ranibizumab (Lucentis) or bevacizumab (Avastin) are available treatment options. PDT is indicated for the treatment of wet AMD with predominantly classic subfoveal CNV (AAO, 2012).

Literature Review: Systematic reviews, randomized controlled trials and case series support PDT with verteporfin for the treatment of predominantly (≥ 50%) classic subfoveal choroidal neovascularization (CNV) caused by AMD. In general, randomized controlled trials compared PDT to placebo and reported significantly less visual loss following PDT. PDT also reduced or stopped fluorescein leakage and restricted lesion growth (Mataix, et al., 2009; Potter, et al., 2007; Tewari, et al., 2007; Wormald, et al., 2007; Azab, et al., 2005; Bressler, et al., 2005; Michels, et al., 2005; Pauleikhoff, 2005; Meads and Hyde, 2004; Schmidt-Erfurth, et al., 2004; Sharma, et al., 2004; Blumenkranz, et al., 2002; Verteporfin in Photodynamic Therapy Study Group, series 2001).

There are a limited number of studies comparing PDT to other established treatment modalities. The Anti-vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in Age-related Macular Degeneration (ANCHOR) study (Brown, et al., 2009) was a multicenter (83 sites), international, randomized controlled trial that evaluated the efficacy and adverse events of patients (n=423) treated with ranibizumab compared to PDT for predominantly classic subfoveal CNV secondary to AMD. Patients were randomized to PDT plus a monthly sham intracocular injection (n=143) or to sham PDT plus a monthly 0.3 milligram (mg) intravitreal ranibizumab injection (n=140) or to sham PDT plus a monthly 0.5 mg intravitreal ranibizumab injection (n=140). The primary intent-to-treat analyses was conducted at 12-months and followed to 24 months. At the two-year follow-up, the visual acuity benefit following ranibizumab compared to PDT was statistically significant (p<0.0001). Compared to baseline, 89.9% of 0.5 mg ranibizumab patients, and 90.0% of 0.3 mg ranibizumab patients lost <15 letters compared to 65.7% of PDT patients. A gain of ≥ 15 letters was achieved by 34% of 0.3 mg and 41% of 0.5 mg ranibizumab patients compared to 6.3% of PDT patients, and visual acuity improved an average of 8.1 letters in the 0.3 mg group and 10.7 letters in the 0.5 mg patients compared to a mean decline of 9.8 letters in PDT patients. At month 18 or over, 50 PDT patients crossed over to receive ranibizumab injections. At 24 months, there was a significantly higher number of patients in the PDT group who had a visual acuity Snellen equivalent of ≥ 20/200 (p<0.001). In the PDT group, 16.1% of patients experienced ≥ 30 letters loss compared to 0%–1.4% in the ranibizumab groups. Changes in total lesion area, total area of CNV, mean area of classic CNV, area of occult CNV with no classic component, total area of leakage from CNV were stable or improved following ranibizumab treatment and were significantly worsened following PDT (p<0.0001 in all cases). Overall, there were no significant differences in ocular and nonocular adverse events between the three groups without the data for patients who crossed over. There was however, a significantly higher incidence of cataract formation in the ranibizumab groups (p=0.03). Limitations of the study include the short-term follow-up, the 50 PDT patients who crossed over to ranibizumab injections prior to 24 months follow-up, and the drop-out rate (n=80).
Sadda et al. (2010) compared lesion anatomical responses to ranibizumab versus PDT in the patients (n=423) in the ANCHOR study described above (Brown, et al., 2009). Baseline lesion characteristics and visual acuity scores were similar in all three groups. Study eyes treated with ranibizumab, on average, exhibited slight lesion growth at 12 and 24 months compared to baseline. In the PDT group, mean lesion area following treatment was significantly larger compared to the 0.3 mg and 0.5 mg ranibizumab dose groups (p<0.0001, each). The mean serous sensory retinal detachment/subretinal fluid decreased significantly from baseline in the ranibizumab groups compared to the PDT group (p<0.001). There was significantly less leakage at 12 and 24 months in the ranibizumab groups compared to the PDT group (p<0.0001, each). There was a significant increase in the area of subretinal fibrous tissue/disciform scar compared to baseline in the PDT group compared to the ranibizumab 0.3 mg group (p=0.0007) at 24 months. In a subset of patients (n=61) at 12 months the center point thickness as measured by optical coherence tomography was significantly more decreased in the pooled ranibizumab patients (p=0.0003). Limitations of the study include the short-term follow-up, the 50 PDT patients who crossed over to ranibizumab injections prior to 24 months follow-up, the drop-out rate (n=80) and the small number of patients that underwent optical coherence tomography.

In a randomized controlled trial, Tufail et al. (2010) compared the efficacy and safety of 1.25 mg intravitreal bevacizumab (IVB) (n=65) for the treatment of neovascular AMD to standard care (control group) (n=66). In the IVB group, patients in whom the standard treatment would have been PDT were treated with placebo PDT. In the control group, the treatment type varied and was based on the type of AMD (i.e., PDT for predominantly classic CNV [n=16]; or 0.3 mg intravitreal pegaptanib [n=38] or sham intravitreal injections for occult or minimally classic CNV [n=12]). Patients received the last treatment at week 48 and were followed to week 54. Significantly more patients gained 15 or more letters from baseline in the IVB group than in the standard care group (p<0.001). The number of patients who lost fewer than 15 letters of visual acuity from baseline was significantly greater in the IVB group than the standard group (p<0.001). At final follow-up there was a significant decrease in the area of CNV leakage in the IVB group compared to the standard group (p<0.3), a significant mean lesion area increase in the standard group compared to IVB (p=0.3), and a significant decrease in central retinal thickness on optical coherence tomography in the IVB group (p=0.08). A subgroup analysis of baseline to week 54 visual acuity showed that 44% of the IVB group gained ≥ 15 letters vs. 0% with PDT; 30% with IVB vs. 5% with pegaptanib; and 25% with IVB vs. 0% sham. The author noted that this subgroup data “should be interpreted with great caution”. There were no significant differences in adverse ocular events between the groups. Limitations of the study as noted by the authors included using visual gain as the primary outcome instead of visual stabilization; treatment in the standard arm was determined according to funding of standard treatment by the National Health Service (NHS) in the United Kingdom; and the comparison of the study group to three different treatment groups. Other limitations include the small heterogeneous patient population, short-term follow-up and nine patients lost to follow-up in the standard treatment group.

Professional Societies/Organizations: The 2012 American Academy of Ophthalmology (AAO) guidelines for the treatment of AMD recommends PDT for the treatment of subfoveal CNV, new or recurrent, with a > 50% classic lesion and an entire lesion of ≤ 5400 microns in greatest linear diameter. PDT may also be considered for the treatment of occult CNV with vision < 20/50 or CNV with lesion <4 Macular Photocoagulation Study (MPS) disc areas when vision is >20/50.

In 2005, the Verteporfin Roundtable Participants, including input from the American Society of Retina Specialists, the Macula Society, and the Retina Society, updated their guidelines on PDT for the treatment of CNV due to AMD and other causes. Viable candidates for PDT included those whose CNV is associated with AMD, pathologic myopia or other causes in which the outcome of lack of treatment would be more detrimental than PDT itself. Verteporfin therapy is recommended to treat eyes that present with a subfoveal lesion with predominantly classic CNV (area of classic CNV occupying ≥ 50% of the area of the entire lesion at baseline). Lesion location should be subfoveal or may be considered for juxtafoveal lesions if the lesion is so close to the fovea that laser photocoagulation might be more harmful than beneficial. For pathological myopia, lesion composition should not influence patient selection for PDT because it has not shown to influence the outcomes of the therapy. According to the authors, PDT should be initiated within one week of the initial diagnostic fluorescein angiogram. Re-treatment may be indicated every three months if there is evidence of fluorescein leakage on revisits.

Pathological Myopia
Pathological myopia (PM) or high myopia is a rare form of shortsightedness in which the eyeball is abnormally long, stretching the retina and the sclera of the eye. This greater axial length may cause areas of atrophy and/or
cracks in the retina leading to leakage of blood. PM is often accompanied by subfoveal CNV, chorioretinal atrophy, and retinal detachment. Historically, treatment options for PM have included laser photocoagulation, macular translocation and submacular surgery with poor results, including immediate, permanent loss of visual acuity. PDT has been shown to be effective in stabilizing and retarding the progression of visual deterioration in PM with predominantly classic subfoveal CNV (Chan, et al., 2005; Lam, et al., 2004).

**Literature Review:** The evidence in randomized controlled trials, nonrandomized comparative studies, and case series support PDT for the treatment of PM. There are a limited number of studies comparing PDT to other treatment modalities (Hayashi, et al., 2008; Hussain, et al., 2008; Costa, et al., 2006; Pece, et al., 2007; Krebs, et al., 2005; Lam, et al., 2004).

**Presumed Ocular Histoplasmosis Syndrome**

Presumed ocular histoplasmosis syndrome (POHS) is a chronic intraocular inflammation caused by the fungus histoplasma capsulatum. Normally, patients are unaware of the disease process until they begin to develop visual disturbances from CNV. Depending on the stage and location of the disease, treatment options include corticosteroids, submacular surgery, and photodynamic therapy. PDT is indicated for the treatment of POHS with CNV because of its ability to selectively treat the target area while preserving surrounding tissue (Oliver, et al., 2005).

**Literature Review:** Although there are a limited number of studies, a randomized controlled trial (n=120) reported significant improvement following PDT compared to placebo in number of lines lost (fewer than eight, p<0.01 and fewer than 15 lost, p=0.01). Visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were also better in the PDT-treated eyes. Case series and retrospective reviews also reported stabilization, and/or improved visual acuity, and/or absence of fluorescein leakage following PDT. Studies comparing PDT to other established treatment modalities for POHS are lacking (Shah, et al., 2005; Liu JC, et al., 2004; Rosenfeld, et al., 2004; Saperstein, et al., 2002; Verteporfin in Photodynamic Therapy Study Group, 2001; Sickenberg, et al., 2000).

**Other Ocular Indications**

PDT has been proposed for the treatment of other ocular conditions including: minimally classic lesions, occult lesions, juxtapfoveal lesions, extrafoveal lesions, neovascular glaucoma, corneal neovascularization, CNV secondary to vascular retinochoroidal diseases (e.g., choroiditis, retinochoroiditis, angioid streaks), CNV with macular dystrophy and diseases without CNV (e.g., choroidal hemangioma and melanoma, retinal hemangiomia and hamartoma, central serious chorioretinopathy (CSCR), and angiomatosus lesions), and polypoidal choroidal vasculopathy, corneal neovascularization, lipid keratopathy and conjunctival ocular surface squamous neoplasia. The number of randomized controlled trials are lacking and most studies have primarily been in the form of case reports and case series with small patient populations (n=3-72), short-term follow-up (e.g., 2-24 months) and variable, nonsignificant outcomes (Hikichi, et al., 2011; Leal, et al., 2010; Ruiz-Moreno, et al., 2010; Tsuchiya, et al., 2009; Mennel, et al., 2007; Yoon, et al., 2007; Ruiz-Moreno, et al., 2006). Visudyne is not FDA approved for these other indications.

**Literature Review:** In a randomized controlled trial, Parodi et al. (2010) compared the effectiveness of laser treatment (LT) (n=17), PDT (n=18) and intravitreal bevacizumab injection (n=19) on visual acuity in patients with juxtapfoveal CNV secondary to pathologic myopia. At the 24-month follow-up, the bevacizumab group maintained its initial improvement in best corrected visual acuity (BCVA) and had a final gain of 1.8 lines compared to baseline. The LT group experienced a nonsignificant visual loss of 1.1 lines, and the mean BCVA in the PDT group was significantly worsened by two lines (p<0.05). Compared to PDT, the bevacizumab group displayed a statistically significant improvement of a mean three line difference (p<0.05). During the first year following treatment, CNV recurrence with subfoveal extension occurred in nine LT eyes (53%) which were subsequently retreated with PDT. A foveal extension occurred in 13 PDT eyes (72%) and four patients treated with bevacizumab developed a CNV foveal extension. Limitations of the study include the lack of a control group, the small patient population, and the short-term follow-up.

To compare the outcomes of treatment, Kaiser et al. (2009) randomly assigned 244 patients to PDT and 120 patients to placebo for the treatment of AMD with subfoveal occult with no classic CNV. Follow-up visits and subsequent therapy occurred for up to 24 months. During the first 12 months of the study, the PDT group received an average of 2.9 treatments compared to 3.3 treatments in the placebo group. Between month 12 and 24, the PDT group received an additional 1.3 treatments compared to 1.7 treatments in the placebo group.
Although less loss of visual acuity was reported in the PDT group, the differences were not statistically significant (p=0.256 at 12 months and p=0.138 at 24 months). With the exception of infusion-related pain following PDT (p<0.01), there were no statistically significant differences in reported adverse events between the two groups.

Chan et al. (2008) recruited 63 patients to participate in a randomized controlled trial evaluating the efficacy of PDT (n=63) for the treatment of acute central serous chorioretinopathy (CSC) of three months or less duration. Subjects had impaired vision, subretinal fluid, and angiographic leakage. Patients were randomized to either treatment with PDT using half-dose verteporfin (n=43) or to placebo (n=21). At the 12-month follow-up visit, a significant difference was seen in the complete resolution of macular subretinal fluid in 37 eyes in the PDT group compared to 11 eyes in the placebo group (p=0.001). The mean logarithm of the minimum angle of resolution, mean lines of best corrected vision acuity, and vision stability/improvement were also significantly improved in the PDT group (p=0.008, p=0.002, p=0.009, respectively). The PDT group had significantly better outcomes in the mean central foveal thickness seen on optical coherence tomography (p=0.001). No complications or adverse events were experienced. Author-noted limitations included the small sample size, smaller number of eyes in the placebo group vs. the PDT group, use of half-dose verteporfin, exclusion of patients with secondary CSC, and the lack of angiography performed at the 12-month follow-up.

Use Outside of the US

Dermatologic Conditions

According to 2013 guidelines endorsed by the European Academy of Dermatology and Venereology, “topical PDT is a widely used non-invasive treatment for certain non-melanoma skin cancers, permitting treatment of large and multiple lesions with excellent cosmesis. High efficacy is demonstrated for PDT using standardized protocols in non-hyperkeratotic actinic keratoses, Bowen’s disease, superficial basal cell carcinomas (BCC) and in certain thin nodular BCC, with superiority of cosmetic outcome over conventional therapies. Recurrence rates following PDT are typically equivalent to existing therapies, although higher than surgery for nodular BCC” (Morton, et al., 2013). The guideline further states that PDT is not recommended for invasive squamous cell carcinoma.

Actinic Keratosis (AK): The National Institute for Clinical Excellence (NICE) (2006) (United Kingdom) guidance states that the evidence is adequate to support the efficacy of PDT for the treatment of AK, but that PDT may be more appropriate for large, superficial lesions especially where there are multiple lesions.

Basal Cell Carcinoma (BCC): In their 2008 guidelines on the management of BCC, The British Association of Dermatologists (BAD) included the PDT as a treatment option for BCC. BAD stated that PDT is a good treatment for primary superficial BCC and a “reasonable treatment for primary low-risk” nBCC (Telfer, 2008). In their guidelines for topical PDT, BAD stated that MAL-PDT and ALA-PDT are effective treatments for BCC. MAL-PDT is effective in the treatment of nodular BCC, but it has a lower efficacy than surgical excision and may be an option when surgical excision is suboptimal (Morton, et al., 2008).

The International Society for Photodynamic Therapy in Dermatology (Braathen, et al., 2007) recommended PDT for the treatment of superficial BCC as a reliable and effective method, yielding excellent or good cosmetic outcomes and offers an advantage in the treatment of large, extensive, and multiple lesions. Studies of MAL-PDT have demonstrated long-term efficacy (five-year follow-up) for the treatment of superficial and nodular BCC.

According to the National Institute for Clinical Excellence (NICE) (2006), the level of evidence is adequate to support the efficacy of PDT for the treatment of BCC.

Bowen’s Disease: In a 2007 guideline for the management of Bowen’s disease, the British Association of Dermatologists (BAD) stated that “PDT has been shown to be equivalent or superior to cryotherapy and 5-FU, either in efficacy and/or in healing.” They explain that PDT may be especially beneficial in the treatment of large lesions on the lower leg and other difficult sites (Cox, et al., 2007). In their 2008 guidelines for PDT, BAD also stated that PDT is equivalent or superior to the use of topical 5-FU and offers particular advantages for large multiple patch disease and for lesions at poor healing sites” (Morton, et al., 2008).
Recommendations by the International Society for Photodynamic Therapy in Dermatology (Braathen, et al., 2007) stated that PDT is as effective as cryotherapy and topical fluorouracil with fewer adverse events and should be considered a first-line therapy for Bowen’s disease. Surgery is recommended for nonresponders.

The National Institute for Clinical Excellence (NICE) (2006) stated that the evidence supports the use of PDT for the treatment of Bowen’s disease especially when there are multiple large, superficial lesions that would otherwise require extensive surgery.

**Acne Vulgaris**: The British Association of Dermatologists (Morton, et al., 2008) stated that although PDT can improve inflammatory acne, “optimization of protocols, to sustain response while minimizing adverse effects, is awaited”.

**Squamous Cell Carcinoma (SCC)**: In their 2007 guidelines for the use of PDT for dermatological conditions, the International Society for Photodynamic Therapy in Dermatology concluded that there was insufficient evidence to support the routine use of PDT for the treatment of SCC (Braathen, et al., 2007).

The British Association of Dermatologists (Morton, et al., 2008) stated that “the high efficacy of topical PDT for in situ SCC and the efficacy figures reported particularly for superficial invasive lesions limited to papillary dermis, suggest that depth of therapeutic effect is the limiting factor for PDT in invasive SCC, with further study required. Current evidence supports the potential of topical PDT for superficial, microinvasive SCC, but in view of its metastatic potential, topical PDT cannot currently be recommended for the treatment of invasive SCC”.

**Psoriasis**: In their guidelines for topical PDT, the British Association of Dermatology (Morton, et al., 2008) stated that the overall body of evidence does not support PDT for the treatment of psoriasis.

**Warts**: The British Association of Dermatologists (Morton, et al., 2008) guidelines on topical PDT stated that “studies continue to support the potential of topical PDT in viral warts, particularly plantar warts, but it appears a relatively painful therapy option, with outcomes dependent on adequate paring and the use of a keratolytic agent pre-PDT”.

**Additional Dermatologic Conditions**: The British Association of Dermatologists guidelines (Neill, et al., 2010) for the management of lichen sclerosus included PDT as a proposed treatment option. Available studies that have investigated PDT for the treatment of vulval lichen sclerosus have included small patient populations (n=10–12). BAD did not recommend PDT has a treatment option for this condition.

**Ocular**

**Age-Related Macular Degeneration**: In a guidance document, National Institute for Clinical Excellence (NICE) (United Kingdom) (2003) recommended PDT for the treatment of wet AMD with a diagnosis of classic with no occult subfoveal CNV and best-corrected visual acuity 6/60 or better. NICE did not recommend PDT for the treatment of AMD when some occult CNV is present.

**Summary**

Evidence in the published peer-reviewed scientific literature and professional societies support photodynamic therapy (PDT) for the treatment of nonhyperkeratotic actinic keratosis (AK). PDT is established as an alternative therapy for the treatment of superficial basal cell carcinoma or Bowen’s disease that is unresponsive to standard medical and/or surgical treatment or in individuals in whom standard therapy is contraindicated or cannot be tolerated. There is also sufficient evidence to support PDT with verteporfin for the treatment of predominantly classic subfoveal choroidal neovascularization (CNV) when the area of the classic lesion comprises ≥ 50% of the entire lesion and is due to wet age-related macular degeneration (AMD), pathological myopia, or presumed ocular histoplasmosis.

PDT has been proposed for the treatment of numerous other dermatologic (e.g., acne vulgaris, nodular basal cell carcinoma, hyperkeratotic actinic keratoses, psoriasis, warts) and ocular conditions (e.g., minimally classic lesions, occult lesions, juxtafoveal lesions, extrafoveal lesions, angioid streaks and neovascular glaucoma). However, there is insufficient evidence in the published peer-reviewed scientific literature to support PDT for the treatment of other dermatologic and ocular conditions. Published studies are primarily in the form of case reports and case series with small patient populations and short-term follow-ups and various treatment regimens.
Photoaging, sebaceous gland hyperplasia and hirsutism are benign conditions which result in untoward cosmetic effects. Treatment for these conditions is for the purpose of improving appearance and not medically necessary.

### Coding/Billing Information

**Note:**
1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.
3. ICD-10-CM Diagnosis Codes are for informational purposes only and are not effective until 10/01/2014.

### Dermatologic Conditions

Covered when medically necessary:

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<th>CPT® Codes</th>
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<td>96567</td>
<td>Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (eg, lip) by activation of photosensitive drug(s), each phototherapy exposure session</td>
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<td>J7308</td>
<td>Aminolevulinic acid HCL for topical administration, 20%, single unit dosage form (354 mg)</td>
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<td>J7309</td>
<td>Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram</td>
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### ICD-10-CM Diagnosis Codes (Effective 10/01/2014)

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<td>D04.0-D04.9†</td>
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<td>L57.0†††</td>
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**Note:**
1. Covered when medically necessary and used to report superficial basal cell carcinoma.
2. Covered when medically necessary and used to report Bowen’s disease.
3. Covered when medically necessary and used to report nonhyperkeratotic actinic keratosis.

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**Cosmetic in Nature/Not Covered:**

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<td>706.9 Unspecified disease of sebaceous glands</td>
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**Ocular Conditions**

**Covered when medically necessary:**

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B39.4  Histoplasmosis capsulati, unspecified
B39.9  Histoplasmosis, unspecified
H44.20-H44.23  Degenerative myopia
H35.32  Exudative age-related macular degeneration

Experimental/Investigational/Unproven/Not Covered:

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