

Corporate Medical Policy

Dermatologic Applications of Photodynamic Therapy

File Name: dermatologic_applications_of_photodynamic_therapy
Origination: 10/2003
Last CAP Review: 10/2021
Next CAP Review: 10/2022
Last Review: 10/2021

Description of Procedure or Service

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

Two common photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester methyl aminolevulinate (MAL). When applied topically, they pass readily through the abnormal keratin overlying the lesion and accumulates preferentially in dysplastic cells. 5-ALA and MAL are metabolized by the underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404–420 nm and 635 nm) generates reactive oxygen species that are cytotoxic, ultimately destroying the lesion. PDT can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results. PDT with topical ALA has been investigated primarily as a treatment of actinic keratoses. It has also been investigated as a treatment of other superficial dermatologic lesions, such as Bowen's disease, acne vulgaris, mycoses, hidradenitis suppurativa, and superficial and nodular basal cell carcinoma. 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 individuals with fair complexions, with a prevalence of >80% in fair-skinned people over the age of 60. In some cases actinic keratosis may progress to squamous cell carcinoma. The available treatments for actinic keratoses can generally be divided into surgical and non-surgical methods. Surgical treatments used to treat one or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodisiccation), and laser surgery. Non-surgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (also known as chemical peels), and dermabrasion. Topical treatments are generally used in patients with multiple lesions and the involvement of extensive areas of skin. Under some circumstances, combinations of different treatment methods may be used.

Non-melanoma skin cancers are the most common malignancies in the Caucasian population. Basal cell carcinoma (BCC) is most often found in light-skinned individuals and is the most common of the cutaneous malignancies. Although the 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's disease is a squamous cell carcinoma (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 non-melanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-fluorouracil, imiquimod, and

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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 ALA, in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp.” The product is applied in the physician’s office.

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

A 5-aminolevulinic acid patch technology (5-ALA Patch) is available outside of the U.S through an agreement between Intendis (part of Bayer HealthCare) and Photonamic GmbH and Co. KG. The 5-ALA patch is not approved by the FDA.

Another variant of PDT for skin lesions is Metvixia® and the Aktelite CL128 lamp, each of which received FDA approval in July 2004. Metvixia® (Galderma, SA, Switzerland; PhotoCure ASA, Norway) consists of the topical application of methyl aminolevulinate (MAL) in contrast to ALA used in the Kerastick procedure, followed by exposure with the Aktelite CL 128 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 (IPL), pulsed dye lasers (PDL), and potassium titanyl phosphate (KTP) lasers have also been used. Metvixia is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation (debridement using a sharp dermal curette) in the physician's office when other therapies are unacceptable or considered medically less appropriate.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for dermatologic applications of photodynamic therapy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Dermatologic Applications of Photodynamic Therapy is covered

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

- Non-hyperkeratotic actinic keratoses of the face and scalp.
- Non-hyperkeratotic actinic keratoses for 4 or more upper extremity lesions.
- 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.

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When Dermatologic Applications of Photodynamic Therapy is not covered

Photodynamic therapy is considered investigational for other dermatologic applications, including, but not limited to, acne vulgaris, high risk basal cell carcinomas, hidradenitis suppurativa, and mycoses.

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

Photodynamic therapy is considered not medically necessary as a treatment of non-hyperkeratotic actinic keratoses in locations other than the face, scalp, and upper extremities, including, but not limited to, the trunk and lower extremities.

Photodynamic therapy is considered not medically necessary as a treatment of 3 or fewer non-hyperkeratotic actinic keratoses on the upper extremities.

Policy Guidelines

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

For individuals who have nonhyperkeratotic actinic keratoses on the face or scalp who receive PDT, the evidence includes randomized controlled trials (RCTs). The 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 nonhyperkeratotic AKs on the upper extremities who receive PDT, the evidence includes RCTs. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. In two placebo-controlled RCTs, significantly more patients had a complete clearance of AKs with ALA/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-fluorouracil and found similar efficacy between the active treatment groups after six months of follow-up. Based on characteristics of patients enrolled in randomized controlled trials, 4 or more upper extremity lesions is an appropriate threshold for use of photodynamic therapy for patients with nonhyperkeratotic actinic keratosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have squamous cell carcinoma in situ who receive PDT, the evidence includes RCTs. The 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

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compared with cryotherapy and 5-fluorouracil. Additionally, adverse events and cosmetic outcomes appear to be better after PDT. Few RCTs have compared PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these other standard treatments. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have noncancerous dermatologic skin conditions (eg, hidradenitis suppurativa, mycoses, port wine stain) who receive PDT, the evidence includes case series, systematic reviews of uncontrolled series, and an RCT for port wine stain. The 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 96567, 96573, 96574, J7308, J7309, J7345

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For EBG entitled: Photodynamic Therapy for the Treatment of Actinic Keratoses

BCBSA Medical Policy Reference Manual, 2.01.44; 11/20/01

ECRI TARGET Report # 810. Photodynamic therapy (PDT) with aminolevulinic acid for treatment of actinic keratosis (AK). November, 2001.

ECRI Hotline Response: Photodynamic Therapy (PDT) with Aminolevulinic Acid for Treatment of Actinic Keratosis (AK). January 27, 2003.

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Coverage Issues Manual Section 35-101. Treatment of Actinic Keratosis. Accessed 1/22/2003.
http://www.cms.hhs.gov/manuals/06_cim/ci35.asp#sect_35_101

Specialty Matched Consultant Advisory Panel - 3/2003

BCBSA Medical Policy Reference Manual; 2.01.44; 4/29/03

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 4/16/04.

Specialty Matched Consultant Advisory Panel - 2/11/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 4/1/05.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 7/20/06.

For policy re-titled: Dermatologic Applications of Photodynamic Therapy

Specialty Matched Consultant Advisory Panel - 4/27/07.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 8/2/07.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 8/14/08.

Specialty Matched Consultant Advisory Panel - 5/2009

Morton CA, McKenna KE, Rhodes LE, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for topical photodynamic therapy: update. Br J Dermatol 2008 Dec;159(6):1245-66. Retrieved on December 8, 2010 from <http://www.guideline.gov/content.aspx?id=13568&search=photodynamic+therapy>

Specialty Matched Consultant Advisory panel review 1-2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 1/14/10

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 1/12/12

Medical Director review 1/2012

Specialty Matched Consultant Advisory Panel review 1/2012

Medical Director review 5/2012

National Comprehensive Cancer Network. Practice Guidelines in Oncology- v2. 2012. Basal cell and squamous cell skin cancers. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/nmssc.pdf

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 1/10/13

Specialty Matched Consultant Advisory Panel review 1/2013

Lansbury L, Bath-Hextall F, Perkins W et al. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ 2013; 347:f6153.

National Comprehensive Cancer Network Practice Guidelines in Oncology Version 2. 2013. Basal

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cell and squamous cell skin cancers. Retrieved from:

http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 1/9/14

Specialty Matched Consultant Advisory Panel review 1/2014

Medical Director review 1/2014

Specialty Matched Consultant Advisory Panel review 1/2015

Medical Director review 2/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 1/15/15

Specialty Matched Consultant Advisory Panel review 1/2016

Medical Director review 1/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 1/15/16

National Comprehensive Cancer Network Practice Guidelines in Oncology Version 1.2017. Basal cell skin cancer. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 12/08/16

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 12/14/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 12/13/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.44, 12/12/2019

Brian Jiang SI, Kempers S, Rich P et al. A Randomized, Vehicle-Controlled Phase 3 Study of Aminolevulinic Acid Photodynamic Therapy for the Treatment of Actinic Keratoses on the Upper Extremities.. *Dermatol Surg*, 2019 Jan 15;45(7). PMID 30640777

Schmieder GJ, Huang EY, Jarratt M. A multicenter, randomized, vehicle-controlled phase 2 study of blue light photodynamic therapy with aminolevulinic acid HCl 20% topical solution for the treatment of actinic keratoses on the upper extremities: the effect of occlusion during the drug incubation period.. *J Drugs Dermatol*, 2013 Feb 5;11(12). PMID 23377520

Taub AF, Garretson CB. A randomized, blinded, bilateral intraindividual, vehicle-controlled trial of the use of photodynamic therapy with 5-aminolevulinic acid and blue light for the treatment of actinic keratoses of the upper extremities.. *J Drugs Dermatol*, 2011 Nov 5;10(9). PMID 22052276

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Policy Implementation/Update Information

For EBG entitled: Photodynamic Therapy for the Treatment of Actinic Keratoses

- 10/03 Specialty Matched Consultant Advisory Panel review 3/03. Original Policy issued.
- 3/3/05 Specialty Matched Consultant Advisory Panel review 2/2005. No changes to criteria. References added.
- 10/20/05 Description section expanded to include discussion of Metvix therapy. Under "When Covered" section added the following: "Photodynamic therapy with methyl aminolevulinate and exposure to red light may be considered medically necessary as a treatment of non-hyperkeratotic actinic keratoses of the face and scalp only." Under "When not Covered" section, added the following: "Photodynamic therapy with methyl aminolevulinate and exposure to red light is considered investigational for the treatment of other dermatologic applications, including but not limited to basal cell carcinomas, Bowen's disease, acne vulgaris, mycoses, or squamous cell carcinoma. Photodynamic therapy as a technique of skin rejuvenation, hair removal, or other cosmetic indications is considered not medically necessary." Added acne vulgaris, mycoses and hidradenitis suppurativa as investigational indications for ALA. Notification given 10/20/05. Effective date 1/5/06.
- 8/21/06 Medical Policy changed to Evidence Based Guideline. (pmo)
- 5/21/07 Reference sources added. No changes to criteria. (pmo)

For policy re-titled: Dermatologic Applications of Photodynamic Therapy

- 6/22/09 EBG name changed from "Photodynamic Therapy for the Treatment of Actinic Keratoses" to "Dermatologic Applications of Photodynamic Therapy". Description section revised. Evidence Based Guideline section now reads "Photodynamic therapy may be appropriate as a treatment of: Non-hyperkeratotic actinic keratoses of the face and scalp; Superficial 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."
- Under When Not Recommended section-first paragraph now reads: "Photodynamic therapy is not recommended for other dermatologic applications, including, but not limited to, acne vulgaris, non-superficial basal cell carcinomas, hidradenitis suppurativa, or mycoses." Second paragraph has been deleted. Medical term definitions and reference sources added. (pmo)
- 6/22/10 Policy Guideline Number(s) removed (amw)
- 2/15/11 Specialty Matched Consultant Advisory Panel review 1-2011. Added HCPCS code J7309 to Billing/Coding section. References updated. (mco)
- 2/7/12 Specialty Matched Consultant Advisory Panel review 1/2012. References updated. Description section updated. Medical Director review 1/2012. No changes to Policy Statements. (mco)
- 6/12/12 Evidence Based Guideline converted to Corporate Medical Policy. Photodynamic therapy may be considered medically necessary as a treatment of: Non-hyperkeratotic actinic keratoses of the face and scalp, Superficial 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. Photodynamic therapy as a technique of skin rejuvenation, hair removal, or other cosmetic indications is considered not medically necessary.

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Photodynamic therapy is considered not medically necessary as a treatment of non-hyperkeratotic actinic keratoses in locations other than the face and scalp, including, but not limited to, the trunk and extremities. Medical Director review 5/2012. Notice given 6/12/12 for effective date 9/18/12. (mco)

- 2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. References updated. No changes to Policy Statements. (mco)
- 2/11/14 Description section updated. Policy Guidelines updated. Specialty Matched Consultant Advisory Panel review 1/2014. Medical Director review 1/2014. References updated. No changes to Policy Statements. (mco)
- 2/24/15 Specialty Matched Consultant Advisory Panel review 1/2015. Medical Director review 2/2015. When Covered section updated to add, “Low-risk (e.g. superficial and nodular)” to the second bullet. When Not Covered section updated to remove “superficial” and add “high risk”. Policy Guidelines section updated. References updated. (td)
- 4/1/16 References updated. Specialty Matched Consultant Advisory Panel review 1/2016. Medical Director review 1/2016. Policy statement unchanged. (td)
- 1/27/17 Specialty Matched Consultant Advisory Panel review 11/30/2016. Policy Guidelines and references updated. No change to policy statement. (an)
- 12/15/17 Codes 96573, 96574, J7345 added to Billing/Coding section. Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (an)
- 3/9/18 Information regarding Ameluz® (aminolevulinic acid hydrochloride) gel added to description section. Policy Guidelines section updated. No change to policy statement or intent. (an)
- 11/9/18 Specialty Matched Consultant Advisory Panel review 10/24/2018 No change to policy statement. (an)
- 10/29/19 References and Policy Guidelines updated. Specialty Matched Consultant Advisory Panel review 10/16/2019. No change to policy statement. (eel)
- 02/11/20 References and Policy Guidelines updated. “Non-hyperkeratotic actinic keratoses for 4 or more upper extremity lesions.” added to When covered section. “Photodynamic therapy is considered not medically necessary as a treatment of 3 or fewer non-hyperkeratotic actinic keratoses on the upper extremities.” added to When not covered section. (eel)
- 11/10/20 References updated. Specialty Matched Consultant Advisory Panel review 10/21/2020. No change to policy statement. (eel)
- 11/2/21 References updated. Specialty Matched Consultant Advisory Panel review 10/21/2020. Medical Director review. No change to policy statement (tt)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.

