Clinical Policy Title: Phototherapy and photochemotherapy for skin conditions

Clinical Policy Number: 16.02.04

Effective Date: October 1, 2015
Initial Review Date: May 20, 2015
Most Recent Review Date: May 1, 2018
Next Review Date: May 2019

Policy contains:
- Photochemotherapy.
- Phototherapy.
- Psoralen ultraviolet A (PUVA).
- Psoriasis.

Related policies:
None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state and federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of phototherapy and photochemotherapy (psoralen ultraviolet A [PUVA]) to be clinically proven and, therefore, medically necessary for the following skin conditions after conventional therapies have failed:
- Severe refractory atopic dermatitis/eczema.
- Mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma).
- Psoriasis.

Select Health of South Carolina considers the use of phototherapy at home to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of PUVA are not medically necessary, including, but not limited to, treatment for the following conditions:
- Keratosis follicularis.
- Lichen amyloidosis.
- Lichen myxedematosus.
- Melasma.
- Low skin tolerance for sunlight.

Alternative covered services:

Biologic systemic agents, nonbiologic systemic agents, and phototherapy including broadband ultraviolet B (BB-UVB) and narrowband ultraviolet B (NB-UVB).

**Background**

Ultraviolet light — a cause of sunburns, wrinkles, and skin cancer — can be used in a medical setting as therapy for certain hard-to-treat skin problems and other medical conditions. The main forms of ultraviolet light are ultraviolet A (UVA) and ultraviolet B (UVB).

PUVA is a topical treatment of disease by exposure to light at a specific portion of the solar spectrum, 320 to 400 nanometers in wavelength. Psoralens are chemicals found in plants that can absorb UV light. PUVA treatment for various skin conditions typically involves administration of an oral drug (e.g., methoxypsoralen) followed by exposure to UVA 45 to 60 minutes later. Other forms of PUVA include:

- Topical PUVA, with subsequent UVA exposure.
- Bath PUVA, which is not approved and rarely used in the United States.
- Paint PUVA, used locally on palms and plantar surfaces of the feet with 8-methoxypsoralen ointment or lotion applied directly to lesions.
- Soak PUVA, in which the area is immersed in a basin of water containing 8-methoxypsoralen.

Originally, PUVA was developed for psoriasis, a relatively common skin disorder. It is also used for conditions such as vitiligo and mycosis fungoides (the most common type of T-cell lymphoma). While mild psoriasis can often be controlled by topical medications, severe cases often require treatments involving UVA light exposure.

Before initiating PUVA therapy, other types of treatment should be discussed with the patient. The potential for PUVA to increase the risk of skin cancer, especially when treating psoriasis, should also be discussed. Persons at elevated risk for skin cancer from PUVA include children and persons with a genetic predisposition, a history of skin cancer, or a history of at least 150 prior PUVA treatments.

Types of toxicity to PUVA includes erythema, pruritus, xerosis, irregular pigmentation, and gastrointestinal symptoms. Most toxicity can be avoided by altering or dividing the dose. Whether PUVA raises the risk of melanoma is controversial. When administered to pregnant women, PUVA has been
associated with a rise in low-weight births, but not congenital anomalies. An expert panel concluded that PUVA is contraindicated for patients with lupus erythematosus, porphyria, or xeroderma pigmentation (Menter, 2010). Caution should be exercised for patients with skin types I and II who tend to burn easily, with a history of arsenic intake, with a likelihood of requiring cyclosporin or methotrexate with previous ionizing radiation therapy, or with a history of melanoma or nonmelanoma skin cancer (Cole, 2017).

PUVA-related guidelines are often specific to a patient’s condition, e.g.:

- A 2014 practice guideline by the American Academy of Dermatology on dermatitis treatment recommended phototherapy as a second-line treatment if emollients, topical steroids, and calcineurin inhibitors have failed, and that phototherapy may be considered for home use if patients are unable to receive the treatment in an office setting (Sidbury, 2014).

- A 2012 guideline on psoriasis from the National Institute for Health and Clinical Excellence (NICE) suggests offering NB-UVB phototherapy to psoriasis patients whose condition cannot be controlled with topical treatments alone, but recommends not using any type of phototherapy as maintenance therapy (NICE, 2012). A 2016 review of guidelines for psoriasis concludes that NB-UVB is an effective treatment option for psoriasis (Mehta, 2016). A 2011 American Academy of Dermatology guideline on psoriasis observes that PUVA is more effective than NB-UVB for thick lesions, while NB-UVB generally results in shorter remission (Menter, 2011).

- A 2012 guideline on alopecia areata from the British Association of Dermatologists recommends against PUVA use due to potentially serious side effects and inadequate evidence of efficacy (Messenger, 2012).

- A 2016 guideline on mycosis fungoides and Sézary syndrome, for which ultraviolet light is often used, suggests a more refined guideline based on patient stage and centers, and in combination with other agents in practice and clinical trials (Olsen, 2016).

- A 2013 guideline recommends PUVA as a second-line therapy (behind NB-UVB) for vitiligo, along with PUVA in various combination therapies for the disease (Taieb, 2013).

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on March 15, 2018. Search terms were: “phototherapy,” “photochemotherapy,” “PUVA therapy,” “UVA,” “UV-B,” “PUVA therapy home,” “psoriasis,” “vitiligo,” “eczema,” “mycosis,” and “fungoides.”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Psoriasis is the condition most studied for phototherapy outcomes. A systematic review of 29 articles (n = 675) of persons with palmoplantar pustular psoriasis found that phototherapy, ciclosporin, and topical corticosteroids each controlled the disease, with PUVA having greater efficacy than UVB therapy (Sevrain, 2014). Another meta-analysis of psoriasis (23 studies, n = 765) also found PUVA to be more efficacious than non-larger targeted UVB phototherapy, although both treatments had positive outcomes (Almutawa, 2015). PUVA’s superiority to NB-UVB was also observed in a 2012 meta-analysis of 29 trials (n = 773) and accomplished these results in fewer sessions (Archier, 2012a).

A 2013 Cochrane review of 13 trials (n = 662) on psoriasis found the PUVA vs. UVB comparison to be hampered by heterogenous evidence, and could not make a definitive conclusion on which was more effective (Chen, 2013). Phototherapy is generally found to work better as part of combination treatments, rather than as monotherapy, in psoriasis patients (Bailey, 2012). Another systematic review of 41 trials (n = 2416) found that PUVA was more effective than NB-UVB as a monotherapy, and NB-UVB worked better than BB-UVB and bath PUVA in treating adults with moderate to severe psoriasis (Almutawa, 2013).

A systematic review of 21 randomized controlled trials (RCTs) including 961 patients determined that NB-UVB and UVA1 phototherapy in moderate to severe dermatitis were helpful, but data on PUVA use and phototherapy in children are scarce (Perez-Ferriols, 2015). Another systematic review of 19 studies (n = 905) found that UVA1 and NB-UVB were the most effective treatments for reducing signs and symptoms of dermatitis (Garritsen, 2014).

Findings from 19 systematic reviews have determined that NB-UVB can be used effectively for chronic atopic eczema, and UVA used for acute eczema (Williams, 2008).

A recent meta-analysis of 38 studies of persons with vitiligo compared NB-UVB phototherapy (n = 1,201) to PUVA phototherapy (n = 227). At six and 12 months of treatment, the UVB group had more “at least mild” responses (74.2 and 75.0 percent) than did the PUVA group (51.4 and 61.6 percent). Marked
responses were more common in the face and neck (44.2 percent) than in the trunk (26.1) and the extremities (17.3) after six months of UVB phototherapy (Bae, 2017). A literature review found that combination therapies for vitiligo, compared to monotherapy, were more effective, especially when phototherapy was included (Bacigalupi, 2012).

A systematic review determined NB-UVB had fewer side effects and was marginally better than PUVA for vitiligo, and that (along with topical corticosteroids) it offers the greatest benefits of any vitiligo treatment (Whitton, 2015). A systematic review of seven studies (n = 232) comparing vitiligo treatment by PUVA and NB-UVB revealed no difference between the two on the rate of patients who achieved over 50 or over 75 percent re-pigmentation, both at p > .05 (Xiao, 2015).

Mycosis fungoides is the most common cutaneous T-cell lymphoma, and conventional therapy is not always effective in treating it. A review of 20 papers documents photodynamic therapy as a promising and well-tolerated option for treating localized lesions, with excellent cosmetic outcomes (Xue, 2017). PUVA and NB-UVB monotherapy were found to be effective first-line interventions for mycosis fungoides; the effectiveness of PUVA either as maintenance therapy or combined with drugs as first-line therapy is uncertain, but may be beneficial for relapse and late-stage disease (Dogra, 2015). A Cochrane review of 14 studies (n = 675) was unable to determine relative efficacy between types of mycosis fungoides treatments (Weberschock, 2012).

Risk of cancer from PUVA was the focus of a systematic review of 41 studies of chronic plaque psoriasis. Risk was elevated for non-melanoma skin cancer for squamous cell carcinomas, even at low exposures, with risk persisting after treatment cessation; for basal cell carcinoma in patients receiving more than 100 PUVA treatments; and for melanoma in persons receiving more than 200 PUVA treatments. No skin cancer risk was associated with NB-UVB use (Archier, 2012b).

PUVA is usually administered in an outpatient setting, but this treatment is also available for home use. Research has yet to demonstrate the efficacy of home phototherapy, which has been used for years despite lack of a consensus on efficacy (Koek, 2006). Rajpara (2010) found home NB-UVB was as safe, effective, and cost-effective as outpatient treatment, was more convenient, and generated higher satisfaction (Rajpara, 2010). One study of home-based phototherapy found NB-UVB to be safer than PUVA (Lapolla, 2011). Regular skin examinations by a dermatologist should be performed as PUVA home treatments are conducted. But a Cochrane review failed to support or refute home-based phototherapy for non-hemolytic jaundice in infants over 37 weeks gestation (Malwade, 2014). Most recently, a systematic review of 23 articles observed high levels of patient satisfaction, high levels of safety, and mostly positive reports of high quality of life after home phototherapy (Franken, 2016). The issue of whether home phototherapy use is safe and effective remains unresolved.

PUVA is used, sometimes effectively, for a variety of skin conditions for which the professional medical literature is limited. For example, in a Cochrane review of 16 studies (11 RCTs), PUVA treatment for cutaneous lichen planus had comparable outcomes to a PUVA bath and NB-UVB (Atzmony, 2016). A review of 14 studies (n = 64) of pediatric patients with pityriasis lichenoides determined that BB-UVB,
NB-UVB, and PUVA had initial clearance rates of 90 percent, 73 percent, and 83 percent, respectively, with recurrence rates of 23.1 percent, 0 percent, and 60 percent, respectively (Maranda, 2016).

Policy updates:

A total of two guidelines/other and five peer-reviewed references were added to, and six peer-reviewed references removed from, this policy in March 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td><strong>Bae (2017)</strong></td>
<td><strong>Key points:</strong></td>
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</table>
| Comparison of phototherapy modes for vitiligo | - Meta-analysis of 35 studies (n = 1428) comparing NB-UVB (n = 1,201) and UVA (n = 227) phototherapy for vitiligo.  
- At six and 12 months after therapy, UVB resulted in a higher percent of patients with "at least a mild response" (74.2 and 75.0), compared to UVA (51.4 and 61.6).  
- Percent of patients with marked responses was 44.2% in the face and neck, 26.1% on the trunk, and 17.3% on the extremities. |
| **Almutawa (2015)** | **Key points:**                   |
| PUVA, UVB and photodynamic therapy (PDT) for psoriasis | - Systematic review and meta-analysis of six RCTs and 17 case series.  
- The primary outcome was 75% reduction in severity score from baseline.  
- Overall quality: low with high risk of bias. Small sample size, study heterogeneity.  
- PUVA had a statistically nonsignificant (P = 0.183) advantage over targeted UVB.  
- The pooled effect estimate of topical PUVA, targeted UVB and PDT were 77%, 61% and 22%, respectively (15-case series).  
- Topical PUVA and targeted UVB phototherapy are effective in treating localized psoriasis. PDT has low efficacy and high percentage of side effects. |
| **Dogra (2015)**  | **Key points:**                   |
| Phototherapy for mycosis fungoides (MF) | - Synthesis of 107 systematic reviews, meta-analyses, national guidelines, RCTs, prospective open label studies, and retrospective case series.  
- For early-stage mycosis fungoides (stages IA, IB, and IIA):  
  o PUVA is a safe, effective, and well tolerated first-line therapy (level of evidence [LOE] 1+, grade of recommendation B).  
  o NB-UVB is comparable to PUVA but has less robust evidence (LOE 2++, grade B).  
  o PUVA with methotrexate, bexarotene, or interferon-alpha-2b has unclear advantage over monotherapy.  
  o NB-UVB preferred in patients with patches and thin plaques.  
  o PUVA preferred for thick plaques and relapse after initial NB-UVB therapy.  
- To induce remission, complete three treatment sessions per week of either PUVA phototherapy or NB-UVB phototherapy until complete remission.  
- In cases of relapse, administer PUVA monotherapy or PUVA combined with adjuvants like methotrexate and interferon (LOE 2+, Grade B).  
- For late-stage mycosis fungoides, above combination therapy may be first-line treatment (LOE
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<tr>
<td></td>
<td>3, grade C).</td>
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<tr>
<td></td>
<td>• No consensus regarding maintenance therapy with phototherapy once in remission.</td>
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<td></td>
<td>• Routine maintenance PUVA therapy not recommended; reserved for early relapse after initial course of phototherapy (LOE 2+, Grade B).</td>
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<td></td>
<td>• Bath-water PUVA has similar efficacy to oral PUVA and may be an alternative in case oral PUVA therapy cannot be administered (LOE 2-, Grade C).</td>
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<td></td>
<td>• In pediatric mycosis fungoides and in hypopigmented mycosis fungoides, NB-UVB and PUVA may be tried (LOE 3, grade D).</td>
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<tr>
<td>Whitton (2015)</td>
<td>Interventions for vitiligo</td>
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<td></td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• Cochrane review of 96 RCTs (4,512 total participants) of all interventions; three RCTs comparing NB-UVB with PUVA eligible for meta-analysis.</td>
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<td>• Overall quality: low with high risk of bias.</td>
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<td>• NB-UVB has fewer side effects and is marginally better than PUVA. Proportion of participants achieving &gt; 75% repigmentation favored NB-UVB compared to PUVA.</td>
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<td>• NB-UVB group reported less nausea in three studies (N = 156) and erythema in two studies (N = 106), but not itching in two studies (N = 106).</td>
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<td></td>
<td>• Very few studies only assessed children or included segmental vitiligo.</td>
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<td>• There is a need for follow-up studies to assess permanence of repigmentation and high-quality RCTs using standardized measures that address quality of life.</td>
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<tr>
<td>Archier (2012)</td>
<td>Cancer risk of PUVA for psoriasis</td>
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<tr>
<td></td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• Systematic review of 41 studies of chronic plaque psoriasis treated with PUVA and NB-UVB.</td>
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<td>• Risk elevated for squamous cell carcinomas after PUVA, even at low exposures; risk persists after treatment cessation.</td>
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<td>• Risk elevated for basal cell carcinoma in patients receiving more than 100 PUVA treatments.</td>
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<td>• Risk elevated for melanoma in persons receiving more than 200 PUVA treatments.</td>
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<tr>
<td></td>
<td>• No skin cancer risk associated with NB-UVB use.</td>
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**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is
not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<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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<tr>
<td>96912</td>
<td>Photochemotherapy; psoralens and ultraviolet A (PUVA)</td>
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<tr>
<td>96913</td>
<td>Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least 4-8 hours of care under direct supervision of the physician (includes application of medication and dressings)</td>
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<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tr>
<td>L20.82</td>
<td>Flexural eczema</td>
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<tr>
<td>L20.84</td>
<td>Intrinsic (allergic) eczema</td>
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<tr>
<td>L40.0</td>
<td>Psoriasis vulgaris</td>
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<tr>
<td>L40.1</td>
<td>Generalized pustular psoriasis</td>
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<tr>
<td>L40.2</td>
<td>Acrodermatitis continua</td>
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<tr>
<td>L40.3</td>
<td>Pustulosis palmaris et plantaris</td>
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<td>L40.4</td>
<td>Guttate psoriasis</td>
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<tr>
<td>L40.8</td>
<td>Other psoriasis</td>
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<tr>
<td>L40.9</td>
<td>Psoriasis, unspecified</td>
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<tr>
<td>L41.3</td>
<td>Small plaque parapsoriasis</td>
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<td>L41.4</td>
<td>Large plaque parapsoriasis</td>
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<td>L41.5</td>
<td>Retiform parapsoriasis</td>
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<td>L41.8</td>
<td>Other parapsoriasis</td>
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<td>Parapsoriasis,</td>
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<tr>
<td>L80</td>
<td>Vitiligo</td>
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<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
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<tbody>
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