Title: Ultraviolet Light Therapy for Skin Conditions

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DESCRIPTION
Ultraviolet (UV) light therapy, including phototherapy, targeted phototherapy and photochemotherapy with psoralen plus ultraviolet A (PUVA), is used for the treatment of certain skin conditions. Phototherapy utilizes UVB light, categorized as either wide-band or narrow-band, which refers to the wavelengths included in the UV light source. Targeted phototherapy describes the use of ultraviolet light that can be focused on specific body areas or lesions. PUVA uses a psoralen derivative in conjunction with long wavelength ultraviolet A (UVA) light (sunlight or artificial) for photochemotherapy of skin conditions.
OBJECTIVE
The objective of this policy is to evaluate the evidence for the efficacy and safety of targeted phototherapy and psoralen plus ultraviolet A in patients with certain skin conditions.

BACKGROUND
Phototherapy
Phototherapy (eg, actinotherapy) is defined as exposure to non-ionizing, ultraviolet (UV) radiation for therapeutic benefit by inducing DNA damage. The therapy involves exposure to type A ultraviolet (UVA) radiation or type B ultraviolet (UVB) radiation or various combinations of UVA and UVB. The differences in these ultraviolet light forms are the length of the waves. UVA wavelength is 320-400 nanometers (NM), broadband (bb) UVB is 280-320 nm and narrowband (nb) UVB is 311-312 nm. UVA is further broken down into UVA1 (340-400nm) and UVA2 (320-340nm). The longer wavelengths emit a lower energy level. UVA bulbs, for example, are used in tanning beds for cosmetic effects because they promote tanning using lower energy with less erythema than UVB.

Psoralen Plus Ultraviolet A
PUVA uses a psoralen derivative in conjunction with long wavelength UVA light (sunlight or artificial) for photochemotherapy of skin conditions. Psoralsens are tricyclic furocoumarins that occur in certain plants and can also be synthesized. They are available in oral and topical forms. Oral PUVA is generally given 1.5 hours before exposure to UVA radiation. Topical PUVA therapy refers to directly applying the psoralen to the skin with subsequent exposure to UVA light. Bath PUVA is used in some European countries for generalized psoriasis, but the agent used, trimethylpsoralen, is not approved by the U.S. Food and Drug Administration (FDA). Paint PUVA and soak PUVA are other forms of topical application of psoralen and are often used for psoriasis localized to the palms and soles. In paint PUVA, 8-methoxypsoralen (8-MOP) in an ointment or lotion form is put directly on the lesions. With soak PUVA, the affected areas of the body are placed in a basin of water containing psoralen. With topical PUVA, UVA exposure is generally administered within 30 minutes of psoralen application.

PUVA has most commonly been used to treat severe psoriasis, for which there is no generally accepted first-line treatment. Each treatment option (eg, systemic therapies such as methotrexate, phototherapy, biologic therapies) has associated benefits and risks. Common minor toxicities associated with PUVA include erythema, pruritus, irregular pigmentation, and gastrointestinal tract symptoms; these generally can be managed by altering the dose of psoralen or UV light. Potential long-term effects include photoaging and skin cancer, particularly squamous cell carcinoma and possibly malignant melanoma. PUVA is generally considered more effective than targeted phototherapy for the treatment of psoriasis. However, the requirement of systemic exposure and the higher risk of adverse reactions (including a higher carcinogenic risk) have generally limited PUVA therapy to patients with more severe disease.
Targeted Phototherapy
Potential advantages of targeted phototherapy include the ability to use higher treatment doses and to limit exposure to surrounding tissue. Broadband ultraviolet B (BB-UVB) devices, which emit wavelengths from 290 to 320 nm, have been largely replaced by narrowband (NB)-UVB devices. NB-UVB devices eliminate wavelengths below 296 nm, which are considered erythemogenic and carcinogenic but not therapeutic. NB-UVB is more effective than BB-UVB and approaches PUVA in efficacy. Original NB-UVB devices consisted of a Phillips TL-01 fluorescent bulb with a maximum wavelength (lambda max) at 311 nm. Subsequently, xenon chloride (XeCl) lasers and lamps were developed as targeted NB-UVB treatment devices; they generate monochromatic or very narrow band radiation with a lambda max of 308 nm. Targeted phototherapy devices are directed at specific lesions or affected areas, thus limiting exposure to the surrounding normal tissues. They may therefore allow higher dosages compared with a light box, which could result in fewer treatments to produce clearing.

The original indication of the excimer laser was for patients with mild to moderate psoriasis, defined as involvement of less than 10% of the skin. Newer XeCl laser devices are faster and more powerful than the original models, which may allow treatment of patients with more extensive skin involvement, 10%–20% of body surface area.

REGULATORY STATUS
In 2001, XTRAC™ (PhotoMedex, Willow Grove, PA), an XeCl excimer laser, was cleared for marketing by FDA through the 510(k) process for the treatment of mild-to-moderate psoriasis. The 510(k) clearance was subsequently obtained for a number of targeted UVB lamps and lasers, including newer versions of the XTRAC system (eg, XTRAC Ultra™), the VTRAC™ lamp (PhotoMedex), the BClear™ lamp (Lumenis, Israel), and the European manufactured Excilite™ and Excilite µ™ XeCl lamps. FDA product code: FTC.

In 2010, the Levia Personal Targeted Phototherapy® UVB device (Daavlin, Bryan, OH; previously manufactured by Lerner Medical Devices, Los Angeles, CA) was cleared for marketing by FDA through the 510(k) process for home treatment of psoriasis.

The oral psoralen products Oxsoralen-Ultra® (methoxsalen soft gelatin capsules) and 8-MOP® (methoxsalen hard gelatin capsules) have been approved by FDA; both are made by Valeant Pharmaceuticals. Topical psoralen products have also received FDA approval (eg, Oxsoralen; Valeant Pharmaceuticals).

POLICY
A. Phototherapy/actinotherapy with UVA is considered medically necessary for the following conditions when moderate to severe and refractory to standard therapies:
   1. Psoriasis
   2. Eczema (atopic dermatitis)
   3. Eosinophilic folliculitis and other skin eruptions of HIV
4. Lichen planus
5. Morphea
6. Parapsoriasis
7. Photodermatoses
8. Mycosis fungoides
9. Vitiligo
  - For up to 24 weeks, 3 treatments per week until improvement or clearing is considered medically necessary.

B. PUVA for the treatment of severe, disabling psoriasis, which is not responsive to other forms of conservative therapy (eg, topical corticosteroids, coal/tar preparations, and ultraviolet light), may be considered medically necessary.
  - For up to 24 weeks, 2-3 PUVA treatments per week (Monday, Wednesday, Friday or Tuesday, Thursday, Saturday) are considered medically necessary for psoriasis until improvement or clearing.
  - Tapered treatments of twice a week then once a week upon improvement (after 24 weeks) may be considered medically necessary. Remissions may last between 3-6 months.
  - Remission therapy of 1-4 treatments per month depending on the severity of the psoriasis may be considered medically necessary.

C. PUVA for the treatment of vitiligo which is not responsive to other forms of conservative therapy (eg, topical corticosteroids, coal/tar preparations, and ultraviolet light) may be considered medically necessary.

D. Targeted phototherapy may be considered medically necessary for the treatment of moderate to severe localized psoriasis for which NB-UVB or PUVA are indicated.

E. Targeted phototherapy may be considered medically necessary for the treatment of mild to moderate localized psoriasis that is unresponsive to conservative treatment.

F. Targeted phototherapy is considered experimental / investigational for the treatment of:
   1. Generalized psoriasis
   2. Vitiligo

G. Home phototherapy using ultraviolet A (UVA) light devices is considered experimental / investigational.

Policy Guidelines
1. Although disease severity is minimally defined by body surface area (mild psoriasis affects less than 5% of the body’s surface area, moderate psoriasis affects 5% to 10%, and severe disease affects more than 10% body surface area), lesion
characteristics (eg, location and severity of erythema, scaling, induration, pruritus) and impact on quality of life are also taken into account.1-3 For example, while 1 handprint is equal to approximately 1% body surface area, lesions on the hands, feet, or genitalia that cause disability may be classified as moderate to severe. While the Psoriasis Area and Severity Index (PASI) may be used as an outcome measure in clinical research, clinical assessment of disease severity is qualitative.

2. Established treatments for psoriasis include use of topical ointments and ultraviolet light (“light lamp”) treatments. Lasers and targeted ultraviolet B (UVB) lamps are considered equivalent devices; targeted UV devices are comparable with UV light panels for treatment purposes. First-line treatment of UV-sensitive lesions may involve around 6 to 10 office visits; treatment of recalcitrant lesions may involve around 24 to 30 office visits. Maintenance therapy or repeat courses of treatment may be required.

3. Phototherapy and PUVA are contraindicated in patients with xeroderma pigmentosum, disorders with significant light sensitivity (eg, albinism), and lupus erythematosus.

4. PUVA is contraindicated in patients who:
   a. are breast-feeding
   b. are pregnant
   c. have a history of melanoma
   d. have a past history of non-melanoma skin cancer
   e. have extensive solar damage
   f. have had previous treatment with ionizing arsenic
   g. have uremia and hepatic failure, but phototherapy may be used.

5. Phototherapy and PUVA should be used with caution in patients with one or more of the following:
   a. Family history of melanoma
   b. Pemphigus or pemphigoid
   c. Immunosuppression
   d. Cataracts and aphakia
   e. Photosensitivity.

6. During a course of PUVA therapy, the patient needs to be assessed on a regular basis to determine the effectiveness of the therapy and the development of adverse effects. These evaluations are essential to ensure that the exposure dose of radiation is kept to the minimum compatible with adequate control of disease. Therefore, PUVA is generally not recommended for home therapy.

**RATIONALE**

Following is a summary of literature update performed through October 25, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated
outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The most appropriate comparator for targeted therapy is narrowband ultraviolet B (NB-UVB), which is an established treatment for psoriasis and can be administered in the home. The efficacy of psoralen plus ultraviolet A (PUVA) has been compared with NB-UVB, which has fewer side effects, or with ultraviolet A (UVA) with placebo.

**Targeted Phototherapy**

**Mild Localized Psoriasis**
The original indication of the excimer laser was mild-to-moderate psoriasis, defined as involvement of less than 10% of the skin. Typically, this patient population has not been considered for light box therapy, because the risks of exposing the entire skin to the carcinogenic effects of ultraviolet B (UVB) light may outweigh the benefits of treating a small number of lesions. The American Academy of Dermatology does not recommend phototherapy for patients with mild localized psoriasis whose disease can be controlled with topical medications, including steroids, coal tar, vitamin D analogues (eg, calcipotriol, calcitriol), tazarotene, and anthralin.4

**Section Summary: Mild Localized Psoriasis**
There is no evidence and no clinical recommendation for targeted phototherapy to treat patients with mild localized psoriasis whose disease can be controlled with topical medications.

**Treatment-Resistant Mild Psoriasis**
Several small studies have suggested that targeted phototherapy can be effective for treatment-resistant lesions. One 2003 patch comparison reported effective clearing (pre Psoriasis Area and Severity Index [PASI] score, 6.2; post-PASI score, 1.0) of treatment-resistant psoriatic lesions; six of the patients had previously received topical treatment, five had received conventional phototherapy, and three had received combined treatments including phototherapy.5 In 2004, the same investigator group reported that 12 of 13 patients with “extensive and stubborn” scalp psoriasis (ie, unresponsive to class I topical steroids used in conjunction with tar and/or zinc pyrithione shampoos for at least 1 month) showed clearing following treatment with the 308-nm laser.6 In a 2006 open trial from Europe, 44 (81%) of 54 patients with palmoplantar psoriasis resistant to combined phototherapy and systemic treatments were cleared of lesions with a single NB-UVB lamp treatment weekly for 8 weeks.7
Section Summary: Treatment-Resistant Mild Psoriasis
Several nonrandomized studies have found that targeted phototherapy can improve health outcomes in patients with treatment-resistant psoriasis.

Moderate-to-Severe Localized Psoriasis
There are several systematic reviews of the literature on targeted phototherapy. Reviews differed in the type of study selected and the comparison interventions. A 2015 systematic review by Almutawa et al considered only RCTs; PUVA was the comparison intervention.8 Reviewers identified 3 RCTs comparing the efficacy of targeted UVB phototherapy with PUVA for treatment of plaque psoriasis. Two of the 3 trials used an excimer laser (308 nm) as the source of targeted phototherapy, and the third used localized NB-UVB light. There was no statistically significant difference between the techniques in the proportion of patients with at least a 75% reduction in psoriasis. The pooled odds ratio (OR) was 3.48 (95% confidence interval [CI], 0.56 to 22.84).

In 2012, Mudigonda et al published a systematic review of controlled studies (RCTs and non-RCTs) on targeted vs nontargeted phototherapy for patients with localized psoriasis.9 Reviewers identified 3 prospective nonrandomized studies comparing the 308-nm excimer laser with NB-UVB. Among these studies was a 2006 study by Goldinger et al that compared the excimer laser with full-body NB-UVB in 16 patients.10 At the end of 20 treatments, PASI scores were equally reduced on the 2 sides, from a baseline of 11.8 to 6.3 for laser and from 11.8 to 6.9 for nontargeted NB-UVB. A 2005 study by Kollner et al included 15 patients with stable plaque psoriasis.11 The study compared the 308-nm laser, the 308-nm excimer lamp, and standard TL-01 lamps. One psoriatic lesion per patient was treated with each therapy (ie, each patient received all 3 treatments). Investigators found no significant differences in the efficacy of the 3 treatments after 10 weeks. The mean number of treatments to achieve clearance of lesions was 24.

Section Summary: Moderate-to-Severe Localized Psoriasis
Systematic reviews of small RCTs and non-RCTs in patients with moderate-to-severe psoriasis have found that targeted phototherapy has efficacy similar to whole body phototherapy or PUVA. Targeted phototherapy is presumed to be safer or at least no riskier than whole body phototherapy, due to risks of exposing the entire skin to the carcinogenic effects of UVB light.

Systematic Reviews
In 2015, Whitton et al updated a Cochrane review of RCTs on treatments for vitiligo.19 The literature search, conducted through October 2013, identified 12 trials on laser light devices: 6 trials evaluated the combination of laser light devices and a topical therapy; 2 evaluated the combination of laser devices and surgical therapy; 3 compared regimens of laser monotherapy; and 1 compared a helium neon laser with a 290- to 320-nm broadband UVB fluorescent lamp. Due to heterogeneity across studies, reviewers did not pool study findings. In most trials, all groups received laser light treatment, alone or as part of combination therapy, and thus the effect of targeted phototherapy could not be isolated. Adverse event reports across the studies included burning, stinging, moderate-to-severe erythema, itching, blistering, and edema.

In 2015, Sun et al published a systematic review of RCTs that focused on the treatment of vitiligo with the 308-nm excimer laser.20 In a literature search conducted through April 2014, reviewers identified 7 RCTs (total N=390 patients) for inclusion. None of the studies was conducted in the United States; five were from Asia and three of those five are available only in Chinese. Three trials compared the excimer laser with an excimer lamp, and four compared the excimer laser...
with NB-UVB. One trial had a sample size of only 14 patients and another, published by Yang et al (2010), did not report repigmentation rates, providing instead, the proportion of patients with various types of repigmentation (perifollicular, marginal, diffuse, or combined). Repigmentation rates at the 75% and 100% level did not differ significantly between groups treated with the excimer laser vs NB-UVB. Reviewers conducted a meta-analysis of the 2 studies not published in English, though results cannot be verified. Results showed that the likelihood of 50% or more repigmentation was significantly higher with the excimer laser than with NB-UVB (relative risk [RR], 1.39, 95% confidence interval [CI], 1.05 to 1.85). Two of the 4 studies discussed adverse events, with itching and burning reported by both treatment and control groups and erythema and blistering reported only by the patient in the laser group.

A 2016 systematic review by Lopes et al identified 3 studies that compared targeted phototherapy using a 308-nm excimer lamp with NB-UVB (315 patients, 352 lesions) and 3 studies that compared the excimer lamp with the excimer laser (96 patients, 412 lesions). No differences between the excimer lamp and NB-UVB were identified for the outcome of 50% or more repigmentation (RR=1.14; 95% CI, 0.88 to 1.48). For repigmentation of 75% or more, only 2 small studies were identified, and they showed a lack of precision in the estimate (RR=1.81; 95% CI, 0.11 to 29.52). For the 3 studies that compared the excimer lamp with the excimer laser, there were no significant differences at the 50% or more repigmentation level (RR=0.97; 95% CI, 0.84 to 1.11) or the 75% or more repigmentation level (RR=0.96; 95% CI, 0.71 to 1.30). All treatments were most effective in lesions located on the face, with the worst response being lesions on the extremities. There was some evidence of an increase in adverse events such as blistering with targeted phototherapy.

Randomized Controlled Trials
An RCT comparing laser with an alternative treatment was published in 2012 by Nistico et al. This nonblinded RCT included 53 patients with localized and generalized vitiligo. Patients were randomized to 1 of 3 treatments for 12 weeks: (1) excimer laser plus vitamin E (n=20); (2) excimer laser plus topical tacrolimus ointment 0.1% and vitamin E (n=20); and (3) vitamin E only (control group, n=13). All patients in the 2 excimer laser groups completed treatment; 1 patient in the control group dropped out. Before and after treatment, 2 independent clinicians rated clinical response; 51% to 75% repigmentation was considered a “good” response and 75% or more repigmentation was considered an “excellent” response. The proportion of patients with a good or excellent response was 11 (55%) of 20 in the laser plus vitamin E group, 14 (70%) of 20 in the laser plus tacrolimus plus vitamin E group, and 0% in the control group. The rate of good or excellent responses did not differ significantly between groups that received excimer laser therapy with and without topical treatment (p=0.36). Response rates were significantly better in both groups receiving laser treatment than in the control group (p<0.001).

In 2017, Zhang et al published an RCT evaluating the use of the 308-nm targeted laser with and without Yiqiqubai granule for the treatment of vitiligo. Yiqiqubai granule is a therapy in traditional Chinese medicine, which is believed to activate blood circulation. The trial had 3 arms: 75 patients received twice-daily oral Yiqiqubai alone, 78 received weekly laser treatments alone, and 80 received both twice-daily oral Yiqiqubai and weekly laser treatments. All groups received treatment for 6 months. Two dermatologists not involved in the treatment assessed before and after pictures of the patients. Quality of life measures consisted of embarrassment, dress, social, and work components, measured on a 5-point scale. Following the 6 months of treatment, the percentages of patients achieving 50% or more repigmentation were 43%, 47%, and 51% for...
the Yiqiqubai alone, laser alone, and combined Yiqiqubai and laser groups, respectively (p<0.05). While the quality of life improved in all 3 treatment arms, patients in the combined treatment arm reported significantly larger improvements than the arms receiving laser or Yiqiqubai alone.

Retrospective Studies
In 2017, Fa et al published a retrospective analysis of 979 Chinese patients (3478 lesions) treated with the 308-nm targeted laser for vitiligo. Patients had Fitzpatrick skin phototype III or IV and were followed for 2 years after last treatment. Repigmentation was assessed by 2 dermatologists. A total of 1374 (39%) lesions reached at least 51% repigmentation, with 1167 of the lesions reaching over 75% repigmentation. Complete repigmentation was seen in 219 lesions. Among the cured lesions, the recurrence rate was 44%. Patients with longer disease duration and older age experienced significantly lower efficacy rates. Application of 16 to 20 treatments resulted in higher repigmentation rates than fewer treatments, and increasing the number of treatments beyond 21 did not appear to improve repigmentation rates. There was no discussion of adverse events.

In another 2017 retrospective analysis, Dong et al evaluated the use of a medium-band (304-312 nm) targeted laser for treating pediatric patients (age ≤16 years) with vitiligo. Twenty-seven patients (95 lesions) were evaluated by 2 dermatologists following a mean of 20 treatments (range, 10-50 treatments). After 10 treatment sessions, 37% of the lesions reached 50% or more repigmentation. After 20 treatment sessions, 54% of the lesions achieved 50% or more repigmentation. Six children experienced adverse events such as asymptomatic erythema, pruritus, and xerosis, all resolving in a few days.

Section Summary: Targeted Phototherapy
A number of RCTs and retrospective analyses have evaluated targeted phototherapy for treating vitiligo. The studies have tended to have small sample sizes, and few were designed to isolate the effect of laser therapy. Moreover, studies were heterogeneous (eg, duration and frequency of therapy sessions, different interventions or combinations of interventions, different comparison interventions). These characteristics made it difficult to pool study findings or to draw conclusions about the efficacy of targeted phototherapy for vitiligo. Two meta-analyses were attempted; however, one could not be verified because the selected studies were not available in English, and one estimate was imprecise due to the small number of studies and participants. Also, studies have suggested a potential for blistering and slight erythema with targeted phototherapy. Larger studies with representative patient populations and standard of care comparators (eg, NB-UVB) are needed to evaluate efficacy and adverse outcomes.

Psoralen Plus Ultraviolet A
A number of RCTs and systematic reviews of RCTs have compared PUVA with other light therapies or with placebo. A 2013 Cochrane review assessed light therapy for psoriasis. However, that review is less useful for this evidence evaluation because reviewers combined results of studies using PUVA and broadband (BB) UVB, rather than reporting outcomes separately for these treatment modalities.

PUVA vs NB-UVB
A 2012 industry-sponsored systematic review by Archier et al focused on studies comparing PUVA to NB-UVB in patients with chronic plaque psoriasis. Pooled analysis of 3 RCTs found a significantly higher psoriasis clearance with PUVA than with NB-UVB (OR=2.79; 95% CI, 1.40 to
5.55). In addition, significantly more patients remained cleared at 6 months with PUVA than with NB-UVB (OR=2.73; 95% CI, 1.18 to 6.27).

**PUVA vs Topical Steroids**

In 2012, Amirnia et al published a trial in which 88 patients with moderate plaque psoriasis were randomized to PUVA or topical steroids. Treatment was continued for 4 months or until clearance was achieved. Clearance was defined as disappearance of at least 90% of baseline lesions. All patients in both groups achieved clearance within the 4-month treatment period. Recurrence (defined as a resurgence of at least 50% of the baseline lesions) was reported significantly more often in the topical steroid group (9/44 [20.5%]) than in the PUVA group (3/44 [6.8%]; p=0.007).

**PUVA vs UVA Without Psoralens**

In 2014, El-Mofty et al published an RCT comparing PUVA with BB-UVA in 61 patients with psoriasis affecting at least 30% body surface area. Clinical outcomes were significantly better in the PUVA group than in the BB-UVA groups. For example, complete clearance was obtained by 23 (77%) of 30 patients in the PUVA group, 5 (31%) of 16 patients in the 10 J/cm² UVA group, and 5 (33%) of 15 patients in the 15 J/cm² UVA group (p=0.020).

In 2009, Sivanesan et al published a double-blind RCT evaluating the efficacy of 8-methoxypsoralen PUVA treatment in patients with moderate-to-severe psoriasis affecting at least 10% body surface area. The trial included 40 patients randomized to PUVA (n=30) and or UVA plus placebo psoralens (n=10). Patients were treated 3 times weekly for 12 weeks. The primary outcome was a 75% or greater improvement in PASI 75 score. At 12 weeks, 19 (63%) of 30 patients in the PUVA group and 0 (0%) of 10 patients in the UVA plus placebo group achieved the primary outcome measure (p<0.001). There were no serious adverse effects.

**Section Summary: Psoralen Plus Ultraviolet A**

RCTs and systematic reviews of RCTs have found that PUVA is more effective than NB-UVB, topical steroids, or UVA without psoralens in patients with moderate-to-severe psoriasis. Due to side effects, PUVA is typically restricted to more severe cases.

**Systematic Reviews**

In 2017, Bae et al published a systematic review and meta-analysis on the use of phototherapy for the treatment of vitiligo. The literature search, conducted through January 2016, identified 35 unique studies for inclusion with 1201 patients receiving NB-UVB and 227 patients receiving PUVA. Category of evidence and strength of recommendation were based on study design of the selected studies. The outcome of interest was repigmentation rate. Meta-analytic results are summarized in Table 1. Adverse events were not discussed.

**Table 1. Response Rates for NB-UVB and PUVA in the Treatment of Vitiligo by Treatment Duration**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration, mo</th>
<th>≥50% Repigmentation (95% CI), %</th>
<th>≥75% Repigmentation (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NV-UVB</td>
<td>6</td>
<td>37.4 (27.1 to 47.8)</td>
<td>19.2 (11.4 to 27.0)</td>
</tr>
<tr>
<td>NV-UVB</td>
<td>12</td>
<td>56.8 (40.9 to 72.6)</td>
<td>35.7 (21.5 to 49.9)</td>
</tr>
<tr>
<td>PUVA</td>
<td>6</td>
<td>23.5 (9.5 to 37.4)</td>
<td>8.5 (0 to 18.3)</td>
</tr>
<tr>
<td>PUVA</td>
<td>12</td>
<td>34.3 (23.4 to 45.2)</td>
<td>13.6 (4.2 to 22.9)</td>
</tr>
</tbody>
</table>

Adapted from Bae et al (2017). CI: confidence interval; NV-UVB: narrowband ultraviolet B; PUVA: psoralens with ultraviolet A.
The 2015 Cochrane review of trials on treatments for vitiligo (discussed in the previous section), identified 12 RCTs evaluating PUVA.19 Four trials assessed oral PUVA alone and eight assessed PUVA in combination with other treatments (eg, calcipotriol, azathioprine, polypodium leucotomos, khellin, or surgical treatment). Seven of the 8 studies used 9-methoxypsoralen. A meta-analysis of 3 studies that compared PUVA with NB-UVB found that a larger proportion of patients receiving NB-UVB achieved >75% repigmentation compared with patients receiving PUVA; however, the difference was not statistically significant (RR=1.60; 95% CI, 0.74 to 3.45). Patients treated with NB-UVB experienced significantly less nausea (RR=0.13, 95% CI, 0.02 to 0.69) and erythema (RR=0.73, 95% CI, 0.55 to 0.98) compared with patients receiving PUVA.

A 1998 meta-analysis of nonsurgical treatments for vitiligo was published by Njoo et al.28 Pooled analysis of 2 RCTs evaluating oral unsubstituted psoralen plus sunlight for generalized vitiligo (97 patients) found a statistically significant treatment benefit for active treatment compared with placebo (pooled odds ratio, 19.9; 95% CI, 2.4 to 166.3). Pooled analysis of 3 RCTs, 2 of oral methoxsalen plus sun and 1 of oral trioxsalen plus sunlight (181 patients), also found a significant benefit for active treatment vs placebo for generalized vitiligo (odds ratio, 3.8; 95% CI, 1.3 to 11.3). Adverse events included nausea, headache, dizziness, and cutaneous pruritus. All studies were published before 1985, had relatively small sample sizes (CIs were wide), and used sun exposure rather than artificial UVA.

Randomized Controlled Trial
In 2007, Yones et al published an RCT that used a psoralen formulation available in the United States.29 This trial was included in both the Bae (2017) and Cochrane (2015) systematic reviews. The trial enrolled 56 patients in the United Kingdom who had nonsegmental vitiligo. Outcome assessment was blinded. Patients were randomized to twice-weekly treatments with methoxsalen hard gelatin capsules (8-MOP) PUVA (n=28) or NB-UVB therapy (n=28). NB-UVB treatments were administered in a Waldmann UV500 cabinet containing 24 Phillips 100 NB-UVB fluorescent tubes. In the PUVA group, the starting dose of irradiation was 0.5 J/cm², followed by 0.25 J/cm²-incremental increases if tolerated. Patients were evaluated after every 16 sessions and followed for up to 1 year. All patients were included in the analysis. The median number of treatments received was 49 in the PUVA group and 97 in the NB-UVB group. At the end of treatment, 16 (64%) of 25 patients in the NB-UVB group had 50% or more improvement in body surface area affected compared with 9 (36%) of 25 patients in the PUVA group. Also, 8 (32%) of 25 in the NB-UVB group and 5 (20%) of 25 of patients in the PUVA group had 75% or more improvement in the body surface area affected. Although authors did not provide p values in their outcomes table, they stated that the difference in improvement did not differ significantly between groups for the patient population as a whole. Among patients who received at least 48 treatments, the improvement was significantly greater in the NB-UVB group (p=0.007). A total of 24 (96%) patients in the PUVA group and 17 (68%) in the NB-UVB group developed erythema at some point during treatment; this difference was statistically significant (p=0.02).

Section Summary: Psoralens With Ultraviolet A
There is evidence from randomized studies, published mainly before 1985, that PUVA is more effective than placebo for treating vitiligo. Meta-analyses have shown that patients receiving NB-UVB experienced higher rates of repigmentation than patients receiving PUVA, though the differences were not statistically significant. Patients treated with PUVA experienced higher rates of adverse events such as nausea and erythema. Analyses of treatment duration found that
repigmentation rates following 12 months of treatment were higher compared with rates following 6 months of treatment.

**SUMMARY OF EVIDENCE**

Evidence supports the safety and effectiveness of phototherapy and photochemotherapy for the treatment of certain dermatologic conditions that are unresponsive to conventional medical management including: psoriasis, eczema (atopic dermatitis), eosinophilic folliculitis and other skin eruptions of HIV, lichen planus, morphea, parapsoriasis, photodermatoses, mycosis fungoides, and vitiligo. Professional societies and evidence in the published peer-reviewed scientific literature support excimer laser therapy for the treatment of patients with psoriasis who are unresponsive to topical agents and/or phototherapy.

Based on the available evidence and clinical guidelines, PUVA may be considered medically necessary in patients with vitiligo who have not responded adequately to conservative therapy.

There is a lack of evidence that home-based PUVA for treating psoriasis is as safe or effective as office-based treatment.

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**American Academy of Dermatology**

The American Academy of Dermatology 2010 guideline on the management of psoriasis recommended targeted phototherapy for patients with mild, moderate, or severe psoriasis with less than 10% involvement of the body surface area. Systemic PUVA with ultraviolet A is indicated in adults with generalized psoriasis who are resistant to topical therapy.

**National Psoriasis Foundation**

In 2017, the National Psoriasis Foundation published a consensus guidance based on a task force review of the literature on the treatment for psoriasis involving skinfolds (inverse or intertriginous) psoriasis. The treatment guidance for intertriginous or genital psoriasis stated: “…there is anecdotal evidence demonstrating the strong clinical efficacy of biologic treatment; with limited knowledge on the effects of biologics on intertriginous or genital psoriasis.” The guidance on inverse psoriasis is provided in Table 2.

**Table 2. Recommendations on Treatment of Inverse Psoriasis**

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line therapy</td>
<td>Low potency topical steroids for periods less than 2-4 wk</td>
</tr>
<tr>
<td></td>
<td>Other topical therapies to consider are tacrolimus, pimecrolimus, calcitriol,</td>
</tr>
<tr>
<td></td>
<td>or calcipotriene to avoid steroid side effects with long-term treatment</td>
</tr>
<tr>
<td>Second- and third-line therapies</td>
<td>Antimicrobial therapy, emollients, and tar-based products</td>
</tr>
<tr>
<td></td>
<td>Axillary involvement can be treated with botulinum toxin injection to reduce</td>
</tr>
<tr>
<td></td>
<td>perspiration and inhibit inflammatory substance release</td>
</tr>
<tr>
<td></td>
<td>Excimer laser therapy or systemic agents</td>
</tr>
</tbody>
</table>

In 2017, the National Psoriasis Foundation also published recommendations based on a review of the literature on the treatment for psoriasis in solid organ transplant patients. Because organ transplant patients are excluded from randomized controlled trials, there are limited data. The recommendations were based on case series (see Table 2).
Table 2. Recommendations on Treatment of Psoriasis for Solid Organ Transplant Patients

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line therapy for mild-to-moderate psoriasis</td>
<td>Topical therapy</td>
</tr>
<tr>
<td>First-line therapy for moderate-to-severe psoriasis</td>
<td>• Acitretin with narrowband ultraviolet light or</td>
</tr>
<tr>
<td></td>
<td>• Narrowband ultraviolet light or</td>
</tr>
<tr>
<td></td>
<td>• Acitretin</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td>Increasing the current anti-rejection drug dose</td>
</tr>
<tr>
<td>Severe psoriasis or refractory cases</td>
<td>Systemic or biologic therapies</td>
</tr>
</tbody>
</table>

British Association of Dermatologists et al
In 2008, guidelines on the diagnosis and management of vitiligo were published by a collaboration of several U.K. organizations, including the British Association of Dermatologists, the Royal College of Physicians of London, and the Cochrane Skin Group.30 The guidelines included the following statements (see Table 3).

Table 3. British Guidelines on the Diagnosis and Management of Vitiligo

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GOE</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUVA therapy should be considered for treatment of vitiligo only in adults who cannot be adequately managed with more conservative treatments. PUVA is not recommended in children.</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>If phototherapy is to be used for treating nonsegmental vitiligo, NB-UVB should usually be used in preference to oral PUVA.</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>A trial of PUVA therapy should be considered only for adults with widespread vitiligo, or localized vitiligo associated with a significant impact on patient's quality of life. Ideally, this treatment should be reserved for patients with darker skin types.</td>
<td>D</td>
<td>3</td>
</tr>
<tr>
<td>Before starting PUVA treatment, patients should be made aware that there is no evidence that this treatment alters the natural history of vitiligo. They should also be made aware that not all patients respond, and that some sites on the body, such as the hands and feet, respond poorly in all patients. They should also be informed of the limit to the number of treatments due to possible adverse effects.</td>
<td>D</td>
<td>3</td>
</tr>
</tbody>
</table>

GOE: grade of evidence; LOE: level of evidence; NB-UVB: narrowband ultraviolet B; PUVA: psoralens with ultraviolet A.

European Dermatology Forum
In 2013, the European Dermatology Forum published consensus guidelines on the management of vitiligo.31 The guidelines stated that oral psoralens with ultraviolet A are commonly used in adults with generalized vitiligo as a second-line treatment. The guidelines also stated that targeted phototherapy is indicated for localized vitiligo, particularly small lesions of recent onset and childhood vitiligo, to avoid adverse effects due to total body irradiation and when total body irradiation is contraindicated. The guidelines were based on expert opinion, not a systematic review of the literature.

Vitiligo Working Group
The Vitiligo Working Group is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, part of the National Institutes of Health. In 2017, the group published guidelines on current and emerging treatments for vitiligo.32 The Working Group indicated that psoralens with ultraviolet A has largely been replaced by narrowband ultraviolet B, but that “PUVA may be considered in patients with darker Fitzpatrick skin phototypes or those with treatment-resistant vitiligo (level I evidence).” The Working Group also stated that “Targeted phototherapy (excimer lasers and excimer lamps) can be considered when <10% of body surface area is affected (level II evidence).”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.
ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02294981</td>
<td>Excimer Laser Phototherapy Outcomes in the Treatment of Psoriasis (Photos)</td>
<td>30</td>
<td>Jun 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT03180866a</td>
<td>Evaluation of Efficacy, Duration of Remission and Safety of a Light and Occlusive Patch Therapy for Plaque Psoriasis</td>
<td>30</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT02999776a</td>
<td>Laser-assisted Topical Administration of Etanercept (Enbrel®) in Patients With Mild to Moderate Plaque-type Psoriasis</td>
<td>30</td>
<td>Jun 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

CODING
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS
96900  Actinotherapy (ultraviolet light)
96912  Photochemotherapy; psoralens, and ultraviolet A (PUVA)
96920  Laser treatment for inflammatory skin disease (psoriasis); total area less than 250 sq cm
96921  Total area 250-500 sq cm
96922  Total area over 500 sq cm
E0691  Ultraviolet light therapy system, includes bulbs/lamps, timer and eye protection; treatment area 2 sq ft or less
E0692  Ultraviolet light therapy system panel, includes bulbs/lamps, timer and eye protection, 4 ft panel
E0693  Ultraviolet light therapy system panel, includes bulbs/lamps, timer and eye protection, 6 ft panel
E0694  Ultraviolet multidirectional light therapy system in 6 ft cabinet, includes bulbs/lamps, timer, and eye protection
J8999  Prescription drug, oral, chemotherapeutic, not otherwise specified

• In 2002, CPT established separate codes (96920-96922) that describe ultraviolet light laser treatment for inflammatory disease (psoriasis) according to the surface area of skin treated (total area <250 cm², 250 cm²–500 cm², >500 cm²).
• The laser treatment codes are distinct from codes that describe the dermatologic use of ultraviolet light, also known as actinotherapy (96900), and photochemotherapy (96910-96913).
### ICD-10 Diagnoses

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B20</td>
<td>Human immunodeficiency virus (HIV) disease</td>
</tr>
<tr>
<td>C84.00</td>
<td>Mycosis fungoides, unspecified site</td>
</tr>
<tr>
<td>L30.9</td>
<td>Dermatitis, unspecified</td>
</tr>
<tr>
<td>L20.9</td>
<td>Atopic dermatitis, unspecified</td>
</tr>
<tr>
<td>L40.0</td>
<td>Psoriasis vulgaris</td>
</tr>
<tr>
<td>L40.1</td>
<td>Generalized pustular psoriasis</td>
</tr>
<tr>
<td>L40.4</td>
<td>Guttate psoriasis</td>
</tr>
<tr>
<td>L40.50</td>
<td>Arthropathic psoriasis, unspecified</td>
</tr>
<tr>
<td>L40.51</td>
<td>Distal interphalangeal psoriatic arthropathy</td>
</tr>
<tr>
<td>L40.52</td>
<td>Psoriatic arthritis mutilans</td>
</tr>
<tr>
<td>L40.53</td>
<td>Psoriatic spondylitis</td>
</tr>
<tr>
<td>L40.54</td>
<td>Psoriatic juvenile arthropathy</td>
</tr>
<tr>
<td>L40.59</td>
<td>Other psoriatic arthropathy</td>
</tr>
<tr>
<td>L40.8</td>
<td>Other psoriasis</td>
</tr>
<tr>
<td>L40.9</td>
<td>Psoriasis, unspecified</td>
</tr>
<tr>
<td>L41.8</td>
<td>Other parapsoriasis</td>
</tr>
<tr>
<td>L41.9</td>
<td>Parapsoriasis, unspecified</td>
</tr>
<tr>
<td>L43.0</td>
<td>Hypertrophic lichen planus</td>
</tr>
<tr>
<td>L43.1</td>
<td>Bullous lichen planus</td>
</tr>
<tr>
<td>L43.3</td>
<td>Subacute (active) lichen planus</td>
</tr>
<tr>
<td>L43.8</td>
<td>Other lichen planus</td>
</tr>
<tr>
<td>L43.9</td>
<td>Lichen planus, unspecified</td>
</tr>
<tr>
<td>L56.8</td>
<td>Other specified acute skin changes due to ultraviolet radiation</td>
</tr>
<tr>
<td>L56.9</td>
<td>Acute skin change due to ultraviolet radiation, unspecified</td>
</tr>
<tr>
<td>L73.9</td>
<td>Follicular disorder, unspecified</td>
</tr>
<tr>
<td>L80</td>
<td>Vitiligo</td>
</tr>
<tr>
<td>L94.0</td>
<td>Localized scleroderma (morphea)</td>
</tr>
</tbody>
</table>

### REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>09-28-2014</td>
<td>Policy added to the bcbsks.com web site on 08-29-2014. Effective on 09-28-2014, 30 days after posting.</td>
</tr>
<tr>
<td>01-08-2015</td>
<td>In Coding section: ▪ Added codes E0691, E0692, E0693, and E0694.</td>
</tr>
<tr>
<td>02-04-2015</td>
<td>In Policy section: ▪ Added &quot;using ultraviolet A (UVA) light devices&quot; to read, “Home phototherapy using ultraviolet A (UVA) light devices is considered experimental / investigational.”</td>
</tr>
<tr>
<td>04-28-2015</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>Updated Rationale section.</td>
</tr>
<tr>
<td></td>
<td>Updated References section.</td>
</tr>
<tr>
<td>05-28-2015</td>
<td>Corrected Revisions section: ▪ Removed &quot;Added codes E0691, E0692, E0693, and E0694&quot; from 02-04-2015 revision date and added under 01-08-2015 revision date.</td>
</tr>
<tr>
<td></td>
<td>In coding section: ▪ Added ICD-10 code L20.9.</td>
</tr>
<tr>
<td>03-02-2016</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>Updated Rationale section.</td>
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REFERENCES


