Light Therapy for Vitiligo

Policy Number: 2.01.86     Last Review: 5/2014

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for light therapy for vitiligo when it is determined to be medically necessary because the criteria shown below are met.

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

When Policy Topic is not covered
Targeted phototherapy is considered investigational for the treatment of vitiligo.

Considerations
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 side 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.

Description of Procedure or Service
Light therapy for vitiligo includes both targeted phototherapy and photochemotherapy with psoralen plus ultraviolet A (PUVA). 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.

Background
Vitiligo is an idiopathic skin disorder that causes depigmentation of sections of skin, most commonly on the extremities. Depigmentation occurs because melanocytes are no longer able to function properly. The cause of vitiligo is unknown; it is sometimes considered to be an autoimmune disease. The most common form of the disorder is non-segmental vitiligo (NSV) in which depigmentation is generalized, bilateral, symmetrical and increases in size over time. In contrast, segmental vitiligo (SV), also called asymmetric or focal vitiligo, covers a limited area of skin. The typical natural history of vitiligo involves stepwise progression with long periods in which the disease is static and relatively inactive, and relatively shorter periods in which areas of pigment loss increase.

There are numerous medical and surgical treatments aimed at decreasing disease progression and/or attaining repigmentation. Topical corticosteroids, alone or in combination with topical vitamin D3 analogs, is a common first-line treatment for vitiligo. Alternative first-line therapies include topical calcineurin inhibitors, systemic steroids and topical antioxidants.

Treatment options for vitiligo recalcitrant to first-line therapy include, among others, psoralens with ultraviolet A and targeted light therapy. PUVA uses a psoralen derivative in conjunction with long wavelength ultraviolet A light (sunlight or artificial) for photochemotherapy of skin conditions. Psoralens
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. With topical PUVA, UVA exposure is generally administered within 30 minutes of psoralen application.

Potential advantages of targeted phototherapy include the ability to use higher treatment doses and to limit exposure to surrounding tissue. Broadband (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. 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 to a light box, which could result in fewer treatments.

**Regulatory Status**

In 2001, an XeCl excimer laser (XTRAC™ by PhotoMedex) received 510(k) clearance from the U.S. Food and Drug Administration (FDA) for the treatment of skin conditions such as vitiligo. The 510(k) clearance has subsequently been obtained for a number of targeted UVB lamps and lasers, including newer versions of the XTRAC system including the XTRAC Ultra™, the VTRAC™ lamp (PhotoMedex), the BClear™ lamp (Lumenis), the 308 excimer lamp phototherapy system (Quantel Medical) and the Excilite™ and Excilite μ™ XeCl lamps. The intended use of all of these devices includes vitiligo among other dermatological indications. Some of the light-emitting devices are handheld.

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

**Rationale**

This policy was created in 2012 with a search of the MEDLINE database through March 6, 2013. The policy was updated with a literature review through February 20, 2014. Following is a summary of the key literature published to date.

**Targeted Phototherapy**

In 2010, Whitton and colleagues published a Cochrane review of randomized controlled trials (RCTs) on treatments for vitiligo. (1) The investigators searched the literature through November 2009 and identified 5 trials on excimer laser therapy. None of these trials included a control group of individuals who did not receive excimer therapy, so the effect of laser therapy cannot be isolated. Four trials compared the combination of excimer laser therapy and a topical therapy to excimer lasers alone or excimer lasers plus a placebo topical treatment. The fifth trial compared different frequencies of excimer laser treatment (once, twice, or three times weekly). The Cochrane investigators did not pool findings of the studies on laser therapy for vitiligo.

Studies continue to be published that compare different types of targeted phototherapy; these studies do not allow us to draw conclusions about the efficacy of targeted phototherapy. For example, in 2013 Shi and colleagues treated patients with either an excimer laser or an excimer lamp and did not find differences in repigmentation rates.(2) In order to adequately evaluate the impact of laser treatment or other targeted phototherapy treatment on vitiligo, RCTs are needed that include a comparison group of patients who receive a treatment other than targeted phototherapy (i.e. an alternative treatment, no treatment, or sham treatment). Subsequent to the publication of the Whitton et al. Cochrane review, 2 RCTs with this design have been published and are described below.
The 2 trials were conducted by the same research group in Italy. In 2012, Nistico and colleagues published a non-blinded RCT that included 53 patients with localized and generalized vitiligo. (3) Patients were randomly assigned to one of 3 treatments for 12 weeks: 1) Excimer laser plus vitamin E (n=20); 2) excimer laser plus topical 0.1% tacrolimus ointment and vitamin E (n=20); 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; 51-75% repigmentation was considered a 'good' response and >75% repigmentation was considered an 'excellent' response. The proportion of patients with a good or excellent response was 11/20 (55%) in the laser plus vitamin E group, 14/20 (70%) in the laser E plus tacrolimus plus vitamin E group, and 0 in the control group. The rate of good or excellent response did not differ significantly between the groups that received excimer laser therapy with and without topical treatment (p=0.36). The response rate was significantly better in both groups receiving laser treatment compared to the control group (p<0.001).

The Italian research group also published a similar 12-week study in 2009 in which topical 4% khellin ointment was used instead of tacrolimus ointment. (4) This study included 48 patients (16 per group), of which 45 (94%) completed treatment. The proportion of patients with a good or excellent response (see definitions above) was 14/16 (88%) in the excimer laser plus vitamin E group, 14/16 (88%) in the excimer laser plus khellin plus vitamin E group, and 1/16 (6%) in the vitamin E only (control) group. The clinical response rates in the 2 groups receiving laser treatment were significantly higher than in the control group.

Section summary: Most published RCTs evaluating targeted phototherapy for vitiligo treated patients in all groups with targeted phototherapy and thus the effect of phototherapy treatment cannot be isolated. Only 2 small RCTs compared excimer laser therapy to a different intervention; these found that excimer laser treatment produced better results than the comparison intervention (vitamin E or UVA).

Psoralens with Ultraviolet A (PUVA)

The 2010 Cochrane review of trials on treatments for vitiligo, discussed above in the section on targeted phototherapy, identified 10 RCTs evaluating oral PUVA. (1) Two trials assessed oral PUVA alone, and 8 assessed PUVA in combination with other treatments e.g., calcipotriol, azathioprine, polypodium leucotomos, khellin, or surgical treatment. Seven of the 8 studies used 9 methoxypsoralen. Six trials were identified on oral PUVA plus sunlight; 2 of these used placebo as the comparison. Due to differences among studies, findings of trials on oral PUVA and on oral PUVA plus sunlight were not pooled.

An earlier meta-analysis of treatments for vitiligo was published in 1998 by Njoo and colleagues. (5) A pooled analysis of 2 RCTs on oral unsubstituted psoralen plus sun for generalized vitiligo (total n=97) found a statistically significant treatment benefit of active treatment compared to placebo (pooled odds ratio [OR]: 19.9, 95% confidence interval [CI]: 2.4 to 166.3). A pooled analysis of 3 RCTs, 2 on oral methoxsalen plus sun and 1 on oral trioxsalen plus sun (total n=181) also found a significant benefit of active treatment versus placebo on generalized vitiligo (OR: 3.8, 95% CI: 1.3 to 11.3). All studies were published prior to 1985, had relatively small sample sizes (confidence intervals were wide), and used sun exposure rather than artificial UVA.

A 2007 RCT, using a psoralen formulation available in the U.S. was published by Yones and colleagues. (6) The study used data on 56 patients in the U.K. who had non-segmental vitiligo. Outcome assessment was blinded. Patients were randomly assigned to receive twice-weekly treatments with methoxsalen hard gelatin capsules (8-MOP) psoralen plus UVA (n=28) or narrow band (NB)-ultraviolet B (UVB) therapy (n=28). The 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 of 25 patients (64%) in the NB-UVB group had greater than 50% improvement in body surface area affected compared with 9 (36%) of 25 patients (36%) in the PUVA group. In addition, 5 of 25 (20%) of patients in the PUVA group and 8 of 25 (32%) in the NB-UVB group had at least 75% improvement in the body surface area affected. The authors did not provide p-values in their outcome table. They stated though, that the difference in improvement did not differ significantly between groups for the patient population as a whole but that, among patients who received at least 48 treatments, 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.

A 2013 RCT used a psoralen formulation available in India which has the active ingredient methoxsalen; this ingredient is available in the U.S. (7) The study included 45 patients with vitiligo covering more than 5% of their body surface area were included; 40 patients completed the study. Patients were randomized to receive 3 weekly treatments of either NB-UVB or PUVA. Treatments continued for 60 sessions or 6 months, whichever came first. At the end of follow-up, the mean percentage reduction in the Vitiligo Area Severity Index (VASI) score was 21.7 in the NB-UVB group and 29.2 in the PUVA group. The difference between groups in the VASI score was statistically significant, favoring the PUVA group, p=004. Four patients in the NB-UVB group and 10 in the PUVA group developed side-effects; none of these were serious enough to lead to discontinuation of phototherapy.

Section summary: There is some evidence from randomized studies, mainly those published prior to 1985, that PUVA is more effective than placebo for treating vitiligo. The limited number of studies comparing PUVA to NB-UVB have had mixed findings.

Summary

Light therapy for vitiligo includes both targeted phototherapy and psoralen plus ultraviolet A (PUVA). There is some evidence from randomized studies, mainly those published prior to 1985, that PUVA is more effective than placebo for treating vitiligo. PUVA for vitiligo is recommended in British guidelines for adults who do not respond to more conservative treatments. 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.

For targeted phototherapy, there is a lack of clinical trial evidence that compares this technique to more conservative treatments or no treatment/placebo, with only one small RCT identified. This evidence is insufficient to determine the efficacy of targeted phototherapy, and it is therefore considered investigational.

Practice Guidelines and Position Statements

In 2008, a guideline on the diagnosis and management of vitiligo was published by several organizations in the U.K. including the British Association of Dermatologists, the Royal College of Physicians of London, and the Cochrane Skin Group. (8) The guideline included the following statements:

- 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. (Grade of recommendation D, Level of evidence 4)

- If phototherapy is to be used for treating nonsegmental vitiligo, NB-UVB should usually be used in preference to oral PUVA. (Grade of recommendation A, Level of evidence 1+)
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 QoL (quality of life). Ideally, this treatment should be reserved for patients with darker skin types. (Grade of recommendation D, Level of evidence 3)

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 body sites, 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 side-effects. (Grade of recommendation D, Level of evidence 3)

In 2013, consensus guidelines on management of vitiligo were published by the European Dermatology Forum. (9) The guidelines stated that oral PUVA is commonly used in adults with generalized vitiligo as second-line treatment. The guideline also stated that targeted phototherapy is indicated for localized vitiligo, particularly small lesions of recent onset and childhood vitiligo, to avoid side effects due to total body irradiation and when total body irradiation is contraindicated. The guidelines were based on expert opinion and not on a systematic review of the literature.

**Medicare National Coverage**
No national coverage determination.

**References**


**Billing Coding/Physician Documentation Information**

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<th>Description</th>
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<td>Photochemotherapy; psoralens and ultraviolet A (PUVA)</td>
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<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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There is no specific CPT code for laser therapy for vitiligo. It should currently be reported using an unlisted CPT (96999) but the CPT codes for laser therapy for psoriasis (96920-96922) might be used.

**Additional Policy Key Words**
N/A

**Policy Implementation/Update Information**

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