Light Therapy for Vitiligo  
Corporate Medical Policy

Description/Summary

Vitiligo is an idiopathic skin disorder that causes depigmentation of sections of skin, most commonly on the extremities. Topical corticosteroids, alone or in combination with topical vitamin D₃ analogs, are 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, ultraviolet B light box therapy and psoralen plus ultraviolet A (PUVA). Targeted phototherapy is also being evaluated.

The evidence for targeted phototherapy in patients who have vitiligo includes randomized controlled trials (RCTs). Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. The studies tend to have small sample sizes, and few were designed to isolate the effect of laser therapy. There is a lack of clinical trial evidence that compares this technique with more conservative treatments or no treatment/placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PUVA in patients who have vitiligo includes RCTs. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. There is some evidence from randomized studies, mainly those published before 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 in patients with vitiligo who have not responded adequately to conservative therapy. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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</table>
| Individuals:  
• With vitiligo | Interventions of interest are:  
• Targeted phototherapy | Comparators of interest are:  
• Topical medications  
• Ultraviolet B light box therapy | Relevant outcomes include:  
• Change in disease status  
• Quality of life |
### Policy

**Coding Information**

There is no specific CPT code for laser therapy for vitiligo. It should currently be reported using an unlisted CPT code (96999), but the CPT codes for laser therapy for psoriasis (96920-96922) might be used.

**Click the links below for attachments, coding tables & instructions.**

*Attachment I - Code Table & Instructions*

**When a service may be considered medically necessary**

Psoralen plus ultraviolet A 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.

**When a service is considered investigational**

Targeted phototherapy is considered investigational for the treatment of vitiligo.

### Policy Guidelines

During a course of psoralen plus ultraviolet A (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.

**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 nonsegmental vitiligo in which depigmentation is generalized, bilateral, symmetrical, and increases in size over time. In contrast, segmental vitiligo, 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, light box therapy with ultraviolet B (UVB) and psoralen plus ultraviolet A (PUVA). Targeted phototherapy is also being evaluated. Potential advantages of targeted phototherapy include the ability to use higher treatment doses and to limit exposure to surrounding tissue. Original UVB devices consisted of a Phillips TL-01 fluorescent bulb with a maximum wavelength (lambda max) of 311 nm. Subsequently, xenon chloride (XeCl) lasers and lamps were developed as targeted 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.

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 ultraviolet A (UVA) radiation. Topical PUVA therapy refers to direct application of psoralen to the skin with subsequent exposure to UVA light. With topical PUVA, UVA exposure is generally administered within 30 minutes of psoralen application.

**Rationale/Scientific Background**

This evidence review was created in 2012 with a search of the MEDLINE database through March 6, 2013. It has been updated with a literature review through November 11, 2015. Following is a summary of the key literature published to date.

**Targeted Phototherapy**

In 2015, Whitton et al published an updated Cochrane review of randomized controlled trials (RCTs) on treatments for vitiligo. The investigators searched the literature through October 2013 and identified 12 trials on laser light devices. Six trials evaluated the combination of laser light devices and a topical therapy and 2 evaluated the combination of laser devices and surgical therapy. Three trials compared regimens of laser monotherapy. The remaining trial compared a helium neon laser and a 290 to 320 nm broadband ultraviolet B (UVB) fluorescent lamp. Due to heterogeneity across studies, the Cochrane authors 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.

In 2015, Sun et al published a systematic review of RCTs that focused on treatment of vitiligo with the 308 nm excimer laser. Review authors identified 7 RCTs with a total of 390 patients. None of the studies were conducted in the United States; 5 were from Asia. Three of the trials compared the excimer laser with an excimer lamp, and 4 studies compared the excimer laser with narrowband ultraviolet B (NB-UVB). The 4 studies with the comparison with NB-UVB are of greatest interest to this review.
However, 2 of these were not published in English, and 1 had a sample size of only 14 patients. The fourth study, published by Yang et al in 2010, did not report efficacy outcomes such as clinical response rate or repigmentation rate. Instead, the investigators reported on the proportion of patients with various types of repigmentation: perifollicular, marginal, diffuse, or combined. Repigmentation rates did not differ significantly between groups treated with the excimer laser versus NB-UVB. The authors of the systematic review conducted a meta-analysis of the 2 studies that were not published in English; thus, results cannot be verified. They reported that the likelihood of a minimum 50% repigmentation rate was significantly higher with the excimer laser compared with NB-UVB (risk ratio, 1.39, 95% confidence interval [CI], 1.05 to 1.85). Review authors also stated that, in qualitative analysis, neither of these studies showed significant benefit of the excimer laser for achieving a minimum 75% repigmentation rate.

One of the few trials comparing laser therapy to an alternative treatment was published in 2012 by Nistico et al. This was a nonblinded RCT that included 53 patients with localized and generalized vitiligo. Patients were randomly assigned to 1 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); 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 greater than 75% 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 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 with the control group (p<0.001).

Section Summary: Targeted Phototherapy
There are a number of RCTs evaluating targeted phototherapy for treating vitiligo. However, studies tended to have small sample sizes, and few were designed to isolate the effect of laser therapy. Moreover, studies were heterogeneous eg, different interventions or combinations of interventions and different comparison interventions. These characteristics make it difficult to pool study findings or to draw conclusions about the efficacy of targeted phototherapy for vitiligo.

Psoralens With Ultraviolet A
The 2015 Cochrane review of trials on treatments for vitiligo, previously discussed in the section on targeted phototherapy, identified 12 RCTs evaluating oral psoralens with ultraviolet A (PUVA). Four trials assessed oral PUVA alone, and 8 assessed PUVA in combination with other treatments, eg, calcipotriol, azathioprine, polypodium leucotomos, khellin, or surgical treatment. Seven of the 8 studies used 9-methoxypsoralen. Due to differences across studies, results from trials of oral PUVA and of oral PUVA plus sunlight were not pooled.

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

In 2007, Yones et al published an RCT that used a psoralen formulation available in the United States. The trial enrolled 56 patients in the United Kingdom who had nonsegmental 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 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 greater than 50% improvement in body surface area affected compared with 9 (36%) of 25 patients in the PUVA group. In addition, 5 (20%) of 25 of patients in the PUVA group and 8 (32%) of 25 in the NB-UVB group had at least 75% improvement in the body surface area affected. Although the authors did not provide p values in their outcome 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, 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 some evidence from randomized studies, mainly those published before 1985, that PUVA is more effective than placebo for treating vitiligo. The limited number of studies comparing PUVA with NB-UVB have had mixed findings.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for targeted phototherapy in patients who have vitiligo includes randomized controlled trials (RCTs). Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. The studies tend to have small sample sizes, and few were designed to isolate the effect of laser therapy. There is a lack of clinical trial evidence that compares this technique with more conservative treatments or no treatment/placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for psoralen plus ultraviolet A (PUVA) in patients who have vitiligo includes RCTs. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. There is some evidence from randomized studies, mainly those published before 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 in patients with vitiligo who have not responded adequately to conservative therapy. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

British Association of Dermatologists et al
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. 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 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 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. (Grade of recommendation D, Level of evidence 3)

European Dermatology Forum
In 2013, the European Dermatology Forum published consensus guidelines on the management of vitiligo. 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 adverse 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.

Regulatory status
In 2001, XTRAC™ (PhotoMedex), an XeCl excimer laser, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for the treatment of skin conditions such as vitiligo. The 510(k) clearance has subsequently been obtained for a number of targeted ultraviolet B 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 dermatologic indications. Some light-emitting devices are handheld. FDA product code: GEX. 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).

Reference Resources


Document Precedence

Blue Cross and Blue Shield of Vermont (BCBSVT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer’s benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, BCBSVT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member’s contract/employer benefit plan language takes precedence.

Audit Information

BCBSVT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, BCBSVT reserves the right to recoup all non-compliant payments.
Administrative and Contractual Guidance

Benefit Determination Guidance

Prior approval is required for services as outlined in this policy. Benefits are subject to all terms, limitations and conditions of the subscriber contract.

An approved referral authorization for members of the New England Health Plan (NEHP) is required. A prior approval for Access Blue New England (ABNE) members is required. NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member’s health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member’s benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member’s benefit.

Coverage varies according to the member’s group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services only (ASO) only group, benefits may vary or not apply. To verify benefit information, please refer to the member’s employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

08/2016 | New Policy. Adopted BCBSA MPRMP# 2.01.86.

Health Care Procedure Coding System (HCPCS) codes related to chemotherapy drugs, drugs administered other than oral method, and enteral/parenteral formulas may be subject to National Drug Code (NDC) processing and pricing. The use of NDC on medical claims helps facilitate more accurate payment and better management of drug costs based on what was dispensed and may be required for payment. For more information on BCBSVT requirements for billing of NDC please refer to the provider portal http://www.bcbsvt.com/provider-home latest news and communications.

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).
Approved by BCBSVT Medical Directors

Joshua Plavin, MD
Senior Medical Director
Chair, Medical Policy Committee

Robert Wheeler MD
Chief Medical Officer

Attachment I
Code Table & Instructions

<table>
<thead>
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<th>Code Type</th>
<th>Number</th>
<th>Description</th>
<th>Policy Instructions</th>
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Type of Service
Medical, DME

Place of Service
Inpatient
Outpatient
Physician’s Office