2.01.86	Targeted Phototherapy and Psoralen with Ultraviolet A for Vitiligo		
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Section:	2.0 Medicine	**Page:**	Page 1 of 16

Policy Statement

I. Psoralen plus ultraviolet A (PUVA) may be considered **medically necessary** for the treatment of vitiligo that is not responsive to other forms of conservative therapy (e.g., topical corticosteroids, coal/tar preparations, ultraviolet light).

II. Targeted phototherapy (i.e., laser light devices) is considered **investigational** for the treatment of vitiligo.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

During psoralen plus ultraviolet A (PUVA) therapy, the individual 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 the disease. Therefore, PUVA is generally not recommended for home therapy.

Coding
See the Codes table for details.

Description

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 D_3 analogues, are common first-line treatments 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.

Related Policies

- Dermatologic Applications of Photodynamic Therapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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Regulatory Status

In 2001, XTRAC™ (PhotoMedex), a xenon chloride (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 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), MultiClear Multiwavelength Targeted Phototherapy System, Psoria-Light™, 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 product, methoxsalen soft gelatin capsules (previously available under the brand name Oxsoralen Ultra), has been approved by the FDA.

Rationale

Background

Vitiligo

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 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.

Treatment

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 D_3analogues, are common first-line treatments 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 narrowband ultraviolet B and psoralen plus ultraviolet A (PUVA).

Targeted phototherapy with handheld lamps or lasers 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 ultraviolet B devices consisted of a Phillips TL-01 fluorescent bulb with a maximum wavelength (lambda max) of 311 nm. Subsequently, xenon chloride lasers and lamps were developed as targeted ultraviolet B treatment devices; they generate monochromatic or very narrowband 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 lightbox, which could result in fewer treatments.

PUVA uses a psoralen derivative in conjunction with long-wavelength ultraviolet A (UVA) 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 the 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.

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Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), 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 a 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 1 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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Targeted Phototherapy

Clinical Context and Therapy Purpose

The purpose of targeted phototherapy in individuals who have vitiligo is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with vitiligo.

Interventions

The therapy being considered is targeted phototherapy. Targeted phototherapy with handheld lamps or lasers is also being evaluated. Potential advantages of targeted phototherapy include the ability to use higher treatment doses and to limit exposure to surrounding tissue.

Comparators

The following therapies are currently being used to treat vitiligo: topical medications and narrowband ultraviolet B (NB-UVB) light box therapy. The most appropriate comparison for targeted phototherapy is NB-UVB, which is considered a standard treatment for active and/or widespread vitiligo based on efficacy and safety.

Outcomes

The general outcomes of interest are a change in disease status, QOL, and treatment-related morbidity. Progression of vitiligo can lead to extreme sensitivity to sunlight, skin cancer, iritis, and

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hearing loss. Quality of life is another relevant outcome (e.g., emotional distress as skin discoloration progresses).

The application of targeted phototherapy can require multiple weekly treatments over several weeks. In time, treatment results can fade or disappear.

Study Selection Criteria

Methodologically credible studies were selected for each indication within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, prefer larger sample size studies and longer duration studies.

Review of Evidence

Systematic Reviews

A systematic review by Lopes et al (2016) 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).[1,] No differences between the excimer lamp and NB-UVB were identified for the outcome of 50% or more repigmentation (relative risk [RR], 1.14; 95% confidence interval [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.

Whitton et al (2015) updated a Cochrane review of RCTs on treatments for vitiligo.[2,] 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.

Sun et al (2015) published a systematic review of RCTs that focused on the treatment of vitiligo with the 308-nm excimer laser.[3,] In a literature search conducted through April 2014, reviewers identified 7 RCTs (N=390) for inclusion. None of the studies were conducted in the U.S.; 5 were from Asia and 3 of those 5 are available only in Chinese. Three trials compared the excimer laser with an excimer lamp, and 4 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),[4,] did not report repigmentation rates, providing instead, the proportion of patients with various types of repigmentation (perifollicular, marginal, diffuse, or combined). Repigmentation rates at 75% and 100% levels did not differ significantly between groups treated with the excimer laser versus 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 (RR, 1.39; 95% CI, 1.05 to 1.85). Two of the 4 studies discussed adverse events, with itching and burning reported

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by both treatment and control groups and erythema and blistering reported only by the patient in the laser group.

Randomized Controlled Trials

Four RCTs comparing targeted phototherapy to alternate treatment options are summarized in Tables 1 through 4 below.[5,6,7,8,9,] Poolsuwan et al (2020) compared the treatment of 36 paired vitiligo lesions with either targeted phototherapy (308-nm excimer light) or NB-UVB in a single-blind study of 36 patients.[5,] Treatment of lesions with targeted phototherapy led to significant reductions in the Vitiligo Area Scoring Index (VASI) score and significantly improved repigmentation grade compared to treatment with NB-UVB; however, the differences between groups in these outcomes were marginal and may not be clinically significant. Wu et al (2019) compared the treatment of 83 paired vitiligo lesions with either 308-nm excimer laser or topical tacrolimus, with both arms receiving concomitant intramuscular betamethasone injections, in a single-blind study of 138 patients.[6,] Excimer laser therapy was associated with a significantly higher proportion of patients with at least 50% repigmentation at 3 months compared to topical tacrolimus. However, interpretation of study results is limited by inadequate description of methods and use of per-protocol analysis, with an evident high rate of patient dropout. An open-label study by Nistico et al (2012) compared 3 different treatment arms in 53 patients with localized or generalized vitiligo: (1) excimer laser plus vitamin E (n=20); (2) excimer laser plus topical tacrolimus ointment 0.1% and oral vitamin E (n=20); and (3) oral vitamin E only (n=13).[7,] The investigators found that patients treated with targeted phototherapy were significantly more likely to achieve a "good" or "excellent" repigmentation response (55% in group 1 and 70% in group 2) than those who received oral vitamin E alone (0%). The rate of good or excellent responses did not differ significantly between groups that received targeted phototherapy with and without topical treatment (p=.36). This study was limited by its open-label design and the fact that the comparator group, oral vitamin E, does not reflect the optimal standard of care treatment for vitiligo. In a randomized trial by Oh et al (2011), matched lesions in 16 patients were randomized to 308-nm excimer laser alone, topical tacalcitol alone, or the combination of excimer laser and topical tacalcitol.[8,] Excimer laser therapy alone and in combination with topical tacalcitol were associated with a significantly higher repigmentation response quartile at 16 weeks compared to topical tacalcitol alone. However, interpretation of study results is limited by inadequate description of methods, and it is unclear whether tacalcitol is comparable to other standard-of-care topical vitamin D_3 analogues.

Table 1. Summary of Key RCT Characteristics

Study (Year)	Countries	Sites	Dates	Participants	Interventions
Poolsuwan et al (2020)[5,]	Thailand	Single-center	NR	Patients 18 to 65 years of age with vitiligo with stable, symmetrically paired lesions who have not had topical therapy for ≥2 weeks or phototherapy or systemic immunosuppressive drugs for ≥8 weeks	• Localized 308-nm excimer light[a] • 311-nm NB-UVB[a]
Wu et al (2019)[6,]	China	Single-center	2012 to 2014	Patients 25 to 48 years of age with vitiligo involving the face or neck	• Intramuscular betamethasone (every 3 to 4 weeks for 3 to 6 months) plus 308-nm excimer laser • Intramuscular betamethasone (every 3 to 4 weeks for 3 to 6 months) plus topical tacrolimus 0.1% twice daily

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Study (Year)	Countries	Sites	Dates	Participants	Interventions
Nistico et al (2012)[7,]	Italy	Single-center	NR	Patients 13 to 56 years of age with localized or generalized vitiligo	• Targeted 308-nm excimer laser plus oral vitamin E 400 IU[b] • Targeted 308-nm excimer laser plus topical tacrolimus 0.1% ointment plus oral vitamin E 400 IU[b] • Oral vitamin E 400 IU alone[b]
Oh et al (2011)[8,]	Korea	Single-center	NR	Patients 15 to 60 years of age with non-segmental vitiligo	• 308-nm excimer laser alone (twice weekly for 16 weeks) • High-concentration topical tacalcitol alone (once daily) • 308-nm excimer laser plus high-concentration topical tacalcitol

IU: international units; NB-UVB: narrowband ultraviolet B; NR: not reported; RCT: randomized controlled trial.
[a] Both interventions given for 3 non-consecutive days per week x 48 treatment sessions.
[b] Frequency of interventions were as follows: Targeted 308-nm excimer laser, twice weekly; oral vitamin E, twice daily; tacrolimus ointment, once daily. All interventions given for 12 weeks.

Table 2. Summary of Key RCT Results

Study	Reduction in VASI score, mean	Repigmentation
Poolsuwan et al (2020)[5,]		
N	36	36
308-nm excimer light	0.55 ± 0.39%	2.36 ± 1.15[a]
NB-UVB	0.43 ± 0.39%	1.94 ± 1.19[a]
p value	<.001	<.001
Wu et al (2019)[6,]		
N	NA	83[e]
Betamethasone + 308-nm excimer laser	NA	• Patients with stable vitiligo at baseline: ≥50% repigmentation at 3 months in 40.8% • Patients with active vitiligo at baseline: ≥50% repigmentation at 3 months in 55.8%
Betamethasone + topical tacrolimus	NA	• Patients with stable vitiligo at baseline: ≥50% repigmentation at 3 months in 10.2% • Patients with active vitiligo at baseline: ≥50% repigmentation at 3 months in 32.3%
p value	NA	• Patients with stable vitiligo at baseline: <.001

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Study	Reduction in VASI score, mean	Repigmentation
		• Patients with active vitiligo at baseline:.024
Nistico et al (2012)[7,]		
N	NA	53
Phototherapy + vitamin E	NA	• Good: 6/20 (30%)[b,c] • Excellent: 5/20 (25%)[b,c]
Phototherapy + tacrolimus + vitamin E	NA	• Good: 8/20 (40%)[b,c] • Excellent: 6/20 (30%)[b,c]
Vitamin E alone	NA	• Good: 0/13 (0%)[b,c] • Excellent: 0/13 (0%)[b,c]
p value	NA	<.001[d]
Oh et al (2011)[8,]		
N	NA	16
308-nm excimer laser alone	NA	NR
Topical tacalcitol alone	NA	NR
308-nm excimer laser + topical tacalcitol	NA	NR
p value	NA	Repigmentation quartile at 16 weeks: • Favoring excimer laser alone vs. tacalcitol alone:.008 • Favoring combination vs. excimer laser alone: NS • Favoring combination vs. tacalcitol alone:.006

NA: not applicable; NR: not reported; NS, not significant; NB-UVB: narrowband ultraviolet B; RCT: randomized controlled trial; VASI: Vitiligo Area Scoring Index
[a] Repigmentation was reported as a graded score from 1 to 4 with 1 being "poor" and 4 being "excellent."
[b] Good repigmentation defined as 51% to 75% repigmentation; excellent repigmentation defined as 76% to 100% repigmentation.
[c] Repigmentation reported as number of patients out of the total number of patients in subgroup (%) for each category.
[d] p value reported for good to excellent repigmentation response in each intervention group versus control (oral vitamin E alone).
[e] Patients evaluated at 3 months (per-protocol analysis).

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Poolsuwan et al (2020)[5,]				5,6. Differences in VASI score and repigmentation do not appear to be clinically significant; clinical significance not defined by investigators	
Wu et al (2019)[6,]	2. Unclear differentiation between stable and active vitiligo	1. Schedule of excimer laser not defined		3. Scant reporting of safety outcomes 5. Clinically significant difference not prespecified	

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Nistico et al (2012)[7,]			2. Phototherapy groups compared to oral vitamin E, which is not optimal standard of care for vitiligo	5. Clinically significant difference in response was not prespecified	
Oh et al (2011)[8,]			1. High-concentration tacalcitol not defined 2. Unclear whether tacalcitol is comparable to other standard topical vitamin D_3 analogues	3. Scant reporting of safety outcomes 4. Definition and relevance of quartile grading for repigmentation unclear; absolute values not reported 5. Clinically significant difference not prespecified	

VASI: Vitiligo Area Scoring Index
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-up[d]	Power[e]	Statistical[f]
Poolsuwam et al (2020)[5,]		1. Single-blinded to investigators only			1. Power calculations not reported	
Wu et al (2019)[6,]	2. Allocation not concealed	1. Single-blinded to evaluators only	1. High loss to follow-up based on number enrolled versus number evaluated at 1, 3, and 6 months 6. Both per protocol and intent to treat analyses reported, but intent to treat analysis used last observation carry-forward imputation		1. Power calculations not reported	2. Inadequate description of inferential statistics
Nistico et al (2012)[7,]	2. Described as an "open" study- does not appear that allocation concealment occurred	1,2. Described as an "open" study- does not appear that blinding occurred			1. Power calculations not reported	

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Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-up[d]	Power[e]	Statistical[f]
Oh et al (2011)[8,]	2. Allocation not concealed	1. Single-blinded to evaluators only	1. Not registered		1. Power calculations not reported	2. Inadequate description of inferential statistics

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Retrospective Studies

Fa et al (2017) retrospectively analyzed 979 Chinese patients (3478 lesions) treated with the 308-nm targeted laser for vitiligo.[10,] Patients had Fitzpatrick skin phototype III or IV and were followed for 2 years after the 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 retrospective analysis, Dong et al (2017) evaluated the use of a medium-band (304 to 312 nm) targeted laser for treating pediatric patients (age ≤16 years) with vitiligo.[11,] Twenty-seven patients (95 lesions) were evaluated by 2 dermatologists following a mean of 20 treatments (range, 10 to 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

For individuals who have vitiligo who receive targeted phototherapy, the evidence includes systematic reviews of RCTs, 4 individual RCTs, and 2 retrospective studies. Individual studies tend to have small sample sizes, and those designed to isolate the effect of laser therapy suffer from inadequate descriptions of methods and other limitations. Two meta-analyses were attempted; however, results from a meta-analysis could not be verified because the selected studies were not available in English, and 1 estimate was imprecise due to the small number of studies and participants. Randomized controlled trials have shown targeted phototherapy to be associated with statistically significant improvements in VASI scores and/or repigmentation compared to alternate treatment options. However, 1 of the RCTs only showed marginal differences between groups in these outcomes, limiting clinical significance; the second compared phototherapy to oral vitamin E, which is not an optimal comparator. Overall, there is a lack of well-designed clinical trial evidence that compares targeted phototherapy with more conservative treatments or no treatment/placebo.

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Psoralens With Ultraviolet A

Clinical Context and Therapy Purpose

The purpose of psoralen plus ultraviolet A (PUVA) in individuals who have vitiligo is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with vitiligo who have not responded to conservative therapy.

Interventions

The therapy being considered is PUVA.

Comparators

The following therapies are currently being used to treat vitiligo: topical medications and NB-UVB light box therapy. The most appropriate comparison for PUVA is NB-UVB, which is considered a standard of care treatment for active and/or widespread vitiligo based on efficacy and safety.

Outcomes

The general outcomes of interest are a change in disease status, QOL, and treatment-related morbidity. Progression of vitiligo can lead to extreme sensitivity to sunlight, skin cancer, iritis, and hearing loss. Quality of life is also a relevant outcome (e.g., emotional distress as skin discoloration progresses).

The application of PUVA can require multiple weekly treatments for up to 6 to 12 months.

Study Selection Criteria

Methodologically credible studies were selected for each indication within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Within each category of study design, prefer larger sample size studies and longer duration studies.

Review of Evidence

Systematic Reviews

Bae et al (2017) published a systematic review and meta-analysis on the use of phototherapy for the treatment of vitiligo.[12,] The literature search, conducted through January 2016, identified 35 unique studies for inclusion with 1201 patients receiving NB-UVB and 227 patients receiving PUVA. The category of evidence and strength of recommendation were based on the study design of the selected studies. The outcome of interest was the repigmentation rate. Meta-analytic results are summarized in Table 5. Adverse events were not discussed.

Table 5. Response Rates to NB-UVB Therapy and PUVA in the Treatment of Vitiligo by Treatment Duration

Treatment	Duration, mo	≥50% Repigmentation (95% CI), %	≥75% Repigmentation (95% CI), %
NB-UVB	6	37.4 (27.1 to 47.8)	19.2 (11.4 to 27.0)
NB-UVB	12	56.8 (40.9 to 72.6)	35.7 (21.5 to 49.9)
PUVA	6	23.5 (9.5 to 37.4)	8.5 (0 to 18.3)

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Treatment	Duration, mo	≥50% Repigmentation (95% CI), %	≥75% Repigmentation (95% CI), %
PUVA	12	34.3 (23.4 to 45.2)	13.6 (4.2 to 22.9)

Adapted from Bae et al (2017).[12,]
CI: confidence interval; NB-UVB: narrowband ultraviolet B; PUVA: psoralen plus ultraviolet A.

The Cochrane review by Whitton et al (2015), which assessed trials on treatments for vitiligo (discussed in the previous section), identified 12 RCTs evaluating PUVA.[2,] Four 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. A meta-analysis of 3 studies that compared PUVA with NB-UVB found that a larger proportion of patients receiving NB-UVB achieved greater than 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 meta-analysis of nonsurgical treatments for vitiligo was published by Njoo et al (1998).[13,] Pooled analysis of 2 RCTs evaluating oral unsubstituted psoralen plus sunlight for generalized vitiligo (N=97) found a statistically significant treatment benefit for active treatment compared with placebo (pooled odds ratio [OR], 19.9; 95% CI, 2.4 to 166.3). Pooled analysis of 3 RCTs, 2 of oral methoxsalen plus sunlight and 1 of oral trioxsalen plus sunlight (181 patients), also found a significant benefit for active treatment versus placebo for generalized vitiligo (OR, 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 ultraviolet A.

Randomized Controlled Trial

Yones et al (2007) published an RCT that used a psoralen formulation available in the U.S.[14,] This trial was included in both the Bae et al (2017) and Whitton et al (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 PUVA (n=28) or NB-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/cm^2, followed by 0.25 J/cm^2-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 patients in the PUVA group had 75% or more improvement in the body surface area affected. Although the authors did not provide p values in their outcomes table, they stated 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=.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=.02).

Section Summary: Psoralens with Ultraviolet A

For individuals who have vitiligo who have not responded to conservative therapy who receive PUVA (photochemotherapy), the evidence includes systematic reviews and RCTs. There is some evidence from randomized studies, mainly those published before 1985, that PUVA is more effective than a placebo for treating vitiligo. When compared with NB-UVB in meta-analyses, results have shown that patients receiving NB-UVB experienced higher rates of repigmentation than patients receiving PUVA, though the differences were not statistically significant. Based on the available evidence and

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clinical guidelines, PUVA may be considered in patients with vitiligo who have not responded adequately to conservative therapy.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Vitiligo Task Force

The international Vitiligo Task Force published a 2023 consensus statement on the management of vitiligo.[15,] First-line recommendations include topical corticosteroids or immunomodulators. The task force does not recommend oral psoralen plus ultraviolet A (PUVA), but recommends topical PUVA as an option for localized lesions. The statement includes recommendations for the use of excimer devices in patients with localized disease.

Vitiligo Working Group

The Vitiligo Working Group (now the Global Vitiligo Foundation) 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.[16,] The Working Group indicated that PUVA has largely been replaced by NB-UVB, 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 Recommendation

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in October 2023 did not identify any ongoing or unpublished trials that may influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for PUVA therapy
  - Prior treatment(s) and response(s) including duration

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements

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are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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	Laser treatment for inflammatory skin disease (psoriasis); 250 sq cm to 500 sq cm
	96922	Laser treatment for inflammatory skin disease (psoriasis); over 500 sq cm
	96999	Unlisted special dermatological service or procedure
HCPCS	J8999	Prescription drug, oral, chemotherapeutic, NOS

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/31/2015	BCBSA Medical Policy adoption
03/01/2016	Policy revision without position change
02/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy title change from Light Therapy for Vitiligo Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2024	Policy reactivated. Previously archived from 09/01/2020 to 02/29/2024.
02/01/2025	Annual review. No change to policy statement. Policy guidelines updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and

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effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Targeted Phototherapy and Psoralen with Ultraviolet A for Vitiligo 2.01.86 **Policy Statement:** I. Psoralen plus ultraviolet A (PUVA) may be considered **medically necessary** for the treatment of vitiligo that is not responsive to other forms of conservative therapy (e.g., topical corticosteroids, coal/tar preparations, ultraviolet light). II. Targeted phototherapy (i.e., laser light devices) is considered **investigational** for the treatment of vitiligo.	**Targeted Phototherapy and Psoralen with Ultraviolet A for Vitiligo 2.01.86** **Policy Statement:** I. Psoralen plus ultraviolet A (PUVA) may be considered **medically necessary** for the treatment of vitiligo that is not responsive to other forms of conservative therapy (e.g., topical corticosteroids, coal/tar preparations, ultraviolet light). II. Targeted phototherapy (i.e., laser light devices) is considered **investigational** for the treatment of vitiligo.

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