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Medical Policy

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Title: Ultraviolet Light Therapy for Skin Conditions

Professional / Institutional
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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.

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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 (e.g., 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. 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. 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 (e.g., 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 (e.g., 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 (e.g., Oxsoralen; Valeant Pharmaceuticals).

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POLICY

A. Phototherapy/actinotherapy with UVA is considered **medically necessary** for up to 24 weeks, 3 treatments per week until improvement or clearing 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

B. Psoralen plus ultraviolet A (PUVA) for the treatment of severe, disabling psoriasis, 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**.

1. 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.
2. 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.
3. 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 (e.g., 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 (i.e., comprising <20% body area) for which NB-UVB or PUVA are indicated.

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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 or psoriatic arthritis
2. First-line treatment of mild psoriasis
3. Vitiligo

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

POLICY GUIDELINES

A. Although disease severity is minimally defined by body surface area (mild psoriasis affects less than 3% of the body's surface area, moderate psoriasis affects 3% to 10%, and severe disease affects more than 10% body surface area), lesion characteristics (e.g., 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.

B. 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.

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

D. PUVA is contraindicated in patients who:
1. are breast-feeding
2. are pregnant
3. have a history of melanoma
4. have a past history of non-melanoma skin cancer
5. have extensive solar damage
6. have had previous treatment with ionizing arsenic
7. have uremia and hepatic failure, but phototherapy may be used.

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E. Phototherapy and PUVA should be used with caution in patients with one or more of the following:
   1. Family history of melanoma
   2. Pemphigus or pemphigoid
   3. Immunosuppression
   4. Cataracts and aphakia
   5. Photosensitivity.

F. 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.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 24, 2022.

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.

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Psoriasis is a common chronic immune-mediated disease characterized by skin lesions ranging from minor localized patches to complete body coverage. There are several types of psoriasis; most common is plaque psoriasis, which is associated with red and white scaly patches on the skin. In addition to being a skin disorder, psoriasis can negatively impact many organ systems and is associated with an increased risk of cardiovascular disease, some types of cancer, and autoimmune diseases (e.g., celiac disease, Crohn disease). Although disease severity is minimally defined by body surface area (mild psoriasis affects < 3% of body surface area, moderate psoriasis affects 3% to 10%, and severe disease affects >10% of body surface area), lesion characteristics (e.g., location and severity of erythema, scaling, induration, pruritus) and impact on QOL are also taken into account. The Psoriasis Area Severity Index (PASI) is a more specific means of quantifying the extent and severity of psoriasis, and is utilized by both clinicians in practice and in clinical trials to monitor disease severity. The PASI takes into account the affected body surface area along with the intensity of redness, scaling, and plaque thickness. Severity scores generated using PASI range from 0 (no disease) to 72 (maximal disease severity); a score >10 generally indicates moderate-to-severe disease. In clinical trials of patients with moderate-to-severe psoriasis, a 75% reduction in PASI (i.e., PASI 75) is a common endpoint. 1,2,3,4,

TARGETED PHOTOTHERAPY FOR MILD LOCALIZED PSORIASIS

Clinical Context and Therapy Purpose

The purpose of targeted phototherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with mild localized psoriasis.

The question addressed in this evidence review is: Does the use of targeted phototherapy improve the net health outcome in patients with localized or generalized psoriasis?

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

Populations

The relevant population of interest is individuals with mild localized psoriasis (<3% body surface area and not affecting hands, feet, face or genitals).

Interventions

The therapy being considered is targeted phototherapy, which is managed by dermatologists and primary care providers.

Comparators

The following therapy is currently being used to treat localized or generalized psoriasis: topical medication which is managed by dermatologists and primary care providers.

Outcomes

The general outcomes of interest are symptoms, change in disease status, quality of life, and treatment-related morbidity.

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Though not completely standardized, follow-up for mild localized psoriasis symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected 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.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
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 (e.g., calcipotriol, calcitriol), tazarotene, and anthralin.[5]

TARGETED PHOTOTHERAPY FOR TREATMENT-RESISTANT MILD PSORIASIS

Clinical Context and Therapy Purpose
The purpose of targeted phototherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with mild psoriasis that is resistant to topical medications.

The question addressed in this evidence review is: Does the use of targeted phototherapy improve the net health outcome in patients with localized or generalized psoriasis?

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

Populations
The relevant population of interest are individuals with mild psoriasis that is resistant to topical medications.

Interventions
The therapy being considered is targeted phototherapy, which is managed by dermatologists and primary care providers.

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Comparators
The following therapy is currently being used to treat mild psoriasis resistant to topical medications: ultraviolet B light box therapy, which is managed by dermatologists and primary care providers.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, and treatment-related morbidity.

Though not completely standardized, follow-up for mild psoriasis that is resistant to topical medications symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the 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.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Clinical Trials
Several small within-subject 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.[6] In 2004, the same investigator group reported that 12 of 13 patients with "extensive and stubborn" scalp psoriasis (i.e., 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.[7] 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.[8]

Section Summary: Treatment-Resistant Mild Psoriasis
For individuals who have mild psoriasis that is resistant to topical medications who receive targeted phototherapy, the evidence includes small (N<60) within-subject studies. Studies have shown that targeted phototherapy can improve mild localized psoriasis that has not responded to topical treatment. 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

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UVB light. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

TARGETED PHOTOTHERAPY FOR MODERATE-TO-SEVERE LOCALIZED PSORIASIS

Clinical Context and Therapy Purpose

The purpose of targeted phototherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with moderate-to-severe localized psoriasis.

The question addressed in this evidence review is: Does the use of targeted phototherapy improve the net health outcome in patients with localized or generalized psoriasis?

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

Populations

The relevant population of interest are individuals with moderate-to-severe localized psoriasis.

Interventions

The therapy being considered is targeted phototherapy, which is managed by dermatologists and primary care providers.

Comparators

The following therapy is currently being used to treat moderate-to-severe localized psoriasis: ultraviolet B light box therapy.

Outcomes

The general outcomes of interest are symptoms, change in disease status, quality of life, and treatment-related morbidity.

Though not completely standardized, follow-up for moderate-to-severe localized psoriasis symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria

Methodologically credible studies were selected 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.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

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Systematic Reviews

There are several systematic reviews of the literature on targeted phototherapy. Reviews differed in the type of study selected and the comparison interventions. A systematic review by Almutawa et al (2015) considered only RCTs; PUVA was the comparison intervention.[9] Reviewers identified three 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 was 3.48 (95% confidence interval, 0.56 to 22.84).

Mudigonda et al (2012) published a systematic review of controlled studies (RCTs and non-RCTs) on targeted vs nontargeted phototherapy for patients with localized psoriasis.[10] Reviewers identified 3 prospective nonrandomized studies comparing the 308-nm excimer laser with NB-UVB. Among these studies was a study by Goldinger et al (2006) that compared the excimer laser with full-body NB-UVB in 16 patients.[11] 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 study by Kollner et al (2005) included 15 patients with stable plaque psoriasis.[12] 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 (i.e., each patient received all three treatments). Investigators found no significant differences in the efficacy of the three treatments after ten weeks. The mean number of treatments to achieve clearance of lesions was 24.

Section Summary: Moderate-to-Severe Localized Psoriasis

For individuals who have moderate-to-severe localized psoriasis who receive targeted phototherapy, the evidence includes systematic reviews of small (N≤25) controlled trials (RCTs and non-RCTs). Systematic reviews of small controlled trials in patients with moderate-to-severe psoriasis have found that targeted phototherapy has efficacy similar to whole-body phototherapy. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome

PSORALEN PLUS ULTRAVIOLET A FOR GENERALIZED PSORIASIS

Clinical Context and Therapy Purpose

The purpose of PUVA is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with generalized psoriasis.
The question addressed in this evidence review is: Does the use of PUVA improve the net health outcome in patients with localized or generalized psoriasis?

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

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Populations
The relevant population of interest are individuals with generalized psoriasis (>10% body surface area).

Interventions
The therapy being considered is PUVA, which is managed by dermatologists and primary care providers.

Comparators
The following therapies are currently being used to treat generalized psoriasis: topical medications and ultraviolet B light box therapy, which is managed by dermatologists and primary care providers.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, and treatment-related morbidity.

Though not completely standardized, follow-up for generalized psoriasis symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the 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.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews and Randomized Controlled Trials
A number of RCTs and systematic reviews of RCTs have compared PUVA with other light therapies or with placebo. A Cochrane review by Chen et al (2013) assessed light therapy for psoriasis.[13]However, that review is less useful for this evidence evaluation because reviewers combined results of studies using PUVA and broadband UVB, rather than reporting outcomes separately for these treatment modalities.

Psoralens and Ultraviolet A versus Narrow Band-Ultraviolet B
An industry-sponsored systematic review by Archier et al (2012) focused on studies comparing PUVA with NB-UVB in patients who had chronic plaque psoriasis.[14] Pooled analysis of 3 RCTs found a significantly higher psoriasis clearance with PUVA than with NB-UVB (odds ratio=2.79; 95% confidence interval, 1.40 to 5.55). In addition, significantly more patients remained cleared

at 6 months with PUVA than with NB-UVB (odds ratio=2.73: 95% confidence interval, 1.18 to 6.27).

Psoralens and Ultraviolet A versus Topical Steroids

Amirnia et al (2012) published a trial in which 88 patients with moderate plaque psoriasis were randomized to PUVA or topical steroids.[15] Treatment was continued for four 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 four-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) (see Table 1).

Psoralens and Ultraviolet A versus Ultraviolet A Without Psoralens

El-Mofty et al (2014) published an RCT comparing PUVA with broadband-UVA in 61 patients who had psoriasis affecting at least 30% body surface area.[16] Clinical outcomes were significantly better in the PUVA group than in the broadband-UVA groups (see Table 1). 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).

Sivanesan et al (2009) 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.[17] 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) (see Table 1). There were no serious adverse events.

Table 1. Summary of Individual RCTs of PUVA vs Other Light Treatments

Study	Intervention Modality	No. of Participants	PUVA Effectiveness	p
El-Mofty et al (2014)[16]	PUVA vs UVA without psoralens	61	Complete clearance obtained by 77% of PUVA group vs 31% and 33% of UVA-only groups	0.020
Amirinia et al (2012)[15]	PUVA vs topical steroids	88	Recurrence reported significantly more often in topical steroid group than PUVA group	0.007
Sivanesan et al (2009)[17]	PUVA vs UVA without psoralens	40	63% of PUVA group had >=75% improvement in PASI 75 score at 12 wk vs 0% of UVA plus placebo group	<0.001

PASI: Psoriasis Area Severity Index; PUVA: psoralen plus ultraviolet A; RCT: randomized controlled trials; UVA: ultraviolet A.

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Section Summary: Psoralen Plus UVA
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.

TARGETED PHOTOTHERAPY FOR THE TREATMENT OF VITILIGO

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 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.

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- 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 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 2. 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	• Localized 308-nm excimer light[a] • 311-nm NB-UVB[a]

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Study (Year)	Countries	Sites	Dates	Participants	Interventions
				immunosuppressive drugs for ≥8 weeks	
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
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

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Study (Year)	Countries	Sites	Dates	Participants	Interventions
					• 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 3. 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%

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Study	Reduction in VASI score, mean	Repigmentation
p value	NA	• Patients with stable vitiligo at baseline: <.001 • 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)

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Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Poolsuwam 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	
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. Clinical context for treatment is unclear; 3. Study population is unclear; 4. Study population not representative of intended use. 5. Study population is subpopulation of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Not CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefits; 2. Not sufficient duration for harms.

Table 5. 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	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]
	concealment occurred					
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.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-up 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Test is not appropriate for outcome type: a) continuous; b) binary; c) time to event; 2. Test is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p-values not reported; 4. Comparative treatment effects not calculated.

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.

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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.

PSORALENS WITH ULTRAVIOLET A

Clinical Context and Therapy Purpose
The purpose of psoralen plus ultraviolet A (PUVA) in patients 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.

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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 6. Adverse events were not discussed.

Table 6. 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)
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 clinical guidelines, PUVA may be considered in patients with vitiligo who have not responded adequately to conservative therapy.

No review or update is scheduled on this Medical Policy. Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

SUPPLEMENTAL INFORMATION

Practice Guidelines And Position Statements

American Academy of Dermatology

The American Academy of Dermatology (2010) guidelines on the management of psoriasis recommended that patients with psoriasis who are compliant could, under dermatologist supervision, be considered appropriate candidates for home ultraviolet B therapy.[5]

Targeted phototherapy was recommended for patients with mild, moderate, or severe psoriasis with less than 10% involvement of the body surface area. Systemic psoralen plus ultraviolet A was indicated in adults with generalized psoriasis 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.[19] 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 7.

Table 7. Recommendations on Treatment of Inverse Psoriasis

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

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.[20] Because organ transplant patients are excluded from randomized controlled trials, there are limited data. The recommendations were based on case series (see Table 8).

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Table 8. Recommendations on Treatment of Psoriasis for Solid Organ Transplant Patients

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

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.[15,] The Working Group indicated that psoralen plus ultraviolet A (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.

No review or update is scheduled on this Medical Policy. Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
96900	Actinotherapy (ultraviolet light)
96912	Photochemotherapy; psoralens, and ultraviolet A (PUVA)
96920	Excimer Laser treatment for (psoriasis); total area less than 250 sq cm
96921	Excimer Laser treatment for (psoriasis); Total area 250-500 sq cm
96922	Excimer Laser treatment for (psoriasis); 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

REVISIONS	
09-28-2014	Policy added to the bcbsks.com web site on 08-29-2014. Effective on 09-28-2014, 30 days after posting.
01-08-2015	In Coding section: ▪ Added codes E0691, E0692, E0693, and E0694.
02-04-2015	In Policy section: ▪ Added "using ultraviolet A (UVA) light devices" to read, "Home phototherapy using ultraviolet A (UVA) light devices is considered experimental / investigational."
04-28-2015	Updated Description section.
	Updated Rationale section.
	Updated References section.
05-28-2015	Corrected Revisions section: ▪ Removed "Added codes E0691, E0692, E0693, and E0694" from 02-04-2015 revision date and added under 01-08-2015 revision date.

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REVISIONS	
10-01-2015	Published 11-10-2015. Effective 10-01-2015 with ICD-10 coding implementation.
	In coding section: ▪ Added ICD-10 code L20.9.
03-02-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-18-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-30-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
02-01-2019	Updated Rationale section.
	Updated References section.
05-23-2021	Updated Rationale section.
	In Policy section: • Added "(i.e., comprising <20% body area)" to Item D • Added "or psoriatic arthritis" to Item F.1 and added F.2 • Replaced "5%" with "3%" in policy guideline 1
	Updated References section.
06-15-2022	Updated Rationale Section
	Updated Policy Section • Changed Section A to read: "Phototherapy/actinotherapy with UVA is considered medically necessary for up to 24 weeks, 3 treatments per week until improvement or clearing for the following conditions when moderate to severe and refractory to standard therapies" • Removed bullet in section A: " For up to 24 weeks, 3 treatments per week until improvement or clearing is considered medically necessary."
	Updated Coding Section ▪ Removed Coding Bullets ○ 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). ▪ Converted ICD-10 Codes to ranges
	Updated References Section
01-24-2023	Updated Rationale Section
	Updated References Section
12-12-2023	Updated Coding Section ▪ Removed ICD-10 Codes ▪ Updated nomenclature for 96920, 96921, and 96922 (eff. 01-01-2024)

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REVISIONS	
12-12-2023	Archived

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