VITILIGO

CHI Formulary Indication Review

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Council of Health Insurance

October 2023

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

5-MOP	5-Methoxypsoralen
8-MOP	8-Methoxypsoralen
BSA	Body Surface Area
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council for Health Insurance
CS	Corticosteroids
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
ExLP	Excimer Lamp
ExLS	Excimer Laser
FDA	Food and Drug Administration
GAD7	Generalized Anxiety Disorder 7
GPP	Good Practice Point
HAS	Haute Autorité de Santé
He-Ne	Helium-Neon Laser
HTA	Health Technology Assessment
IDF	CHI Drug Formulary
IQWIG	Institute for Quality and Efficiency in Healthcare
JAK	Janus Kinase
JDA	Japanese Dermatology Association
KUVA	Khellin/Ultraviolet A Radiation
MEL	Monochromatic Excimer Laser
NBUVB	Narrow Band Ultraviolet B Light
NICE	National Institute for Health and Care Excellence
NSV	Non-Segmental Vitiligo
OMP	Oral Mini-Pulse Therapy

PBAC	Pharmaceutical Benefits Advisory Committee
PHQ-4	Patient Health Questionnaire-4
PHQ9	Patient Health Questionnaire-9
PUVA	Psoralen/Ultraviolet A Radiation
PUVASOL	Psoralen and UVA Obtained by Solar Light
SFDA	Saudi Food and Drug Authority
SV	Segmental Vitiligo
TCI	Topical Calcineurin Inhibitors
TG	Thyroglobulin
TIM	Topical Ascomycin Immunomodulating Macrolactams
TMP	Trimethylpsoralen
TPO	Thyroid Peroxidase
TSH	Thyroid Stimulating Hormone
UVA	Ultraviolet A Light
UVB	Ultraviolet B Light
VIPS	Vitiligo Impact Patient Scale
VitiQoL	Vitiligo-Specific Quality-of-Life Instrument

Executive Summary

Vitiligo is an acquired pigmentary skin condition characterized by immune-mediated destruction of melanocytes and by the decrease or absence of pigmentary cells from the epidermis leading to the formation of white macules and patches on the body[1]. Vitiligo is associated with few autoimmune disorders; thyroid disorders being mostly prominent[2]. The etiology and pathogenic mechanisms of vitiligo are still poorly understood which has hindered the progress in diagnosis and treatment[3].

Vitiligo is classified into 3 subtypes based on distribution: generalized, segmental, and localized[2]. **Generalized** vitiligo (also referred to as non-segmental vitiligo), which is the most common form of vitiligo, involves loss of pigment (depigmentation) in patches of skin all over the body. **Segmental** vitiligo is an uncommon form of localized vitiligo, characterized by dermatomal distribution. It is often unilateral, asymmetrical and never crosses the midline of body. **Localized** vitiligo is characterized by the development of a few patches that appear in one or few areas of the body. The degree of severity of the disease depends on the body surface affected.

Vitiligo can be manifested as distinct clinical variants: **trichrome** (lesions that have a tan zone of varying width between normal and totally depigmented skin, which exhibits an intermediate hue[4]), **marginal inflammatory** (a unique subset of vitiligo vulgaris presenting with scattered depigmented, pruritic patches surrounded by a raised, erythematous border[5]), **quadrichrome** (additional presence of marginal or perifollicular hyperpigmentation; recognized more frequently in darker skin types, particularly in areas of repigmentation), and **pentachrome** (additional blue-gray hyperpigmented macules, representing areas of melanin incontinence). Less common variants include the **confetti** type or vitiligo ponctue. (Several tiny, discrete hypomelanotic macules[6]). Finally, the **Koebner Phenomenon** is described as vitiligo following an injury to the skin, such as a scratch, scrape, or burn[7]. Initial lesions occur most frequently on the hands, forearms, feet, and face, favoring a periocular or perioral distribution[2]. Other patterns include **lip-tip** vitiligo (affecting mostly the lips and fingertips), **acrofacial** vitiligo (involves the lips or other parts of the face plus the hands and/or feet), and **focal** vitiligo (affects only a small area of the body)[7]. Finally, **universal** vitiligo involves most of the body[7].

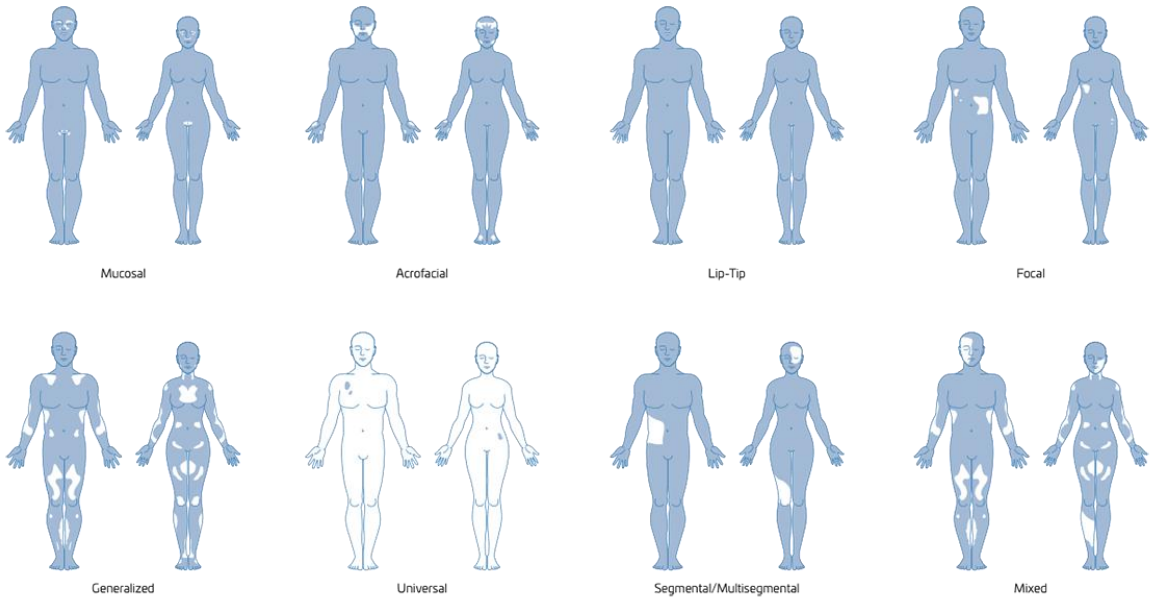


Figure 1. *Patterns of Vitiligo. Retrieved from https://www.umassmed.edu/vitiligo/blog/blog-posts1/2020/05/patterns-of-vitiligo/*

Underreporting of vitiligo across all skin types may be a concern, as some healthcare providers may perceive it as a cosmetic issue rather than recognizing it as a well-defined autoimmune disease[8].

The global prevalence of vitiligo is estimated to range from 0.5% to 2% of the population; the prevalence reported by most studies is 0.6%. However, it is important to bear in mind that Vitiligo prevalence rates vary geographically. For instance, higher prevalence rates are recorded in Africa and India[8]. In Saudi Arabia, as of 2020, the prevalence of Vitiligo was reported at 3.12%[9]. Vitiligo is found to affect both males and females at similar rates and is not limited to specific racial, ethnic, or socioeconomic groups. While it can manifest at any age, it is most commonly observed during the second and third decades of life. Approximately one-third of individuals with vitiligo develop the condition during childhood, while a significant majority, around 70% to 80%, experience its onset before reaching the age of 30 years[10].

Vitiligo manifests clinically as white patches on the skin, appearing in a symmetrical pattern. These patches are especially prominent in individuals with darker skin tones. The affected areas are distinguishable by clearly defined, pearly white or depigmented spots and irregularly shaped macules and patches, which can be oval, round, or linear in form. Their edges are raised, varying in size from a few millimeters to centimeters, and they expand outward from the center. Depigmentation may lead to psychological distress, social stigmatization, and low self-esteem[2].

If left untreated, the depigmented skin will render the patient more prone to sunburn and skin cancer. In addition, cochlear melanocyte loss may lead to hearing loss. Other complications that are likely to be burdensome to the patient's quality of life include social stigmatization and mental stress[2].

This report compiles all clinical and economic evidence related to vitiligo according to the relevant sources. The ultimate objective of issuing Vitiligo guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to vitiligo patients in Saudi Arabia**. The main focus of the review was on North American, European and other International guidelines issued within the last five years. To elaborate, North American guidelines detailed prognostic factors as well as pharmacological and non-pharmacological approaches for the management of vitiligo. Furthermore, European guidelines emphasize diagnosis, classification, therapy, and supportive care for vitiligo. International guidelines elaborated on treatment of vitiligo aimed at children, pregnant patients, nursing mothers and the elderly.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in Vitiligo were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The management of vitiligo involves a **multidisciplinary approach**. Various methods are employed for treating vitiligo, encompassing a range of topical and systemic medications, phototherapy, laser therapy, and surgical interventions. Topical treatments consist of corticosteroids, calcineurin inhibitors, and vitamin-D analogs. Phototherapy, specifically narrowband UV-B with a 311-312nm wavelength, is a highly effective treatment, promoting repigmentation in early and localized cases. Surgical treatments are reserved for segmental or localized vitiligo affecting small areas. Newly emerging methods for the management of vitiligo include the pharmacological management with topical ruxolitinib and the use of RECELL® medical device for restoration of pigmentation; both of which were FDA approved in 2022 and 2023 respectively; however, neither is SFDA registered.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of Vitiligo.

Major recommendations for suggested drug therapies are summarized in the tables below:

Table 1. SFDA-Registered Drugs for the Treatment of Vitiligo

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Mometasone Furoate (Topical)	Preferred treatment option for children and adults with limited vitiligo and extrafacial involvement	**1st**	Grade A[11]	No HTA Recommendations were issued by the concerned HTA bodies.
Methyl-prednisolone Aceponate (Topical)	Preferred treatment option for children and adults with limited vitiligo and extrafacial involvement	**1st**	Strong Recommendation[12]	No HTA Recommendations were issued by the concerned HTA bodies.
Betamethasone Valerate (Topical)	Preferred treatment option for children and adults with limited vitiligo and extrafacial involvement	**1st**	Strong Recommendation[13]	No HTA Recommendations were issued by the concerned HTA bodies.
Dexamethasone (Oral)	Oral-Mini Pulse course for acute, rapidly progressive vitiligo	**1st**	Strong Recommendation[12]	No HTA Recommendations were issued by the concerned HTA bodies.
Betamethasone (Oral)	Oral-Mini Pulse course for acute, rapidly progressive vitiligo	**1st**	Strong Recommendation[14]	No HTA Recommendations were issued by the concerned HTA bodies.
Tacrolimus (Topical)	An alternative used for intermittent regimens or if	**2nd**	Strong Recommendation[14]	No HTA Recommendations were issued by the

	patients cannot tolerate topical corticosteroids			concerned HTA bodies.
Pimecrolimus (Topical)	An alternative used for intermittent regimens or if patients cannot tolerate topical corticosteroids	**2nd**	Strong Recommendation[14]	No HTA Recommendations were issued by the concerned HTA bodies.
Methoxsalen (Oral)	Used as part of a phototherapy regimen; specifically in patients with non-segmental vitiligo or for patients with unclassified vitiligo	**2nd**	Strong Recommendation[15]	No HTA Recommendations were issued by the concerned HTA bodies.

Table 2. Non-SFDA-Registered Drugs for the Treatment of Vitiligo

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Ruxolitinib (Topical)	Adult and pediatric patients (Aged over 12 years) with Nonsegmental Vitiligo	1st	Strong Recommendation[16]

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, there are no guidelines published by Saudi bodied on the clinical management of Vitiligo.

1.2 North American Guidelines

1.2.1 American Academy of Dermatology - Vitiligo: A Comprehensive Overview Part II: Treatment Options and Approach to Treatment (2010)

The American Academy of Dermatology (AAD) conducted a comprehensive overview on vitiligo. It was published in two parts: the first covered the epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up[17], and the second detailed the treatment options and approach to treatment[13]. For brevity purposes, only part II will be included in this report. The main recommendations issued are detailed below[13]:

- There are various treatment options for vitiligo: these include but are not limited to non-surgical, surgical, and alternative options.
- Nonsurgical options include pharmacological approaches (using topical or systemic therapy), phototherapy, photochemotherapy, and laser therapy.
- Surgical options include melanocyte cell suspension transplantation and skin grafting.
- Other suggested approaches include camouflage products, psychotherapy, and depigmentation therapy.
- The treatment efficacy is based on several factors such as the type of vitiligo that the patient is subjected to, the duration and distribution of the disease and the use of combination regimens in the treatment process.

Individual Prognostic Factors:

- In patients who are left untreated, disease progression is attributed to mucosal involvement, a family history of vitiligo, the Koebner Phenomenon, and the presence of non-segmental vitiligo.
- Patients with the following characteristics are more likely to respond to therapy: younger patients, those with recent onset of disease, darker skin types, and lesions of the face, neck, and trunk.

1. **Pharmacological Therapy**

    a. **Corticosteroids**

- The **first line** therapy for vitiligo is **topical corticosteroid** (CS) therapy; these agents may be used as monotherapy or as adjunctive therapy.
- Systemic corticosteroids play an important role in stopping disease progression and inducing repigmentation; however, limitations to their use include their side effect profile.
- If patients are treated with corticosteroids, frequent monitoring and regular steroid holidays are recommended to limit and potentially prevent side effects.
- Higher response rates are seen in children compared to adults with head and neck lesions having the greatest response to treatment.
- Regardless of route, CS combination with light therapy yields a favorable outcome.

    b. **Topical Calcineurin Inhibitors**

- The off-label use of topical calcineurin inhibitors (TCIs) has been shown to be safe and effective in the treatment of vitiligo for both adults and children.
- TCIs are also known to enhance the effect of light/laser therapy.
- Given the lack of local side effects and efficacy comparable to topical CSs, TCIs are appropriate for intermittent long-term use and for those who cannot tolerate topical CSs.
- Face and neck lesions respond best, and occlusion may help with recalcitrant lesions on the extremities.
- Concerns regarding potential systemic absorption may be alleviated by limiting the application of TCIs to a small body surface area, such as the face.

    c. **Vitamin D3 Analogs**

- Calcipotriene is a topical vitamin D3 analog with an antiproliferative effect on keratinocytes, an immunomodulatory effect, and an ability to enhance melanocyte development and melanogenesis.
- Topical vitamin D3 analogs are mostly beneficial when combined with topical CS; repigmentation rates increase, the delay in the onset of repigmentation shortens, and there is a greater stability of repigmentation compared with either, as monotherapy. The combination therapy is effective in some previously steroid nonresponsive patients.

- Off-label use of the fixed-combination calcipotriene 0.005% and betamethasone 0.05% topical products once daily is another treatment option.

2. Phototherapy

- Phototherapy is ideally reserved for patients who fail topical therapy or for those with lesions of large surface areas.
- Narrowband UVB phototherapy is superior to PUVA phototherapy – specifically, 311nm NBUVB; however, PUVA yields quicker results.
- UVA phototherapy is almost always given in conjunction with Psoralen (A photosensitizer); however, the combination increases the risk of melanoma and nonmelanoma skin cancers.

3. Laser Therapy

- The **Monochromatic Excimer Laser** or MEL (308nm) is the most used laser therapy for the treatment of Vitiligo.
- As per Casacci et al[18], MEL has proven to lead to better clinical outcomes compared to NBUVB phototherapy.
- In most clinical trials, the MEL is used one to three times a week for an initial course of 12 weeks; 11 to 22 sessions are required on average to see repigmentation, more in poorly responsive acral areas.
- **Bioskin**, a device regarded as microphototherapy, transmits focused 311nm UVB phototherapy; all other tested modalities resulted in enhanced repigmentation rates when used in combination with Bioskin compared to use as monotherapy.
- For patients with segmental vitiligo who have poorer responses to conventional treatment compared to non-segmental vitiligo, the **632.8-nm helium neon (HeNe) laser** is recommended; whereby, repigmentation begins following 16 to 17 treatments; however, this is not a standard therapy regimen.

4. Photochemotherapy

- The furocoumarin psoralens 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), and trimethylpsoralen (TMP) have been successfully used for the management of vitiligo when given in combination with UVA therapy.
- The use of topical 8-MOP is limited to patients with small lesions (< 5% body surface area), or who are younger than 12 years of age in whom systemic Psoralen/Ultraviolet A Radiation (PUVA) phototherapy is contraindicated.

- **Regimen:** the frequency of treatment is one to three times per week.

  Twenty to thirty minutes after application of an even layer, the skin is exposed to UVA radiation, initially at 0.25 to 0.5 J/cm^2.

  Two to three times a week, exposure time is increased in small steps (15-30 seconds) up to a maximum of 10 minutes. Then, a marginally higher strength of topical psoralen preparation is prescribed, and the same time intervals are followed.

  This procedure is repeated until a dosage and exposure time are attained that produce erythema but not burning.

  The patients need to wash off the remaining 8-MOP with soap and water immediately after the irradiation and apply UVA sunblock to avoid additional environmental UVA exposure.

- It is suggested that another agent, **Khellin**, is administered topically or orally and is said to have vasodilatory effects.

  Studies suggest that Khellin exhibits a stimulatory effect on melanogenesis and melanocyte proliferation when combined with UVA light.

  Compared directly to PUVA, Khellin/Ultraviolet A Radiation (KUVA) phototherapy required higher doses and a longer duration of treatment to achieve the same response, but patients experienced fewer side effects than with PUVA phototherapy.

- **L-Phenylalanine** is an essential amino acid used in the initiation of melanogenesis in melanocytes. It can be applied topically or taken orally.

  Treatment of vitiligo with L-Phe can be used for any patient with access to natural or UVA light.

  The patient population who responds best is that with less than 25% body surface area affected, a disease onset before 21 years of age, and with generalized, symmetrical lesions.

5. Antioxidants

- Topical and oral antioxidants may have a role in protecting melanocytes from destruction by reactive oxygen species. They are given as **adjunct therapies**.
- Vitamin E, vitamin C, alphalipoic acid, ginkgo biloba, topical catalase, superoxide dismutase, and polypodium leucotomos have been used in vitiligo.

6. **Surgical Therapies**

- Surgical treatment should be reserved for patients with stable vitiligo refractory to non-surgical therapy.
- Surgical procedures include blister graft, split-thickness skin graft, punch graft and autologous melanocyte suspension transplant.
- The blister graft and punch graft are more favorable since they do not require general anesthesia and leave the patient unscathed.
- The split-thickness skin graft can be useful to cover large areas but yields less desirable cosmetic outcomes at the donor site.
- For patients with focal or segmental vitiligo, Autologous Melanocyte Suspension Transplant is an appropriate alternative to tissue grafting.

7. **Depigmentation**

- Depigmentation is the treatment of choice for patients who fail repigmentation therapy or have extensive disease.
- Topical agents that depigment normal skin include monobenzone (also called monobenzyl ether of hydroquinone, or MBEH) which induces melanocyte death.
- Depigmenting agents and laser therapy only provide temporary cosmetic relief.

8. **Camouflage**

Camouflage creates a cosmetically pleasing appearance and should be recommended to patients at all stages of treatment. It may be temporary such as makeup, self-tanning agents, or it may be permanent as tattoos. Camouflage improves patient scores on the Dermatology Quality of Life Index.

Figure 2 details the treatment algorithm recommended by the AAD for the management of vitiligo.

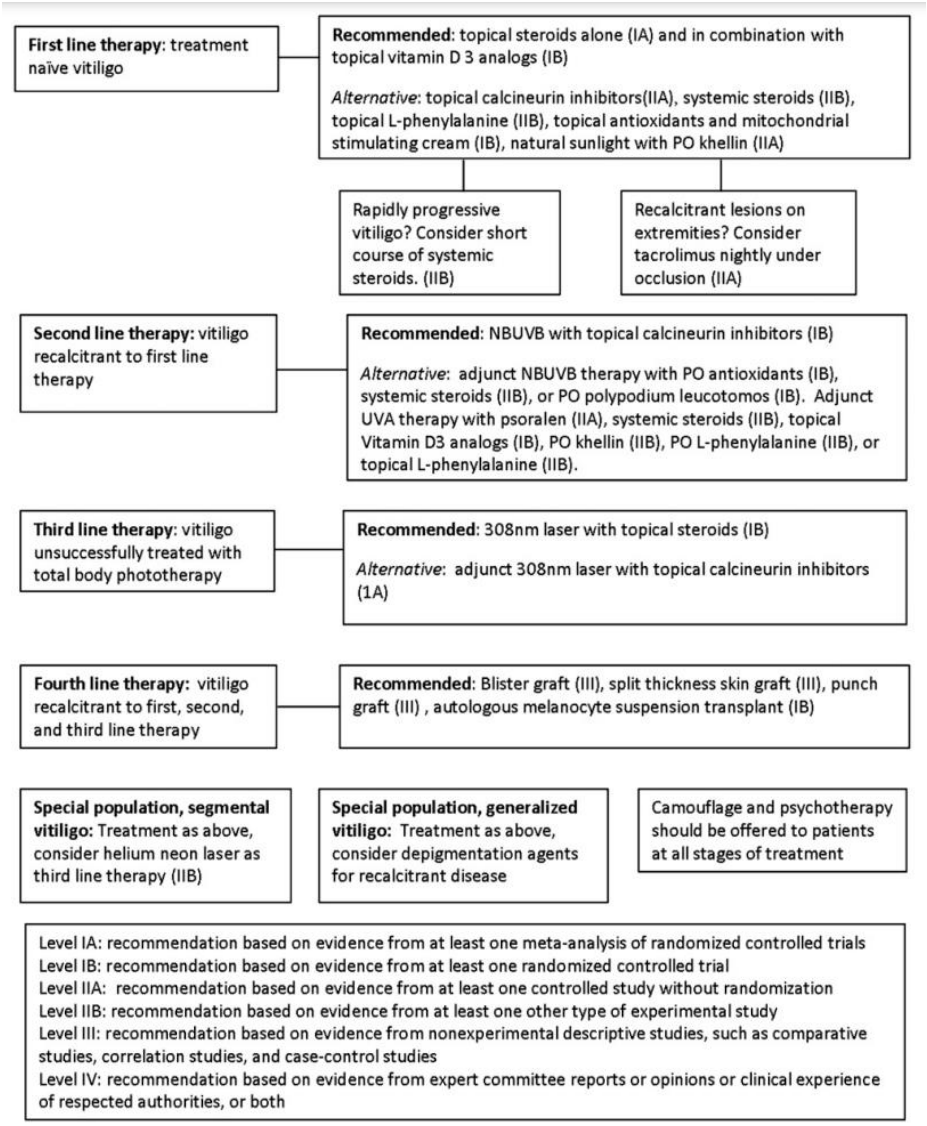


Figure 2. *AAD Treatment Approaches for the Management of Vitiligo. Retrieved from Felsten LM, Alikhan A, Petronic-Rosic V. Vitiligo: A comprehensive overview: Part II: Treatment options and approach to treatment. J Am Acad Dermatol. 2011;65(3):493-514.*

1.3 European Guidelines

1.3.1 S1 Guideline: Diagnosis and Therapy of Vitiligo (2022)

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The German Dermatological Society, Professional Society of German Dermatologists, Austrian Society of Dermatology and Venereology, German Society of Dermatosurgery, Deutscher Vitiligo Verein and the Vitiligo European Task Force

issued clinical practice guidelines for the diagnosis and therapy of vitiligo; the recommendations are detailed below[19]:

Diagnosis & Classification

- Vitiligo may be diagnosed on the basis of clinical features.
- A biopsy is not required; however, it may be considered for differential diagnosis – ruling out any other possible skin condition with similar manifestations.
- Photographic documentation is required as it allows for objectivation of the extent of the current depigmentation and that of disease activity and response to therapy.
- Instruments for assessing the extent of vitiligo include:
    - Affected body surface area (BSA) in percent based on the rule of nine.

      As recommended in the Japanese guidelines for the management of vitiligo, manifestation can be classified as severe (BSA > 30 %), moderate (BSA 10–30 %), and mild (BSA < 10 %), although there is no general consensus.
    - Vitiligo European Task Force (VETF) Score
    - Vitiligo Area Scoring Index (VASI)
    - Vitiligo Extent Score (VES)/Self-Assessment Vitiligo Extent Score (SA-VES)
- Given the increased prevalence of thyroid diseases, determination of TSH as well as TPO and TG antibodies is recommended as initial screening test and then annually in vitiligo patients.

Therapy of Vitiligo

- For limited vitiligo and extrafacial involvement, **topical corticosteroids** are regarded as first-line therapy.
- Potent class III corticosteroids are recommended; these include mometasone furoate for a period of 3 to 6 months.
- **Topical calcineurin inhibitors** are prescribed off-label as an alternative to topical corticosteroids in vitiligo.
- TCIs are safe in terms of long-term application; with a lower risk of skin atrophies as an adverse drug reaction compared to topical corticosteroids.
- TCIs are to be applied twice daily and depending on the response, for 6-12 months.

- In case of successful repigmentation, proactive therapy applied twice weekly helps reduce the risk of recurrence.
- For patients with non-segmental vitiligo, narrow-band UVB (**NB-UVB)** twice or thrice a week is the optimal treatment option, and it could be used as monotherapy or as an adjunct therapy with topical corticosteroids or topical calcineurin inhibitors; the treatment effect is evaluated after 3 months.

  Therapy duration is not to exceed 12-24 months.
- If topical therapy is deemed not feasible (attributed to the extent of the disease) in patients with generalized vitiligo and in case of active, progressive vitiligo, NB-UVB is indicated.
- NB-UVB has proven to be superior to systemic PUVA therapy with the face and neck being the most responsive areas.
- Irradiation is to be discontinued after six months at the latest in case of absent repigmentation.
- In patients with rapidly progressing non-segmental vitiligo, a combination of NB-UVB and systemic corticosteroids may be used.
- **308-nm Excimer Laser** and **308-nm Excimer Lamp** are effective treatment options for repigmentation; Excimer therapy treats targeted vitiligo lesions.
- The combination of either options with topical and systemic medications as corticosteroids or topical calcineurin inhibitors strengthens the effect of targeted light therapy.
- For patients with acute, rapidly progressing vitiligo, **oral mini-pulse therapy with corticosteroids** using dexamethasone, prednisone or methylprednisolone for two consecutive days a week may be considered to achieve disease arrest with a therapy duration of 3-6 months.

  This form of therapy is not recommended as monotherapy.
- For patients with stable segmental and focal vitiligo who are not responsive to pharmacological therapy, **surgical procedures** are suspected. The optimal surgical technique is selected based on the location of skin lesions, individual expertise and available equipment.

Supportive Therapy

- Highly potent broad-spectrum sunscreens are recommended to be applied due to the increased sensitivity of skin lesions to sunlight.
- The covering of vitiligo lesions may be facilitated by dermato-cosmetic products such as creams, sprays, liquid or compact formulations, concealers, and fixing sprays.
- Psychotherapy is highly recommended to help the patient cope with their mental distress and to enhance quality of life.
- Depigmentation should only be considered in extremely rare cases and after exploitation of all therapeutic options. It is important to keep in mind that such techniques may lead to the irreversible destruction of melanocytes.

1.3.2 British Association of Dermatologists Guidelines for the Management of People with Vitiligo (2021)

The British Association of Dermatologists (BAD) has issued guidelines for the management of vitiligo; it has opted for the following Grades of Recommendation/Level of Evidence to support its claims[20]:

Table 3. BAD Strength of Recommendations/Level of Evidence

Strength	Wording	Symbol	Definition
Strong recommendation for the use of an intervention	'Offer' (or similar, e.g., 'use', 'provide', 'take', 'investigate' etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policymakers, it would be a useful performance indicator
Weak recommendation for the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; many patients would choose the intervention, but many would not; clinicians would need to consider the pros

			and cons for the patient in the context of the evidence; for policymakers it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation against the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the intervention

Good practice point (GPP) recommendations (R) are derived from informal consensus.

Vitiligo Classification

Table 4. Classification of Vitiligo. Adapted from BAD Guidelines for the Management of People with Vitiligo (2021)

	Subtype	Definition
Vitiligo/NSV	Acrofacial	Involved sites are usually limited to face, head, hands, feet.
	Generalized	Acrofacial vitiligo may later progress to include other body sites.
	Universal	Most extensive form of vitiligo. This term is used when depigmentation covers > 80% of total body surface.
	Mucosal	Usually refers to the involvement of oral and/or genital mucosae.
	Mixed	Concomitant occurrence of NSV and segmental vitiligo.
	Rare variants	• Follicular

		• Vitiligo minor (incomplete defect in pigmentation with a pale skin color compared with healthy skin) • Vitiligo punctata (1-1.5 mm sharply demarcated macules)
Segmental vitiligo	Uni-, bi- or plurisegmental	Presence of one or more depigmented macules distributed on one side of the body.
Undetermined or unclassified vitiligo	Focal	Small, isolated patch, which has not evolved into NSV after a period of at least 2 years and does not fit into a segmental distribution.
	Mucosal	One mucosal site in isolation.

General Recommendations

- A full history is to be collected for vitiligo patients including but not limited to the site and type of vitiligo (Segmental/Non-Segmental), disease extent (Affected body surface area), disease stability, speed of onset, trigger factors, quality of life, psychological and psychosocial impact, and personal and family history of associated thyroid dysfunction or other autoimmune disease. **(GPP)** As per the BAD, disease stability is defined as per the following table:

Table 5. Definition of Disease Stability for Vitiligo. Adapted from BAD Guidelines for the Management of People with Vitiligo (2021)

Vitiligo (NSV and SV)	Definition	Recommendations
Stable	The following criteria should be met:[a] • No new lesions developing within the last 12 months; • Lack of progression of old lesions within the last 12 months.	[a]Assessment of overall stability is inaccurate and unreliable, whereas individual lesion stability is more reliable. Ideally, stability should be assessed using a patient self-reporting, clinical scoring system (e.g. VASI or VETF) and serial digital imaging of specific lesions
Progressive	New lesions developing or old vitiliginous lesions progressing within the last 12 months[a]	
Rapidly progressive	No international consensus exists; **abrupt** deterioration in developing new lesions or increase in size of old lesions	-

Regressive	Spontaneous repigmentation of existing vitiliginous lesions	-

- The quality of life and level of psychological distress associated with living with vitiligo are to be assessed and monitored using the following tools: Patient Health Questionnaire-4 (PHQ-4), Patient Health Questionnaire-9 (PHQ9), Generalized Anxiety Disorder 7 (GAD7) and Dermatology Life Quality Index (DLQI), and more specifically the Vitiligo Impact Patient Scale (VIPs) or the vitiligo-specific quality-of-life instrument (VitiQoL). **(↑↑)**
- Treatment response of progression of the disease are evaluated through medical photography/digital imaging of the skin of patients with vitiligo. The imaging is taken at the initiation of treatment and at intervals of 3-6 months. **(GPP)**
- HCPs are to offer sunscreen with 4-star or 5-star UVA rating and sun protection factor of 50 to vitiligo patients, to be applied to affected patches and surrounding skin prior to sun exposure. **(GPP)**

Pharmacological Therapy

- The first line treatment in primary or secondary care of vitiligo is a **potent/very potent topical corticosteroid** once daily all while avoiding the periocular area. **(↑↑)**
- In patients with facial vitiligo, **topical tacrolimus 0.1% ointment** twice daily is recommended. The ointment can also be used as an alternative to topical corticosteroids. **(↑)**
- Topical tacrolimus 0.1% ointment twice daily under occlusion on photo exposed areas is also recommended for patients with nonfacial vitiligo as an alternative to corticosteroids. **(↑)**
- After having weighed the risk versus benefits, HCPs may consider an intermittent regimen of a once daily application of topical corticosteroids with or without TCIs.

  Intermittent regimens are considered for patients with vitiligo in areas with thinner skin such as the periocular region, genital area and skin flexures.

  Intermittent regimens include:

  - One week of potent or very potent corticosteroids and at least 1 week off

  OR

    - One week of potent or very potent topical corticosteroids alternating with ≥ 1 week of topical calcineurin inhibitor **(GPP)**

- The use of topical treatments is reassessed at an interval of 3-6 months to check for improvement. **(GPP)**
- There is insufficient evidence to support the use of topical vitamin D analogues in people with vitiligo. **(θ)**
- After having conducted psychological assessment and/or intervention , **depigmentation therapies** may be considered in patients with extensive vitiligo and a substantial negative psychological impact. **(GPP)**
- For patients with rapidly progressive vitiligo, **oral betamethasone** 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg per month for a further 3 months **in combination with NB-UVB** may be considered in order to arrest disease activity. **(↑)**

  An equivalent dose of **alternative oral corticosteroids** may be considered if betamethasone is not available. **(GPP)**
- In case of extensive/progressive disease and an inadequate response to topical therapy, HCPs may consider starting the patient on **NB-UVB** as first-line phototherapy.

  Combination therapy with topical corticosteroids or topical calcineurin inhibitors may be considered for localized sites. **(↑↑)**
- If NB-UVB is unavailable or in case of lack of responsiveness, **PUVA or PUVAsol** may be considered in adults with vitiligo. **(↑)**
- In patients with localized vitiligo, **excimer laser or light** may be considered in combination with **topical calcineurin inhibitors**.

  Patients are to be informed about the heightened risk of development of skin cancer that accompanies the combination regimen.
- If adults with nonsegmental vitiligo on the hands and feet are non-responsive to other treatments, **CO2 laser in combination with 5-fluorouracil** may be considered. The regimen is as follows: Apply 5-fluorouracil once daily for 7 days per month for 5 months; CO2 laser treatments once a month for 5 months.

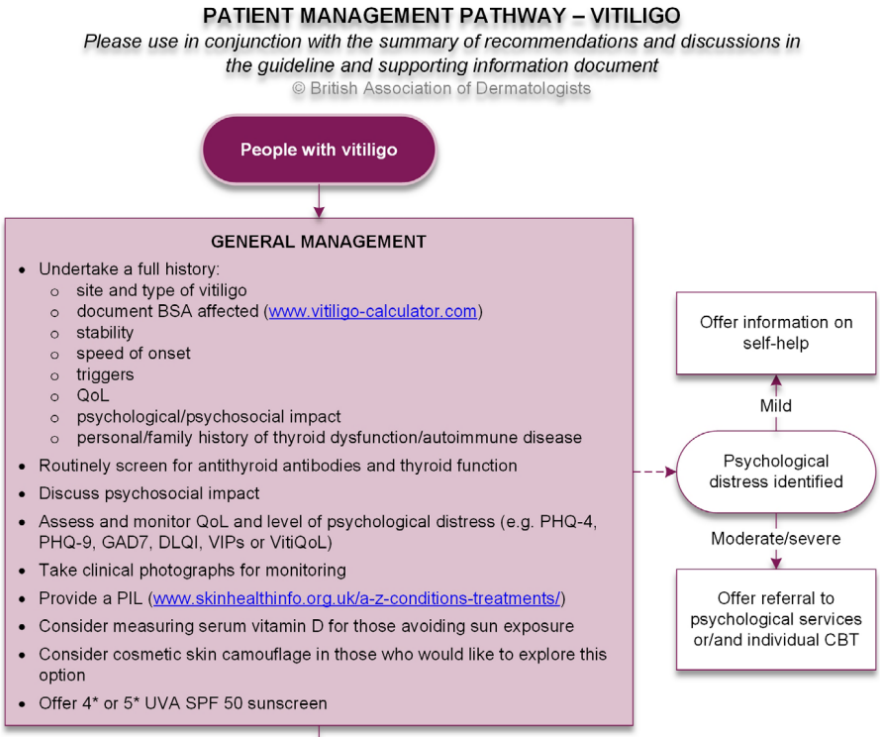
<u>Surgical Therapies</u>

- In patients with stable, segmental, or non-segmental vitiligo who do not respond to other treatments, cellular grafting as blister grafting or cell suspension may be considered. **(↑)**

Skin Camouflage Therapy

- Skin camouflage may be considered for patients who are willing to explore that option. **(↑)**

The BAD has proposed the following algorithm for the management of Vitiligo:



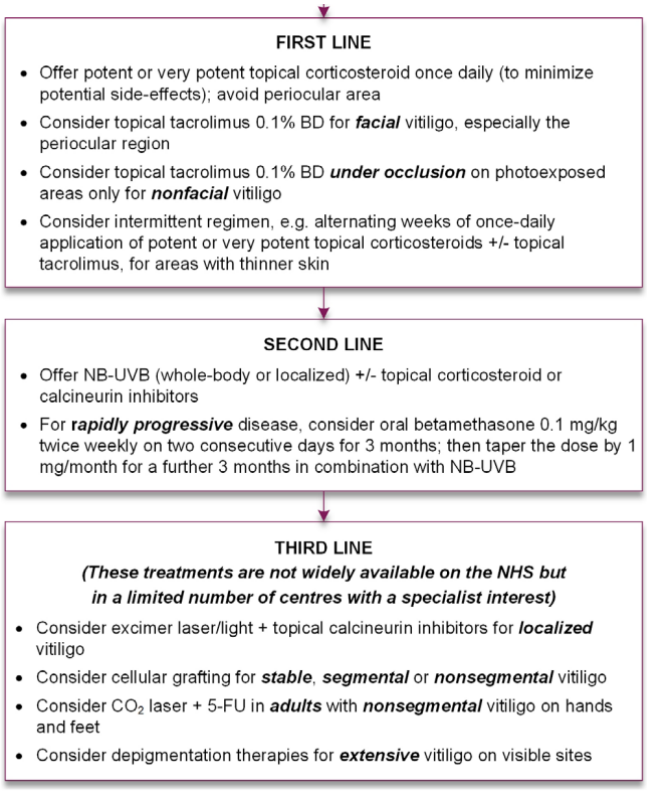


Figure 3. *Management Pathway for People with Vitiligo. Retrieved from BAD Guidelines for the Management of People with Vitiligo (2021).*

1.3.3 Guidelines for the Management of Vitiligo: The European Dermatology Forum Consensus (2012)

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The European Dermatology Forum (the writing group of the Vitiligo European Task Force [VETF] in cooperation with the European Academy of Dermatology and Venereology [EADV] and the Union Européenne des Médecins Spécialistes [UEMS]) has issued guidelines for the management of vitiligo. The issued recommendations are detailed below[12]:

<u>The Use of Topical Corticosteroids</u>

- For children and adults with limited extrafacial involvement, a once daily application of potent corticosteroids is advised; not exceeding a 3-month treatment duration.

  A discontinuous treatment regimen may be opted; 15 days per month for 6 months with a strict assessment of response based on photographs.

- The use of Mometasone Furoate or Methylprednisolone Aceponate are the preferred treatment options whereby both have negligible systemic effects.

The Use of Topical Ascomycin Immunomodulating Macrolactams

- For adults and children with new and actively spreading lesions on the skin, TIM may be considered as an alternative to topical steroids; to be applied topically twice daily with a treatment duration of 6 months. Longer treatment durations of 12 months may be suggested if moderate and daily sun exposure is deemed effective.
- The use of TIM should be restricted to selected areas such as the head and neck regions.

Phototherapies

- Photochemotherapy:
    - For adults with generalized vitiligo, oral PUVA is recommended as a second line therapy.
    - Oral KUVA has fallen out of practice since it has been associated with significant hepatotoxicity.
    - For patients with generalized NSV, NB-UVB is recommended.

      Total body treatment with NB-UVB is suggested for active spreading vitiligo and for lesions covering > 15-20% of the body surface area.
    - For localized vitiligo and childhood-onset vitiligo, targeted phototherapies are recommended.

      These targeted phototherapies are recommended in cases where total body irradiation is contraindicated.
    - If no repigmentation is achieved within the first 3 months of treatment or in case the patient achieves < 25% repigmentation after 6 months of treatment, irradiation is stopped.
    - The maximum duration of phototherapy is 1-2 years; maintenance irradiation is not recommended.

Combination Therapies

- Topical Steroids and Phototherapy:

  TCS and UVB sources such as NB-UVB and 308 nm excimer lasers or lamps may be used for the treatment of lesions found in challenging areas, especially those over bony prominences.

TCS are to be applied once daily (3 weeks out of 4) to lesions for the first 3 months of phototherapy.

- TCI and Phototherapy:

  The combination of TCI and UV radiation has been found to be superior to the use of each agent as monotherapy.

- Vitamin D Analogues and Phototherapy:

  The combination of Vitamin D and phototherapy has not been recommended due to its limited efficacy.

- Phototherapy After Surgery:

  In order to enhance repigmentation, phototherapy is recommended to be used for 3 to 4 weeks following surgical procedures.

Oral Mini-Pulse Therapy

- For fast-spreading vitiligo, weekend OMP starting with low doses (2.5 mg daily) of dexamethasone may be considered; To stop vitiligo progression, the optimal duration of OMP therapy is between 3 and 6 months.

Antioxidant Supplementation

- During the reactivation phase of vitiligo and during UV therapy, antioxidant supplementation may be useful.

Surgical Interventions

- Surgery should be opted for following the failure of standard pharmacological therapy, specifically for patients with SV or other forms of localized vitiligo.
- Patients with the stable form of NSV and a negative history of Koebner Phenomenon are eligible or surgery but are subject to a higher risk of relapse.

Depigmenting Agents

- After having opted for other treatment lines/regimens, patients with extensive disfiguring vitiligo should be offered the possibility of depigmentation.
- Monobenzone is a potent depigmenting agent and not a cosmetic skin bleach
- Depigmentation can also be obtained by using a Q-switched ruby laser, alone or in combination with methoxyphenol.

Other Interventions

- Camouflage may be an appropriate cosmetic approach whereby the following options are used: Self-tanning agents (Gel, cream, lotion, spray), highly pigmented cover creams, dermal pigmentation, and cosmetic tattoos.
- Psychological intervention may help with the stigma and mental distress.

Figure 4 outlines the treatment algorithms for both SV and NSV.

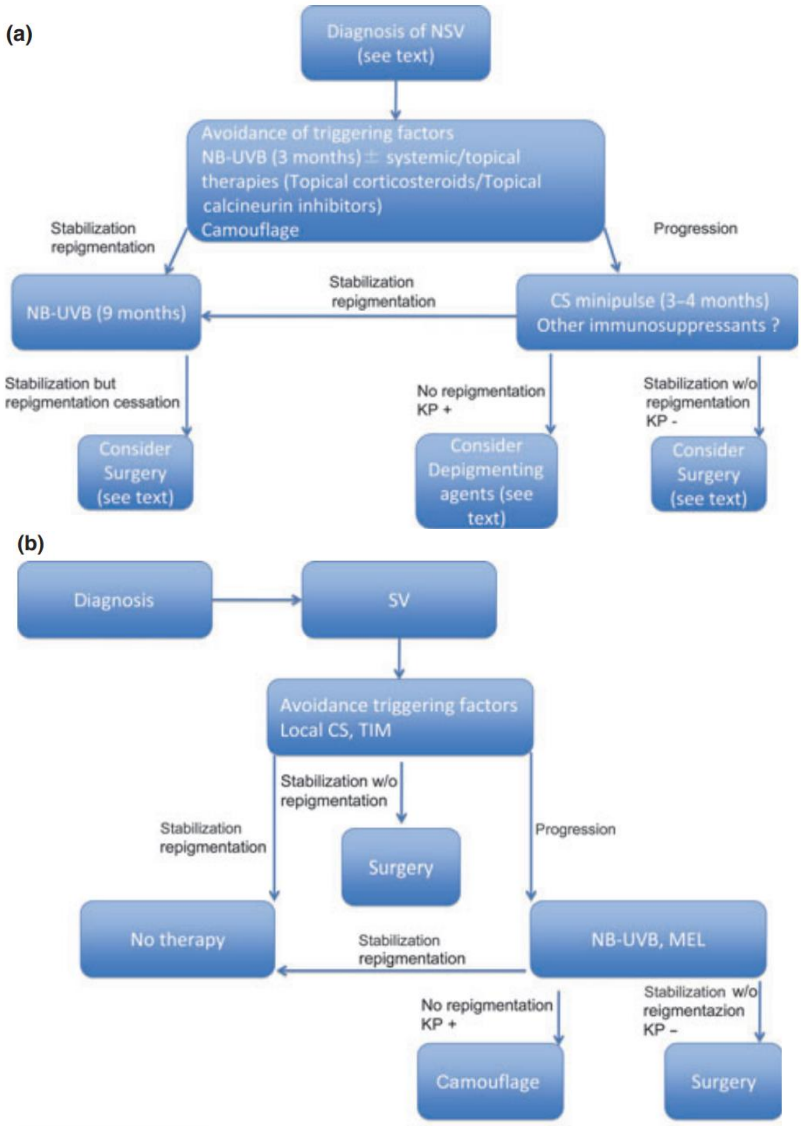


Figure 4. *Treatment Algorithms for the Management of Patients with nonsegmental vitiligo (NSV) (a) or segmental vitiligo (SV) (b). Retrieved from the European Dermatology Forum Consensus (2012)*

1.4 International Guidelines

1.4.1 Guidelines for the Diagnosis and Treatment of Vitiligo in Japan [2013]

The Vitiligo Japanese Task Force was organized for the proposition of the guideline for the diagnosis and the treatment of vitiligo in cooperation with the Japanese Dermatology Association (JDA)[11]; the following grades of recommendation and levels of evidence were opted:

Table 6. Japanese Dermatology Association Grade of Recommendation/Level of Evidence

Criteria for Levels of Evidence and Grades of Recommendation	
Levels of evidence	
I	Systematic review or meta-analyses
II	One or more randomized controlled trial(s)
III	Controlled study without randomization
IV	Analytical epidemiological studies (cohort studies and/ or case–control studies)
V	Descriptive studies (case reports and/or case accumulation studies)
VI	Expert committee reports or opinions from each specialist
Grades of recommendation	
A	Strongly recommended to perform (there should be at least one level I or II study that indicates effectiveness)
B	Recommended to perform (there should be at least one level II study of low quality, level III of good of quality or level IV of extremely good quality that indicates effectiveness)
C1	Can be considered for use, but there is insufficient evidence (level III–IV evidence of low quality, plural level V of good quality or level IV approved by the committee)
C2	Not recommended for use because there is no evidence (there is no evidence that indicates effectiveness or there is evidence that indicates no effects)
D	Recommended to avoid (there is good evidence that indicates no effect or harmful effects)

Topical Corticosteroids

- Topical corticosteroids are effective first line agents for mild or moderate vitiligo present on 10-20% of the body surface area. **(Grade A)**
- Class 4 (Medium) corticosteroids are suggested to be applied to lesions once daily for 4 months in patients aged 15 years or below. **(Grade A)**
- Class 2 (Very Strong) or Class 3 (Strong) corticosteroids are recommended to be applied to lesions for 4-6 months in patients aged 16 and above. **(Grade A)**
- Shifting to a second line or alternative therapy is deemed appropriate if there is no repigmentation after 2 months of topical corticosteroid treatment. **(Grade A)**
- Phototherapy with NB-UVB is the first-line treatment for patients with NSV. **(Grade B)**

Topical Vitamin D3 Analogs

- The use of topical Vitamin D3 analogs in combination with phototherapy (PUVA or NB-UVB) is deemed effective. **(Grade C1)**
- Monotherapy with topical Vitamin D3 is also used; however, it is less efficient than the combination therapy. **(Grade C2)**

Topical Tacrolimus

- The use of TCI (specifically Tacrolimus) applied topically twice daily with occlusion has been deemed effective for the management of vitiligo; its use should be evaluated 3 or 4 months after initial use. **(Grade B)**
- Combination therapy with phototherapy is **contraindicated** in Japan.

Phototherapy

- PUVA therapy is effective for the management of Vitiligo. **(Grade B)**
- NB-UVB is used as a first line regimen in adult patients with vitiligo. **(Grade B)**
- It is suggested that NB-UVB therapy is superior to PUVA therapy, with higher efficacy, lower disease recurrence and lower occurrence of adverse reactions. **(Grade B)**
- In children with vitiligo, the course of NB-UVB is not to exceed 12 months. (Or 200 treatments) If the patient is not responding to therapy 6 months after initiation, then phototherapy continuation is discouraged.
- 308-nm excimer laser or light therapy is useful for spotted and patched vitiligo lesions and on lesions where repigmentation is expected. **(Grade C1)**

Oral Corticosteroids

- Oral corticosteroids are deemed effective for the management of vitiligo. **(C1)**
- Kim et al's[21] proposed regimen: The dose of oral prednisolone (0.3 mg/kg) was given initially for 2 months, then half of the initial dose was given for the third month, and the dose was halved again for the fourth and final month. This therapy induced repigmentation in 70.4% of vitiligo patients.

Grafting and Surgical Treatment

- Grafting and surgical treatments should only be performed for stable and treatment-resistant vitiligo on cosmetically sensitive regions. **(Grade A-C1)**
- Surgical options include:
    - Split-thickness skin grafting (Best option when surgical treatment is required)
    - Epidermal grafting
    - Mini-grafting (Not recommended due to poor cosmetic results and side effect profile)
    - Autologous non-cultured melanocyte-keratinocyte cell transplantation/injection
    - Autologous cultured melanocyte transplantation/ injection **(Grade A-C1)**
- The treatment of vitiligo has improved with the use of epithelial cell suspensions (**ReCell®**, Spray-On Skin; Avita Medical, Cambridge, UK) for autologous non-cultured melanocyte-keratinocyte cell transplantation/injection and autologous cultured melanocyte transplantation/injection. **(Grade A-C1)**

The treatment algorithm followed by the JDA is detailed in figure 5.

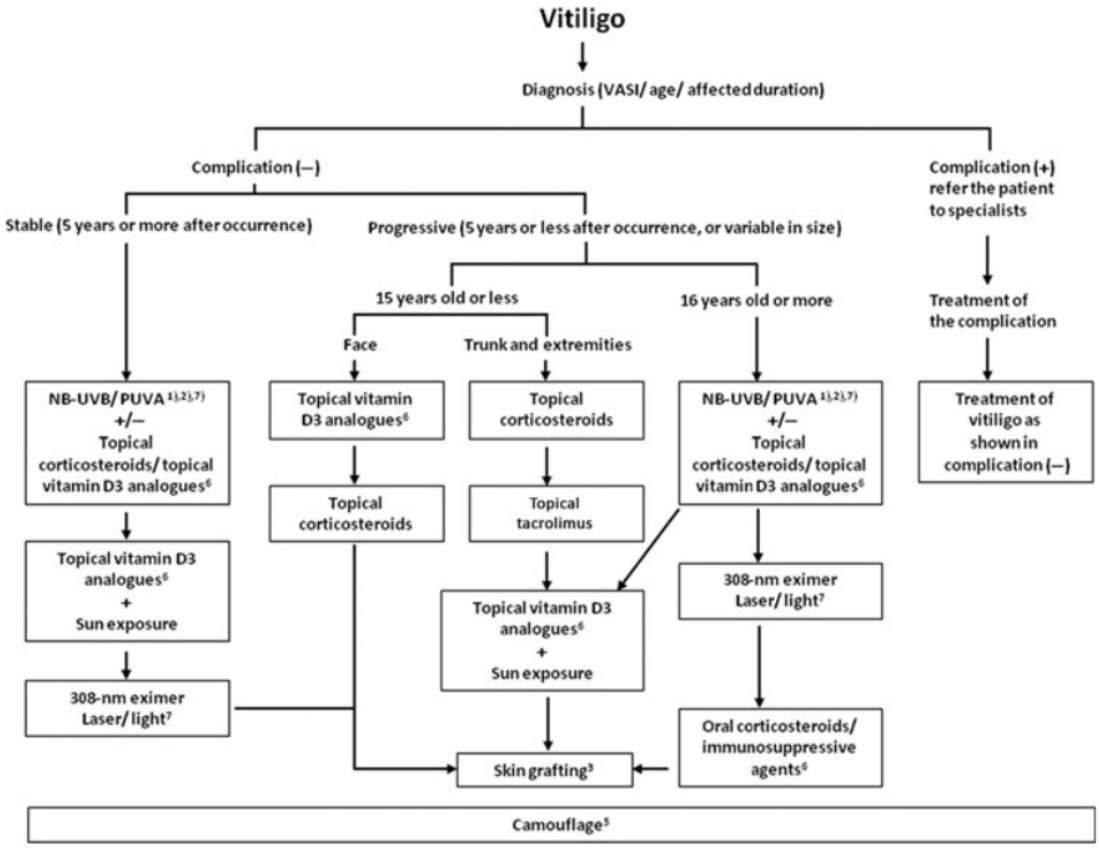


Figure 5. *Treatment Algorithm for Vitiligo. Retrieved from the JDA Guidelines for Vitiligo (2013)*

Alternative Therapy:

- Camouflage has proven effective in enhancing the quality of life of vitiligo patients. **(Grade C-1)**
- Topical bleaching agents may also be used for generalized stable and treatment resistant vitiligo. **(Grade C-1)**

1.4.2 Consensus on the Diagnosis and Treatment of Vitiligo in China (2021)

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The Vitiligo Expert Group of the Dermatovenereology Professional Committee and Chinese Society of Integrated Chinese and Western Medicine have released a consensus for the management of Vitiligo in China; the recommendations are detailed below[15]:

Rules for Disease Management

1. **Active Phase of Vitiligo**

    a. **Unclassified Vitiligo**

For unclassified vitiligo, the preferred treatments include 308 nm excimer laser therapy, MEL therapy, and NB-UVB therapy.

Unclassified vitiligo is managed with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) such as Tacrolimus and Pimecrolimus. Additionally, topical application of 0.1% 8-methoxypsoralen or other psoralen-containing preparations and topical vitamin D3 derivatives are also options. In cases of rapid progression, systemic corticosteroids should be considered as an early intervention to arrest the spread of vitiligo.

    b. **NSV and Mixed Vitiligo**

The treatment options available include TCS, TCI, systemic corticosteroids (For patients with a VIDA score > 3), NB-UVB, 308 nm excimer laser, and MEL.

For phototherapy, the starting dose should be set at half or one-third of the standard dosage used for routine treatment in patients with rapid disease progression.

Vitiligo enlargement (May potentially be induced by phototherapy-triggered oxidative stress) can be prevented by concomitant administration of systemic corticosteroids and antioxidants.

    c. **SV**

For patients with treatment resistant and stable SV, surgical treatment is recommended.

Surgical approaches include suction blister autologous epidermal grafting, mini-grafting, ultrathin epidermal grafts, and transplantation of autologous epidermal cell suspension or melanocytes.

2. **Stable Phase of Vitiligo**

    a. **Unclassified Vitiligo**

Treatment options for unclassified vitiligo include topical photosensitizers (Methoxsalen, 8-Methoxypsoralen), TCS, TCI, and vitamin D3 analogs. Autologous epidermal grafting or transplantation of autologous cultured melanocytes are also recommended.

b. NSV and Mixed Vitiligo

Phototherapies, autologous epidermal grafting, or autologous melanocyte transplantation are recommended with treatment preferably administered at the exposed sites or regions of interest.

Topical medications are prescribed for NSV and mixed vitiligo in accordance with the recommendations for stable unclassified vitiligo.

c. SV

For patients with stable SV, autologous epidermal grafting and autologous melanocyte transplantation are recommended.

Other treatment options include surgical approaches including suction blister mini-grafting, ultrathin epidermal grafts, and transplantation of autologous cultured epidermal cell suspension.

Childhood Vitiligo

- In children aged less than 2 years, moderate potency topical corticosteroids are recommended for treatment. The regimen would preferably be intermittent to prevent any potential adverse drug reactions or side effects.
- In children older than 2 years, high potency or moderate potency topical corticosteroids are recommended.
- TCIs may also be used; specifically, Tacrolimus and Pimecrolimus.
- Topical Vitamin D may also be opted for as a treatment option in children.
- In case of rapidly progressive vitiligo, appropriate treatment would include a low dose of oral prednisone (5–10mg per day) for 2– 3 weeks, re-administration may take place after an interval of 4–6 weeks if need be.
- Phototherapy may be considered in children.

Maintenance Therapy

- Following the achievement of complete or satisfactory repigmentation, maintenance therapy is required for an additional 3-6 months.
- To prevent disease relapse and re-depigmentation, TCIs may be used once or twice weekly for 3-6 months.
- Once maximum repigmentation has been achieved, maintenance phototherapy treatment should be continued twice a week for the first month, once a week for the second month, and once every 2 weeks for subsequent months.

1.4.3 Consensus on the Treatment of Vitiligo – Brazilian Society of Dermatology (2020)

The Brazilian Society of Dermatology has issued guidelines for the management of vitiligo; the recommendations are detailed below[14]:

Topical Corticosteroids

- For localized unstable vitiligo, the first line therapy would consist of monotherapy with topical corticosteroids.
- TCS may be used concomitantly with phototherapy in generalized lesions.
- Facial lesions and lesions that are limited in size respond best to treatment.
- After 8 weeks of continuous topical corticosteroid use, it is recommended that another topical agent is introduced. (Rotational therapy)

  This helps with reducing exposure to the potential harm associated with prolonged TCS use, specifically their side effect profiles.
- Treatment interruption is recommended if repigmentation is not achieved after 3 months of initiation of therapy.

Calcineurin Inhibitors

- TCIs have been shown to be safe and effective for the treatment of vitiligo; specifically, Tacrolimus and Pimecrolimus. The face and photo-exposed areas are mostly responsive.
- TCIs are the first-choice agents for the treatment of lesions on the head and neck; they are to be applied twice daily.
- TCIs are to be applied twice weekly as maintenance therapy following phototherapy.
- The FDA included a black box warning on the medication package as a preventive measure, due to the theoretical risk of lymphoma and non-melanoma skin cancer, based on studies in animal models and the use of a systemic calcineurin inhibitor.

Other Topics

- No consensus was reached on the use of Calcipotriol, Pseudocatalase, and Khellin.

Systemic Therapies

- Oral corticosteroids may be used to contain the progression of lesions in patients with active disease, and to induce repigmentation.
- Oral mini-pulses of corticosteroids may be used such as betamethasone or dexamethasone.
- Dexamethasone regimen: 2.5 to 10 mg for two consecutive days/week for three to six months.
- Betamethasone regimen: 5 to 7.5 mg for two consecutive days/week for three to six months.

Phototherapy

- In both unstable and stable vitiligo, a combination of phototherapy and systemic corticosteroid therapy, preferably in the form of OMP is recommended. Antioxidants may be added to the treatment regimen.
- TCIs and TCS may be used concomitantly with phototherapy. (Tacrolimus may not be used immediately before irradiation)
- NB-UVB or PUVA are recommended in patients with extensive generalized vitiligo.
- In localized vitiligo, it is recommended to use emitters of NB-UVB or local UVA, aimed only at the lesions. ExLs and ExLp are also recommended for this type of localized lesion.
- Children may be subject to topical PUVA.
- In pregnant women, no teratogenicity was linked to the use of PUVA; therefore, it should be used as a second option in phototherapy.
- Pregnant women may also be treated with NB-UVB. (First choice)
- ExLP is characterized by a larger treatment field compared to ExLS; therefore, HCPs are able to treat larger areas in a shorter period of time.
- A minimum of 6 months of treatment is required to evaluate the effectiveness of phototherapy.
- A maximum response may be achieved with a longer treatment time of one year.

Surgical Therapy

- Surgical therapy is indicated for stable cases that are non-responsive to clinical treatments; patients with SV may be more responsive to surgical approaches.

- The choice of the surgical approach depends on several factors including but not limited to the size of the lesion, the anatomical area to be treated, and the surgeon's experience.

Treatment in Children, Pregnant Women, Nursing Mothers and Elderly

- In the pediatric and pregnant populations, the use of NB-UVB is recommended over PUVA. This is attributed to better effectiveness of NB-UVB and lower incidence of side effects and carcinogenesis.
- Phototherapy is suggested to be initiated in children if they exhibit little or no response to topical therapy, rapid progression of the disease and the ability to collaborate with HCPs for therapy initiation.

  Patients are required to be aged older than 7 years.
- Combination therapy using TCIs and phototherapy may be suggested; however, the risk of carcinogenesis is to be taken into consideration.
- The use of oral corticosteroids is associated with an elevated incidence of fractures both in the pediatric and elderly patient populations. Therefore, its use must be moderate and avoided in patients with moderate to high risk for fractures.
- Oral corticosteroids were also deemed Category C for pregnant patients; therefore, their use is not recommended.
- In children, TCIs applied twice daily are preferred specifically when treating areas as the face, neck and intertriginous areas.
- Topical medium-potency and high-potency corticosteroids are the first line therapy for pediatric vitiligo on the body, except for intertriginous and genital sites.
- Children with a high phototype and facial lesions are prescribed intermittent regimens with 2–3-week intervals for a maximum of 6 months.
- In pregnant or lactating patients with vitiligo, a cautious use of TCS of mild-potency or moderate-potency is indicated.

  HCPs are to be cautious in terms of reduced time and area of treatment.
- Topical tacrolimus can be suggested as a second line agent in pregnant or lactating patients.
- In elderly patients, a combination of topical therapy and phototherapy are recommended.

The following treatment algorithm was proposed by the Brazilian Society of Dermatology:

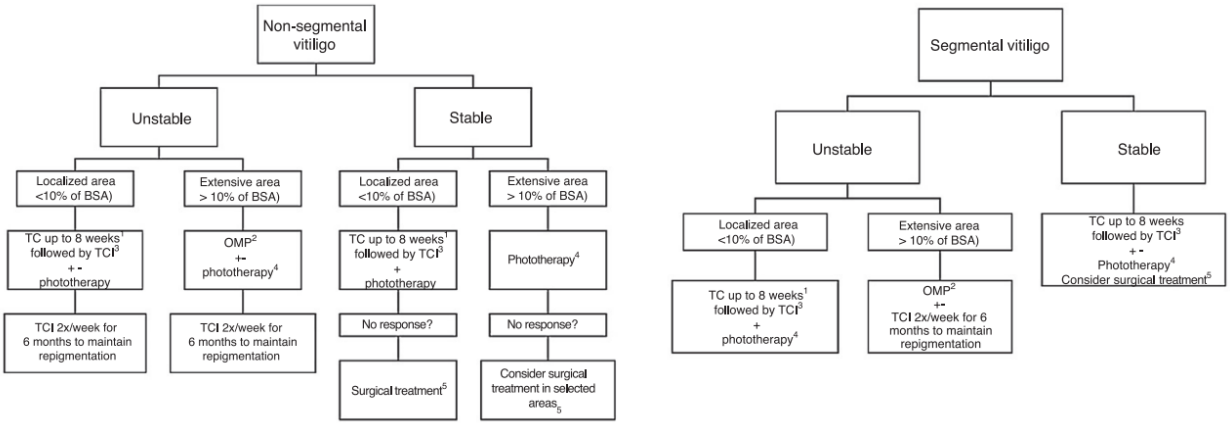


Figure 6. *Brazilian Society of Dermatology Treatment Algorithm for Vitiligo. Retrieved from the Brazilian Society of Dermatology Consensus on the Treatment of Vitiligo (2020)*

1.5 Systematic Reviews & Meta Analyses

The table below details a systematic review and meta-analysis issued in **2023 and 2020 respectively** for Vitiligo.

Table 7. Systematic Reviews and Meta-Analyses for Vitiligo

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Huang et al. (2023)[22]	"Compound Glycyrrhizin Tablets Combined with the 308 Nm Excimer Laser in the Treatment of Vitiligo: A Systematic Review and Meta-Analysis"	To determine the clinical efficacy of compound glycyrrhizin tablets combined with the 308 nm excimer laser in the treatment of vitiligo.	**Primary outcome measures:** Clinical effectiveness and adverse events (AEs). **Secondary outcome measures:** Changes in the T helper cell 17 (Th17) and Treg subsets before and after treatment. Efficiency, high efficiency, and	In the treatment of vitiligo, compound glycyrrhizin tablets combined with the 308 nm excimer laser are more effective than the 308 nm excimer laser alone OR = 3.33, p< 0.00001, 95% confidence interval [2.25, 4.92], and there are no serious adverse reactions. It is a safe and efficient way of treatment.

				cure were defined as effective treatments.	
2	Phan et al. (2020)[23]	"Repigmentation in Vitiligo Using Janus Kinase (JAK) Inhibitors with Phototherapy: Systematic Review and Meta-Analysis"	To determine the expected response of vitiligo to JAK inhibitor therapy and factors which influence response rates.	The main outcome studied was response to treatment; whereby, good response was defined as repigmentation >50% or a "good" or "excellent" outcome and partial response was defined as some repigmentation <50%.	Good response was achieved in 57.8%, partial response in 22.2%, and none or minimal response in 20% of cases. When subgrouped according to site, facial vitiligo had the highest good response rate (70%), compared to extremities (27.3%) and torso/non-sun exposed areas (13.6%). Concurrent phototherapy was significant associated with higher rates of good overall response (P<0.001) and good facial response (P<0.001). There is promising low-quality evidence regarding the effectiveness of JAK inhibitors in vitiligo. Concurrent UVB phototherapy appears to improve efficacy of JAK inhibitors for vitiligo.

Section 2.0 Drug Therapy

2.1 Topical Corticosteroids

2.1.1 Mometasone Furoate

Information on Mometasone Furoate is detailed in the table below[24,25]:

Table 8. Mometasone Furoate Drug Information

SCIENTIFIC NAME MOMETASONE FUROATE	
SFDA Classification	Prescription
SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80
Drug Class	Corticosteroids, Plain
Drug Sub-class	Corticosteroids, Potent (Group III)
ATC Code	D07XC03
Pharmacological Class (ASHP)	Topical Corticosteroids
DRUG INFORMATION	
Dosage Form	Cream, Ointment, Solution
Route of Administration	Topical
Dose (Adult) [DDD]*	Once daily application for 3-6 months
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Once daily application for 3 months
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE, MD, QL
AGE (Age Edit)	The use of topical Mometasone Furoate is not recommended in patients less than 2 years of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A

MD (Physician Specialty Edit)	Mometasone Furoate should be prescribed by a physician who has experience in the treatment of Vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Treatment is to be carried out up until a maximum of 6 months in adults and 3 months in pediatric patients.
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Burning, pruritus, and skin atrophy. **Most serious:** Paresthesia, dyschromia, telangiectasia, bacterial skin infections.
Drug Interactions*	**Category X:** Aldesleukin
Special Population	**Older Adults:** Because of the risk of adverse effects associated with systemic absorption, topical corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration. **Pediatrics:** Children may absorb proportionally larger amounts after topical application and may be more prone to systemic effects. HPA axis suppression, intracranial hypertension, and Cushing syndrome have been reported in children receiving topical corticosteroids. Prolonged use may affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	In general, use of the least potent product in limited amounts is recommended during pregnancy. Mild to moderate potency corticosteroids are preferred; potent to very potent topical corticosteroids should only be used as

	alternative therapy in limited amounts under obstetrical care. Pregnant patients should avoid application of topical corticosteroids to areas with high percutaneous absorption and caution should be used when applying to areas prone to striae formation.
Lactation	Although the manufacturer recommends that caution be used, topical corticosteroids are generally considered acceptable for use in patients who are breastfeeding. Avoid application of topical corticosteroids to the nipple and areola area until breastfeeding ceases.
Contraindications	Hypersensitivity to mometasone furoate or any component of the formulation. Viral lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations relating to tuberculosis or syphilis, eruptions following vaccinations, acne vulgaris, rosacea, pruritus without inflammation; ophthalmic use; use with occlusive dressings.
Monitoring Requirements	Adrenal suppression with extensive/prolonged use (ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test); response to treatment; ocular changes.
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. **Contact dermatitis:** Allergic contact dermatitis can occur and is usually diagnosed by failure to heal rather than

	clinical exacerbation; discontinue use if irritation occurs and treat appropriately. **Immunosuppression:** Prolonged use may result in fungal or bacterial superinfection; discontinue if dermatological infection persists despite appropriate antimicrobial therapy. **Ocular effects:** Topical corticosteroids, including mometasone, may increase the risk of posterior subcapsular cataracts and glaucoma. Monitor for ocular changes. Avoid contact with eyes. **Systemic effects:** Topical corticosteroids may be absorbed percutaneously. Absorption of topical corticosteroids may cause manifestations of Cushing's syndrome, hyperglycemia, or glycosuria. Absorption is increased by the use of occlusive dressings, application to denuded skin, or application to large surface areas.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Mometasone Furoate.**

Table 9. Mometasone Furoate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Mometasone Furoate	NICE	Not available
	CADTH	Not available

	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Mometasone Furoate

Mometasone Furoate is used off-label as a **first line** management for Vitiligo. It is applied topically once daily for a maximum duration of 6 months in adults and 3 months in children. Its use is limited by the heightened risk of paresthesia, dyschromia, telangiectasia, bacterial skin infections.

2.1.2 Methylprednisolone Aceponate

Information on Methylprednisolone Aceponate is detailed in the table below[24,25]:

Table 10. Methylprednisolone Aceponate Drug Information

SCIENTIFIC NAME METHYLPREDNISOLONE ACEPONATE	
SFDA Classification	Prescription
SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80
Drug Class	Corticosteroids, Plain
Drug Sub-class	Corticosteroids, Potent (Group III)
ATC Code	D07AC14
Pharmacological Class (ASHP)	Topical Corticosteroids
DRUG INFORMATION	
Dosage Form	Cream
Route of Administration	Topical
Dose (Adult) [DDD]*	Methylprednisolone Aceponate is applied thinly once per day to the diseased areas of skin. In general, the duration of use should not exceed 12 weeks in adults.
Maximum Daily Dose Adults*	N/A

Dose (pediatrics)	Methylprednisolone Aceponate is applied thinly once per day to the diseased areas of skin. The duration of use should not exceed 4 weeks in children.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment is necessary.
Prescribing edits*	AGE, MD, QL
AGE (Age Edit)	The safety of Methylprednisolone Aceponate cream in children below the age of 3 years has not been established.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Methylprednisolone Aceponate is to be prescribed by a physician who has experience in the treatment of vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	In general, the duration of use should not exceed 12 weeks in adults and 4 weeks in children.
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Application site burning and pruritus. **Most serious:** Skin atrophy, telangiectasia, perioral dermatitis, and folliculitis.
Drug Interactions*	No noted drug interactions.
Special Population	**Older Adults:** Because of the risk of adverse effects associated with systemic absorption, topical corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration. **Pediatrics:** Children may absorb proportionally larger amounts after topical application and may be more

	prone to systemic effects. HPA axis suppression, intracranial hypertension, and Cushing syndrome have been reported in children receiving topical corticosteroids. Prolonged use may affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	The use of topical preparations containing corticoids should be avoided during the first trimester of pregnancy. Treating large areas, prolonged use or occlusive dressings should be avoided during pregnancy. The clinical indication for treatment must be carefully reviewed and the benefits weighed against the risks in pregnant women.
Lactation	Caution should be exercised when administered to a nursing woman. Nursing mothers should not be treated on the breasts. Treating large areas, prolonged use or occlusive dressings should be avoided during lactation.
Contraindications	Tuberculous or syphilitic processes in the area to be treated; viral diseases (e.g., varicella, herpes zoster), rosacea, perioral dermatitis, ulcers, acne vulgaris, atrophic skin diseases and postvaccination skin reactions in the area to be treated. Hypersensitivity to the active substance or to any of the excipients.
Monitoring Requirements	Adrenal suppression with extensive/prolonged use (ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test); response to treatment; ocular changes.
Precautions	Additional specific therapy is required in bacterially infected skin diseases and/or in fungal infections.

	Contact with the eyes, deep open wounds and mucosae is to be avoided. After application of Methylprednisolone aceponate 0.1% ointment to 60 % skin surface area under occlusive conditions for 22 hours, suppression of plasma cortisol levels and influence on circadian rhythm was observed in adult healthy volunteers. Extensive application of topical corticosteroids to large areas of the body or for prolonged periods of time, in particular under occlusion, significantly increases the risk of systemic side effects. Methylprednisolone aceponate cream is also not recommended for use in children under 3 years of age. As known from systemic corticoids, glaucoma may also develop from using local corticoids (e.g., after large-dosed or extensive application over a prolonged period, occlusive dressing techniques, or application to the skin around the eyes). Two excipients contained in Methylprednisolone aceponate 0.1% cream (Cetostearyl alcohol and butyl hydroxytoluene) may cause local skin reactions (e.g., contact dermatitis). Butyl hydroxytoluene may also cause irritation in the eyes and mucous membranes.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health

Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methylprednisolone Aceponate.**

Table 11. Methylprednisolone Aceponate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methylprednisolone Aceponate	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Methylprednisolone Aceponate

Methylprednisolone Aceponate is used off-label as a first line management for Vitiligo. It is applied thinly once per day to the diseased areas of skin.
In general, the duration of use should not exceed 12 weeks in adults and 4 weeks in pediatric patients. Its use is limited by the heightened risk of skin atrophy, telangiectasia, perioral dermatitis and folliculitis.

2.1.3 Betamethasone Valerate

Information on Betamethasone Valerate is detailed in the table below[24,25]:

Table 12. Betamethasone Valerate Drug Information

SCIENTIFIC NAME BETAMETHASONE VALERATE	
SFDA Classification	Prescription
SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80
Drug Class	Corticosteroids, Plain
Drug Sub-class	Corticosteroids, Potent (Group III)
ATC Code	D07AC01
Pharmacological Class (ASHP)	Topical Corticosteroids
DRUG INFORMATION	

Dosage Form	Cream, Ointment, Cutaneous Suspension
Route of Administration	Topical
Dose (Adult) [DDD]*	May be applied once or twice daily to the affected area.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	May be applied once or twice daily to the affected area.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE, QL, MD
AGE (Age Edit)	Betamethasone Valerate is not recommended to be used in children less than 1 year of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Betamethasone Valerate is to be prescribed by a physician who is experienced in the treatment of vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Ointment dose may not exceed 50g a week.
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Skin atrophy, burning, irritation. **Most serious:** Paresthesia, dermatitis, telangiectasia.
Drug Interactions*	**Category X:** Aldesleukin
Special Population	**Pediatrics:** Use of augmented formulations in patients <13 years of age is not recommended. For all formulations, children may absorb proportionally larger amounts after

	topical application and may be more prone to systemic effects. HPA axis suppression, intracranial hypertension, and Cushing syndrome have been reported in children receiving topical corticosteroids. Prolonged use may affect growth velocity; growth should be routinely monitored in pediatric patients. Use lowest dose possible for shortest period of time to avoid HPA axis suppression.
Pregnancy	In general, use of the least potent product in limited amounts is recommended during pregnancy. Mild to moderate potency corticosteroids are preferred; potent to very potent topical corticosteroids should only be used as alternative therapy in limited amounts under obstetrical care. Pregnant patients should avoid application of topical corticosteroids to areas with high percutaneous absorption, and caution should be used when applying to areas prone to striae formation.
Lactation	Topical corticosteroids are generally considered acceptable for use in patients who are breastfeeding. Avoid application of topical corticosteroids to the nipple and areola area until breastfeeding ceases. If needed, apply topical corticosteroids immediately after breastfeeding, then clean nipples prior to the next feeding.
Contraindications	Treatment of rosacea, acne vulgaris, perioral dermatitis, or pruritus without inflammation; viral diseases; untreated bacterial, fungal, parasitic, syphilis, and tubercular infection involving the skin; eruptions following vaccinations; application to eyes; <18 years of age.

Monitoring Requirements	HPA axis suppression and adrenal insufficiency, especially in children or with augmented formulation use; ocular symptoms.
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. **Contact dermatitis:** Allergic contact dermatitis can occur and is usually diagnosed by failure to heal rather than clinical exacerbation; discontinue use if irritation occurs and treat appropriately. **Immunosuppression:** Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. **Ocular effects:** Topical corticosteroids, including betamethasone, may increase the risk of posterior subcapsular cataracts and glaucoma. Monitor for ocular symptoms. Avoid contact with eyes. **Skin reactions:** Discontinue if skin irritation or contact dermatitis occurs; do not use in patients with decreased skin circulation. **Systemic effects:** Topical corticosteroids may be absorbed percutaneously. Absorption of topical corticosteroids may cause manifestations of Cushing syndrome (rare), hyperglycemia, or glycosuria. Absorption is increased by the use of occlusive dressings, application to

	denuded skin, application to large surface areas, or prolonged use.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Betamethasone Valerate.**

Table 13. Betamethasone Valerate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Betamethasone Valerate	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Betamethasone Valerate

Betamethasone Valerate is used off-label as a first line treatment for Vitiligo. It is applied once or twice daily topically with a maximum quantity limit of 50g a week. Its use is limited by its heightened risk of developing paresthesia, dermatitis, and telangiectasia.

2.2 Systemic Corticosteroids

2.2.1 Dexamethasone

Information on Dexamethasone is detailed in the table below[24,25]:

Table 14. Dexamethasone Drug Information

SCIENTIFIC NAME DEXAMETHASONE	
SFDA Classification	Prescription

SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB02
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	2.5 to 10 mg for two consecutive days/week for three to six months.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Low dose oral mini pulse steroid regimen for two consecutive days/week for 3 months.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, QL, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Dexamethasone is to be prescribed by a physician who is experienced in the treatment of Vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	The duration of treatment leads up to 3-6 months.
ST (Step Therapy)	For patients with acute, rapidly progressing vitiligo, oral mini-pulse therapy with dexamethasone for two

	consecutive days a week may be considered to achieve disease arrest.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Hypertension, tachycardia, nausea. **Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma and cataracts.
Drug Interactions*	**Category X:** Aldesleukin BCG (Intravesical) Brivudine Cladribine Desmopressin Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec

	Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Teratogenic effects: Pregnancy Category C Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Contraindications	Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections
Monitoring Requirements	Hemoglobin, occult blood loss, blood pressure, serum potassium, blood glucose, creatine kinase (if symptoms of myopathy occur), bone mineral density; intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression.
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of

	hypothalamic-pituitary-adrenal axis, particularly in younger children. **Cardiovascular disease:** Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Monitor blood pressure. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture. **GI disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Hepatitis B:** Reactivation may occur. **Ocular disease:** Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. **Pheochromocytoma:** Pheochromocytoma crisis (may be fatal) has been reported after administration of systemic corticosteroids. Consider the risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma.

	Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **Immunizations:** Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted. **Propylene glycol:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. **Sulfite:** Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-

	threatening or less severe asthmatic episodes in susceptible patients.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Dexamethasone.**

Table 15. Dexamethasone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Dexamethasone	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Dexamethasone

For acute, rapidly progressive vitiligo, weekend OMP starting with low doses (2.5 mg daily) of dexamethasone may be considered. To stop vitiligo progression, the optimal duration of OMP therapy is between 3 and 6 months. Its use is limited by the heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma and cataracts.

2.2.2 Betamethasone

Information on Betamethasone is detailed in the table below[24,25]:

Table 16. Betamethasone Drug Information

SCIENTIFIC NAME BETAMETHASONE	
SFDA Classification	Prescription
SFDA Approval	Off-label

US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB01
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	5 to 7.5 mg for two consecutive days/week for three to six months.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Low dose oral mini pulse steroid regimen for two consecutive days/week for 3 months.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, QL, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Betamethasone is to be prescribed by a physician who is experienced in the treatment of Vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	The duration of treatment leads up to 3-6 months.
ST (Step Therapy)	For patients with acute, rapidly progressing vitiligo, oral mini-pulse therapy with Betamethasone for two consecutive days a week may be considered to achieve disease arrest.
EU (Emergency Use Only)	N/A

PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Hypertension, tachycardia, nausea. **Most serious:** Cardiac arrhythmia, edema, cushingoid state, HPA-axis suppression, ulcerative esophagitis.
Drug Interactions*	**Category X:** BCG (Intravesical) Brivudine Cladribine Desmopressin Indium 111 Capromab Pendetide Macimorelin Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Pimecrolimus Ritlecitinib Ruxolitinib (Topical) Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Teratogenic effects: Pregnancy Category C Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Systemically administered corticosteroids appear in human milk

	and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Contraindications	Hypersensitivity to betamethasone or any component of the formulation; Herpes simplex of the eye; systemic fungal infections; vaccinia; cerebral malaria; use in areas with local infection.
Monitoring Requirements	Growth in children, risk of infection
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal axis, particularly in younger children. **Anaphylactoid reactions:** Rare cases of anaphylactoid reactions have been observed in patients receiving corticosteroids. **Immunosuppression:** Prolonged use of corticosteroids may increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate infections, or limit response to killed or inactivated vaccines. **Kaposi sarcoma:** Prolonged treatment with corticosteroids has been associated with the development of Kaposi sarcoma (case reports); if noted, discontinuation of therapy should be considered. **Myopathy:** Acute myopathy has been reported with high-dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve

	ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed. **Psychiatric disturbances:** Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Preexisting psychiatric conditions may be exacerbated by corticosteroid use. **Cardiovascular disease:** Use with caution in patients with HF and/or hypertension; use has been associated with electrolyte disturbances, fluid retention, and hypertension. Dietary modifications may be necessary. Use with caution in patients with a recent history of myocardial infarction (MI); left ventricular free wall rupture has been reported after the use of corticosteroids. **Diabetes:** Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia. **Gastrointestinal disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, peptic ulcer, ulcerative colitis) due to perforation risk. Avoid ethanol may enhance gastric mucosal irritation. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Ocular disease:** Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Not recommended for the

	treatment of optic neuritis; may increase frequency of new episodes. Consider routine eye exams in chronic users. **Osteoporosis:** Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures. **Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroidism and decreases in hypothyroidism. **Discontinuation of therapy:** Withdraw therapy with gradual tapering of dose. **Polysorbate 80:** Betamethasone sodium phosphate formulations may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Betamethasone.**

Table 17. Betamethasone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Betamethasone	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT- Betamethasone

For acute, rapidly progressive vitiligo, Betamethasone may be administered 5 to 7.5 mg for two consecutive days/week for three to six months. To stop vitiligo progression, the optimal duration of OMP therapy is between 3 and 6 months. Its use is limited by the heightened risk of developing cardiac arrhythmia, edema, cushingoid state, HPA-axis suppression and ulcerative esophagitis.

2.3 Topical Calcineurin Inhibitors

2.3.1 Tacrolimus

Information on Tacrolimus is detailed in the table below[24,25]:

Table 18. Tacrolimus (Topical) Drug Information

SCIENTIFIC NAME TACROLIMUS (Topical)	
SFDA Classification	Prescription
SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label

Indication (ICD-10)	L80
Drug Class	Immunosuppressant Agents
Drug Sub-class	Calcineurin Inhibitor
ATC Code	D11AH01
Pharmacological Class (ASHP)	Topical Calcineurin Inhibitors
DRUG INFORMATION	
Dosage Form	Ointment
Route of Administration	Topical
Dose (Adult) [DDD]*	Apply thin layer of 0.1% ointment to affected area twice daily; reassess every 3 to 6 months for adequate response.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	A thin layer is to be applied to the affected area twice daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE, MD, ST
AGE (Age Edit)	Tacrolimus ointment is not approved for use in children younger than 2 years of age. Only tacrolimus 0.03% ointment is indicated for use in children 2 to 15 years of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Tacrolimus should be prescribed by a physician who is experienced in the treatment of Vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	TCIs are appropriate for intermittent long-term use and for those who cannot tolerate topical CSs.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	

Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache, burning sensation of the skin, pruritus, erythema. **Most serious:** Paresthesia, peripheral edema, hypersensitivity reactions and flu-like symptoms.
Drug Interactions*	**Category X:** Abatacept Abemaciclib Abrocitinib Acalabrutinib Adalimumab Alemtuzumab Amsacrine Anakinra Anifrolumab Antithymocyte Globulin (Equine) Antithymocyte Globulin (Rabbit) Asciminib Avacopan Axicabtagene Ciloleucel AzaCITIDine AzaTHIOprine Baricitinib Basiliximab Belatacept Belimumab Belinostat Betamethasone (Systemic) Bimekizumab Blinatumomab Brentuximab Vedotin Brexucabtagene Autoleucel Brodalumab Busulfan Cabazitaxel Canakinumab Capecitabine CARBOplatin

	Carfilzomib Carmustine Certolizumab Pegol Chlorambucil Ciltacabtagene Autoleucel CISplatin Cladribine Clofarabine Copanlisib Corticotropin Cortisone CycloPHOSphamide CycloSPORINE (Systemic) Cytarabine (Conventional) Dacarbazine DACTINomycin Daratumumab Dasatinib DAUNOrubicin (Conventional) Deflazacort Deucravacitinib DexAMETHasone (Systemic) Dinutuximab DOCEtaxel Doxifluridine DOXOrubicin (Conventional) DOXOrubicin (Liposomal) Duvelisib Eculizumab Efgartigimod Alfa Elivaldogene Autotemcel Elotuzumab Elranatamab Emapalumab Epcoritamab EpiRUBicin Etanercept Etoposide Etoposide Phosphate

	Everolimus Filgotinib Fingolimod Floxuridine Fludarabine Fludrocortisone Fluorouracil (Systemic) Fotemustine Gemcitabine Gemtuzumab Ozogamicin Glofitamab Golimumab Guselkumab Hydrocortisone (Systemic) Hydroxyurea Ibritumomab Tiuxetan Ibrutinib IDArubicin Idecabtagene Vicleucel Idelalisib Ifosfamide Imatinib Inebilizumab InFLIXimab Inotuzumab Ozogamicin Irinotecan (Conventional) Irinotecan (Liposomal) Isatuximab Ixabepilone Ixekizumab Leflunomide Lenalidomide Lisocabtagene Maraleucel Lomustine Loncastuximab Tesirine Lurbinectedin Lutetium Lu 177 Dotatate Lutetium Lu 177 Vipivotide Tetraxetan Melphalan

	Melphalan Flufenamide Mercaptopurine Methotrexate MethylPREDNISolone Mirikizumab MitoMYcin (Systemic) MitoXANTRONE Mizoribine Mogamulizumab Mosunetuzumab Mycophenolate Natalizumab Nelarabine Niraparib Obinutuzumab Ocrelizumab Ofatumumab Omacetaxine Ozanimod PACLitaxel (Conventional) PACLitaxel (Protein Bound) Pacritinib Palbociclib Panobinostat PAZOPanib Pegcetacoplan (Systemic) PEMEtrexed Pentostatin Pirtobrutinib Pixantrone Polatuzumab Vedotin Pomalidomide PONATinib Ponesimod Pozelimab PRALAtrexate PrednisoLONE (Systemic) PredniSONE Procarbazine

	Raltitrexed Ravulizumab Ribociclib Rilonacept Risankizumab Ritlecitinib RiTUXimab RomiDEPsin Rozanolixizumab Ruxolitinib (Systemic) Ruxolitinib (Topical) Sacituzumab Govitecan Sarilumab Satralizumab Secukinumab Selinexor Siltuximab Siponimod Sirolimus (Conventional) Sirolimus (Protein Bound) Sirolimus (Topical) Spesolimab Sutimlimab Tacrolimus (Systemic) Tafasitamab Talquetamab Tazemetostat Teclistamab Tegafur Temozolomide Temsirolimus Teniposide Teplizumab Teriflunomide Thioguanine Thiotepa Tisagenlecleucel Tocilizumab Tofacitinib

	Trabectedin Treosulfan Triamcinolone (Systemic) Trifluridine and Tipiracil Ublituximab Umbralisib Upadacitinib Ustekinumab Vedolizumab Venetoclax Vilobelimab VinBLAStine Vinflunine Vinorelbine Voclosporin Zanubrutinib
Special Population	**Pediatrics:** Use in children <2 years of age is not approved, only the 0.03% ointment should be used in children ages 2 to 15 years.
Pregnancy	When preferred treatments are insufficient, topical tacrolimus may be used in pregnant patients.
Lactation	Apply tacrolimus immediately after breastfeeding; avoid use on nipples and clean nipples prior to the next feeding.
Contraindications	Hypersensitivity to tacrolimus or any component of the formulation.
Monitoring Requirements	Monitor for the development of any skin manifestation.
Precautions	**Infection:** Do not apply to areas of active bacterial or viral infection; infections at the treatment site should be cleared prior to therapy. Patients with atopic dermatitis are predisposed to skin infections, and tacrolimus therapy has been associated with risk of developing eczema herpeticum, varicella zoster, and herpes simplex.

	Lymphadenopathy: May be associated with development of lymphadenopathy; possible infectious causes should be investigated. Discontinue use in patients with unknown cause of lymphadenopathy or acute infectious mononucleosis. **Malignancy:** Avoid use on malignant or premalignant skin conditions (eg, cutaneous T-cell lymphoma). Limit sun and ultraviolet light exposure; use appropriate sun protection. **Renal failure:** Acute renal failure has been observed (rarely) with topical use. **Immunosuppression:** Should not be used in immunocompromised patients. Safety and efficacy have not been evaluated. **Skin diseases with altered absorption:** Not recommended for use in patients with skin disease which may increase systemic absorption (eg, Netherton's syndrome).
Black Box Warning	**Malignancy:** Although a causal relationship has not been established, rare cases of malignancy (ie, skin cancer and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus ointment. Avoid continuous long-term use of topical calcineurin inhibitors, including tacrolimus ointment, in any age group, and limit application to areas of involvement with atopic dermatitis. **Pediatrics:** Tacrolimus ointment is not indicated for use in children younger than 2 years of age. Only tacrolimus 0.03% ointment is indicated for use in children 2 to 15 years of age.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Tacrolimus.**

Table 19. Tacrolimus (Topical) HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tacrolimus	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Tacrolimus

Topical Tacrolimus is prescribed off-label as an alternative to topical corticosteroids in vitiligo. Tacrolimus is applied as a thin layer to affected area twice daily; with a reassessment for adequate response required every 3 to 6 months. Its use is limited by the heightened risk of developing paresthesia, peripheral edema, hypersensitivity reactions and flu-like symptoms.

2.3.2 Pimecrolimus

Information on Pimecrolimus is detailed in the table below[24,25]:

Table 20. Pimecrolimus (Topical) Drug Information

SCIENTIFIC NAME PIMECROLIMUS (Topical)	
SFDA Classification	Prescription
SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80

Drug Class	Immunosuppressant Agents
Drug Sub-class	Topical Calcineurin Inhibitors
ATC Code	D11AH02
Pharmacological Class (ASHP)	Topical Calcineurin Inhibitors
DRUG INFORMATION	
Dosage Form	Cream
Route of Administration	Topical
Dose (Adult) [DDD]*	Apply twice daily for 6 months. Treatment beyond 12 months may be useful; long-term safety has not been established.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Apply a thin layer to affected area twice daily; limit application to affected areas only.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment is necessary.
Prescribing edits*	AGE, MD, ST
AGE (Age Edit)	Pimecrolimus is not indicated for use in children younger than 2 years.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Pimecrolimus should be prescribed by a physician who has experience in the treatment of Vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	TCIs are appropriate for intermittent long-term use and for those who cannot tolerate topical CSs.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache, burning, fever, application site reaction. **Most serious:** Upper Respiratory Tract Infections, nasopharyngitis, and skin infections.

Drug Interactions*	**Category X:** Abatacept Abemaciclib Abrocitinib Acalabrutinib Adalimumab Alemtuzumab Amsacrine Anakinra Anifrolumab Antithymocyte Globulin (Equine) Antithymocyte Globulin (Rabbit) Asciminib Avacopan Axicabtagene Ciloleucel AzaCITIDine AzaTHIOprine Baricitinib Basiliximab Belatacept Belimumab Belinostat Betamethasone (Systemic) Bimekizumab Blinatumomab Brentuximab Vedotin Brexucabtagene Autoleucel Brodalumab Busulfan Cabazitaxel Canakinumab Capecitabine CARBOplatin Carfilzomib Carmustine Certolizumab Pegol Chlorambucil Ciltacabtagene Autoleucel CISplatin

	Cladribine Clofarabine Copanlisib Corticotropin Cortisone CycloPHOSphamide CycloSPORINE (Systemic) Cytarabine (Conventional) Dacarbazine DACTINomycin Daratumumab Dasatinib DAUNOrubicin (Conventional) Deflazacort Deucravacitinib DexAMETHasone (Systemic) Dinutuximab DOCEtaxel Doxifluridine DOXOrubicin (Conventional) DOXOrubicin (Liposomal) Duvelisib Eculizumab Efgartigimod Alfa Elivaldogene Autotemcel Elotuzumab Elranatamab Emapalumab Epcoritamab EpiRUBicin Etanercept Etoposide Etoposide Phosphate Everolimus Filgotinib Fingolimod Floxuridine Fludarabine Fludrocortisone

	Fluorouracil (Systemic) Fotemustine Gemcitabine Gemtuzumab Ozogamicin Glofitamab Golimumab Guselkumab Hydrocortisone (Systemic) Hydroxyurea Ibritumomab Tiuxetan Ibrutinib IDArubicin Idecabtagene Vicleucel Idelalisib Ifosfamide Imatinib Inebilizumab InFLIXimab Inotuzumab Ozogamicin Irinotecan (Conventional) Irinotecan (Liposomal) Isatuximab Ixabepilone Ixekizumab Leflunomide Lenalidomide Lisocabtagene Maraleucel Lomustine Loncastuximab Tesirine Lurbinectedin Lutetium Lu 177 Dotatate Lutetium Lu 177 Vipivotide Tetraxetan Melphalan Melphalan Flufenamide Mercaptopurine Methotrexate MethylPREDNISolone Mirikizumab MitoMYcin (Systemic)

	MitoXANTRONE Mizoribine Mogamulizumab Mosunetuzumab Mycophenolate Natalizumab Nelarabine Niraparib Obinutuzumab Ocrelizumab Ofatumumab Omacetaxine Ozanimod PACLitaxel (Conventional) PACLitaxel (Protein Bound) Pacritinib Palbociclib Panobinostat PAZOPanib Pegcetacoplan (Systemic) PEMEtrexed Pentostatin Pirtobrutinib Pixantrone Polatuzumab Vedotin Pomalidomide PONATinib Ponesimod Pozelimab PRALAtrexate PrednisoLONE (Systemic) PredniSONE Procarbazine Raltitrexed Ravulizumab Ribociclib Rilonacept Risankizumab Ritlecitinib

	RiTUXimab RomiDEPsin Rozanolixizumab Ruxolitinib (Systemic) Ruxolitinib (Topical) Sacituzumab Govitecan Sarilumab Satralizumab Secukinumab Selinexor Siltuximab Siponimod Sirolimus (Conventional) Sirolimus (Protein Bound) Sirolimus (Topical) Spesolimab Sutimlimab Tacrolimus (Systemic) Tafasitamab Talquetamab Tazemetostat Teclistamab Tegafur Temozolomide Temsirolimus Teniposide Teplizumab Teriflunomide Thioguanine Thiotepa Tisagenlecleucel Tocilizumab Tofacitinib Trabectedin Treosulfan Triamcinolone (Systemic) Trifluridine and Tipiracil Ublituximab Umbralisib

	Upadacitinib Ustekinumab Vedolizumab Venetoclax Vilobelimab VinBLAStine Vinflunine Vinorelbine Voclosporin Zanubrutinib
Special Population	**Immunocompromised patients:** Should not be used in immunocompromised patients, including patients on concomitant systemic immunosuppressive therapy. **Pediatric:** Use of Pimecrolimus in children < 2 years of age is not recommended, particularly since the effect on immune system development is unknown.
Pregnancy	Adverse events were not observed in animal reproduction studies following topical application.
Lactation	It is not known if Pimecrolimus is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.
Contraindications	Hypersensitivity to Pimecrolimus or any component of the formulation.
Monitoring Requirements	N/A
Precautions	**Infection:** Do not apply to areas of active bacterial or viral infection; local infections at the treatment site should be resolved prior to therapy.

	Local symptoms: May cause local symptoms (eg, burning, pruritus, soreness, stinging) during first few days of treatment. **Lymphadenopathy:** May be associated with development of lymphadenopathy; possible infectious causes should be investigated. Discontinue use in patients with unknown cause of lymphadenopathy or acute infectious mononucleosis. **Malignancy:** [US Boxed Warning]: Topical calcineurin inhibitors (including Pimecrolimus) have been associated with rare cases of lymphoma and skin malignancy; avoid use on malignant or premalignant skin conditions (eg, cutaneous T-cell lymphoma). **Skin papilloma:** Skin papilloma (warts) have been observed with use; discontinue use if there is worsening of skin papillomas or they do not respond to conventional treatment. **Atopic dermatitis:** Diagnosis should be reconfirmed if sign/symptoms do not improve within 6 weeks of treatment. **Erythroderma:** Safety not established in patients with generalized erythroderma. **Skin diseases which may increase systemic absorption:** Not recommended for use in patients with Netherton's syndrome or skin conditions which may increase the potential for systemic absorption.
Black Box Warning	**Pediatrics:** Pimecrolimus is not indicated for use in children younger than 2 years. **Appropriate Use:** Long-term safety of topical calcineurin inhibitors has not been established. Continuous long-term use of topical calcineurin inhibitors,

	including Pimecrolimus, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis. **Malignancy:** Although a causal relationship has not been established, rare cases of malignancy (eg, skin malignancy, lymphoma) have been reported in patients treated with topical calcineurin inhibitors including Pimecrolimus.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Pimecrolimus.**

Table 21. Pimecrolimus (Topical) HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Pimecrolimus	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Pimecrolimus

Pimecrolimus is prescribed off-label as an alternative to topical corticosteroids in vitiligo. Pimecrolimus is applied twice daily for 6 months. Treatment beyond 12 months may be useful; long-term safety has not been established. Its use is limited by the heightened risk of developing upper respiratory tract Infections, nasopharyngitis, and skin infections.

2.4 Psoralens

2.4.1 Methoxsalen

Information on Methoxsalen is detailed in the table below[24,25]:

Table 22. Methoxsalen (Topical) Drug Information

SCIENTIFIC NAME METHOXSALEN (Topical)	
SFDA Classification	Prescription
SFDA Approval	Off-label
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	L80
Drug Class	Psoralen
Drug Sub-class	Psoralen
ATC Code	D05BA02
Pharmacological Class (ASHP)	Psoralen
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Topical
Dose (Adult) [DDD]*	Apply to the affected area of the skin and allow to dry for one to two minutes, then apply again within two to two and one-half hours before UVA exposure. (Topical formulation strengths are at 1% which is not appropriate for patient use; it has to be diluted to 0.1% by a compounding pharmacist.)
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Recommended for use in children over the age of 12 years: apply to the affected area of the skin and allow to dry for one to two minutes, then apply again within two to two and one-half hours before UVA exposure.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in manufacturer's labeling.
Prescribing edits*	AGE, CU, MD, ST
AGE (Age Edit)	Methoxsalen is not recommended to be used in patients less than 12 years of age.
CU (Concurrent Use Edit)	Psoralens are to be used concomitantly with phototherapy for the management of Vitiligo.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Methoxsalen is to be prescribed by a physician who has experience in the management of Vitiligo.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	PUVA is recommended as an alternative to NB-UVB in vitiligo patients who are candidates for phototherapy.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Hyperkeratosis pruritus, and nausea. **Most serious:** Malignant melanoma, squamous cell carcinoma of the skin and cataract.
Drug Interactions*	**Category X:** Aminolevulinic Acid (Systemic) Fezolinetant
Special Population	**Pediatrics:** Safety and efficacy have not been established in children <12 years of age for vitiligo. The long-term effects of treatment (including potential cataract formation, skin cancer development, and premature skin aging) are unknown in children.
Pregnancy	Adverse events were observed in animal reproduction studies.

Lactation	It is not known if methoxsalen (systemic) is excreted in breast milk. The manufacturer recommends that caution be exercised when administering methoxsalen (systemic) to nursing women.
Contraindications	Hypersensitivity to methoxsalen (psoralens) or any component of the formulation; diseases associated with photosensitivity (eg, albinism, lupus erythematosus, porphyria [cutanea tarda, erythropoietic and variegate], xeroderma pigmentosum); invasive squamous cell cancer (oral only); aphakia; melanoma or history of melanoma (oral only).
Monitoring Requirements	CBC with differential (baseline and every 6-12 months), liver and renal function tests (baseline and every 6-12 months), antinuclear antibodies (baseline and every 6-12 months); ophthalmic exam (pretreatment and yearly); signs/symptoms of skin cancer, burns, and photosensitivity.
Precautions	**Actinic degeneration:** Exposure to sunlight and/or ultraviolet radiation may result in premature aging of the skin. **Burns:** Serious burns may occur from ultraviolet radiation or sunlight (even if exposed through glass) if the recommended dose and/or exposure schedule is not maintained. Avoid direct and indirect sunlight for 24 hours after treatment. **Cataracts:** Methoxsalen concentrates in the lens; eyes should be shielded from direct and indirect sunlight for 24 hours after methoxsalen exposure to prevent possible formation of cataracts. **Photosensitivity:** Avoid sun (including sun lamp) exposure for 24 hours after

	methoxsalen ingestion or administration. Protective clothing, eyewear, and sunscreen (do not apply sunscreen to psoriatic areas) should be used for 24 hours after combined methoxsalen/UVA therapy. Do not use in sunburned patients until they have fully recovered; pre-existing sunburn may obscure evaluation of response; advise patients to avoid sunbathing for 24 hours prior to treatment and for 48 hours after treatment. Use extreme caution in patients who have significant exposure to the sun through their occupation. **Skin cancer:** Therapy may lead to increased risk of skin cancer (basal cell, melanoma, and squamous cell); this risk may be increased with fair skin or prior exposure to prolonged tar and UVB treatment, ionizing radiation, or arsenic. **Thromboembolic events:** Have been reported, including pulmonary embolism and deep vein thrombosis in patients with graft-versus-host disease. **Basal cell carcinoma:** Use with caution in patients with multiple basal cell carcinomas or a history of basal cell carcinoma; observe closely. **Cardiovascular disease:** Use with caution in patients with cardiovascular disease (may not be able to tolerate the heat stress or prolonged standing related to UVA treatment conditions). **Hepatic impairment:** Methoxsalen undergoes hepatic metabolism; use with caution in patients with hepatic impairment.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Vitiligo treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methoxsalen.**

Table 23. Methoxsalen HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methoxsalen	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT - Methoxsalen

Methoxsalen is indicated for the management of vitiligo through coadministration with phototherapy. The SFDA registered topical formulation strength is at 1% which is not appropriate for patient use; it has to be diluted to 0.1% by a compounding pharmacist. The regimen is as follows: 20 to 30 minutes after application of an even layer of Psoralen, the skin is exposed to UVA radiation, initially at 0.25 to 0.5 J/cm^2. Two to three times a week, exposure time is increased in small steps (15-30 seconds) up to a maximum of 10 minutes. Then, a marginally higher strength of topical psoralen preparation is prescribed and the same time intervals are followed. This procedure is repeated until a dosage and exposure time are attained that produce erythema but not burning. The use of Methoxsalen is limited by the heightened risk of developing malignant melanoma, squamous cell carcinoma of the skin and cataract.

2.5 Other Drugs

2.5.1 Ruxolitinib (Opzelura®)

Topical Ruxolitinib was approved by the FDA in July of 2022 and by the EMA in April of 2023. It is indicated for the topical treatment of nonsegmental vitiligo in adult and pediatric patients aged 12 years and older. Topical Ruxolitinib is applied as a thin layer twice daily to affected areas of up to 10% body surface area. Patients should not use more than one 60 gram tube per week or one 100 gram tube per 2 weeks. Furthermore, the use of Opzelura® in combination with therapeutic biologics, other

JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

2.5.2 RECELL Autologous Cell Harvesting Device®

RECELL® is a **medical device** approved by the FDA in June of 2023 for the treatment of Vitiligo. In March of 2019, Avita Medical suspended the sales of RECELL® in the European Union amid reports of certain non-conformities. RECELL® is the **first FDA-approved therapeutic device** offering a one-time treatment at the point-of-care. Using the device, a clinician prepares and delivers autologous skin cells from pigmented skin to stable depigmented areas, offering a safe and effective treatment for vitiligo[26].

Section 3.0 Key Recommendations Synthesis

Vitiligo Diagnosis

- Vitiligo may be diagnosed on the basis of clinical features.
- A biopsy is not required; however, it may be considered for differential diagnosis – ruling out any other possible skin condition with similar manifestations.
- Photographic documentation is required as it allows for objectivation of the extent of the current depigmentation and that of disease activity and response to therapy.
- Instruments for assessing the extent of vitiligo include:
    - Affected body surface area (BSA) in percent based on the rule of nine.

      As recommended in the Japanese guidelines for the management of vitiligo, manifestation can be classified as severe (BSA > 30 %), moderate (BSA 10–30 %), and mild (BSA < 10 %), although there is no general consensus.
    - VETF Score
    - Vitiligo Area Scoring Index (VASI)
    - Vitiligo Extent Score (VES)/Self-Assessment Vitiligo Extent Score (SA-VES)
- Given the increased prevalence of thyroid diseases, determination of TSH as well as TPO and TG antibodies is recommended as initial screening test and then annually in vitiligo patients.

Vitiligo Classification

The following table details the classification of Vitiligo as per the BAD[20]:

Table 24. Classification of Vitiligo. Adapted from BAD Guidelines for the Management of People with Vitiligo (2021)

	Subtype	Definition
Vitiligo/NSV	Acrofacial	Involved sites are usually limited to face, head, hands, feet.
	Generalized	Acrofacial vitiligo may later progress to include other body sites.

	Universal	Most extensive form of vitiligo. This term is used when depigmentation covers > 80% of total body surface.
	Mucosal	Usually refers to the involvement of oral and/or genital mucosae.
	Mixed	Concomitant occurrence of NSV and segmental vitiligo.
	Rare variants	• Follicular • Vitiligo minor (incomplete defect in pigmentation with a pale skin color compared with healthy skin) • Vitiligo punctata (1-1.5 mm sharply demarcated macules)
Segmental vitiligo	Uni-, bi- or plurisegmental	Presence of one or more depigmented macules distributed on one side of the body.
Undetermined or unclassified vitiligo	Focal	Small, isolated patch, which has not evolved into NSV after a period of at least 2 years and does not fit into a segmental distribution.
	Mucosal	One mucosal site in isolation.

History Collection

- A full history is to be collected for vitiligo patients including but not limited to the site and type of vitiligo (Segmental/Non-Segmental), disease extent (Affected body surface area), disease stability, speed of onset, trigger factors, quality of life, psychological and psychosocial impact, and personal and family history of associated thyroid dysfunction or other autoimmune disease. **(GPP)**

Pharmacological Therapy

- The first line treatment in primary or secondary care of vitiligo is a **potent/very potent topical corticosteroid** once daily all while avoiding the periocular area. **(↑↑)**
- In patients with facial vitiligo, **topical tacrolimus 0.1% ointment** twice daily is recommended. The ointment can also be used as an alternative to topical corticosteroids. **(↑)**
- Topical tacrolimus 0.1% ointment twice daily with or without occlusion on photo exposed areas is also recommended for patients with nonfacial vitiligo as an alternative to corticosteroids. **(↑)**

- After having weighed the risk versus benefits, HCPs may consider an intermittent regimen of a once daily application of topical corticosteroids with or without TCIs.

  Intermittent regimens are considered for patients with vitiligo in areas with thinner skin such as the periocular region, genital area and skin flexures.

  Intermittent regimens include:

  - One week of potent or very potent corticosteroids and at least 1 week off

  OR

  - One week of potent or very potent topical corticosteroids alternating with ≥ 1 week of topical calcineurin inhibitor **(GPP)**

- The use of topical treatments is reassessed at an interval of 3-6 months to check for improvement. **(GPP)**
- There is insufficient evidence to support the use of topical vitamin D analogues in people with vitiligo. **(0)**
- After having conducted psychological assessment and/or intervention, **depigmentation therapies** may be considered in patients with extensive vitiligo and a substantial negative psychological impact; however, they are last resort options. **(GPP)**
- For patients with rapidly progressive vitiligo, **oral Betamethasone** 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg per month for a further 3 months **in combination with NB-UVB** may be considered in order to arrest disease activity. **(↑)** Another treatment option includes **oral Dexamethasone** given as 2.5 to 10 mg for two consecutive days/week for three to six months. **(Strong Recommendation)**
- In case of extensive/progressive disease and an inadequate response to topical therapy, HCPs may consider starting the patient on **NB-UVB** as first-line phototherapy.

  Combination therapy with topical corticosteroids or topical calcineurin inhibitors may be considered for localized sites. **(↑↑)**

- If NB-UVB is unavailable or in case of lack of responsiveness, **PUVA or PUVAsol** may be considered in adults with vitiligo. **(↑)**
- In patients with localized vitiligo, **excimer laser or light** may be considered alone or in combination with **topical calcineurin inhibitors**.

  Patients are to be informed about the heightened risk of development of skin cancer that accompanies the combination regimen.

- If adults with nonsegmental vitiligo on the hands and feet are non-responsive to other treatments, **CO2 laser in combination with 5-fluorouracil** may be considered. The regimen is as follows: Apply 5-fluorouracil once daily for 7 days per month for 5 months; CO2 laser treatments once a month for 5 months.

Grafting and Surgical Treatment

- Grafting and surgical treatments should only be performed for stable and treatment-resistant vitiligo on cosmetically sensitive regions. **(Grade A-C1)**
- Surgical options include:
    - Split-thickness skin grafting (Best option when surgical treatment is required)
    - Epidermal grafting
    - Mini-grafting (Not recommended due to poor cosmetic results and side effect profile)
    - Autologous non-cultured melanocyte-keratinocyte cell transplantation/injection
    - Autologous cultured melanocyte transplantation/ injection **(Grade A-C1)**
- The treatment of vitiligo has improved with the use of epithelial cell suspensions (**ReCell®**, Spray-On Skin; Avita Medical, Cambridge, UK) for autologous non-cultured melanocyte-keratinocyte cell transplantation/injection and autologous cultured melanocyte transplantation/injection. **(Grade A-C1)**

Skin Camouflage Therapy

- Skin camouflage may be considered for patients who are willing to explore that option. **(↑)**

Treatment in Children, Pregnant Women, Nursing Mothers and Elderly

- In the pediatric and pregnant populations, the use of NB-UVB is recommended over PUVA. This is attributed to better effectiveness of NB-UVB and lower incidence of side effects and carcinogenesis.
- Phototherapy is suggested to be initiated in children if they exhibit little or no response to topical therapy, rapid progression of the disease and the ability to collaborate with HCPs for therapy inititation.

  Patients are required to be aged older than 7 years.

- Combination therapy using TCIs and phototherapy may be suggested; however, the risk of carcinogenesis is to be taken into consideration.
- The use of oral corticosteroids is associated with an elevated incidence of fractures both in the pediatric and elderly patient populations. Therefore, its use must be moderate and avoided in patients with moderate to high risk for fractures.
- Oral corticosteroids were also deemed Category C for pregnant patients; therefore, their use is not recommended.
- In children, TCIs applied twice daily are preferred specifically when treating areas as the face, neck and intertriginous areas.
- Topical medium-potency and high-potency corticosteroids are the first line therapy for pediatric vitiligo on the body, except for intertriginous and genital sites.
- Children with a high phototype and facial lesions are prescribed intermittent regimens with 2-3 week intervals for a maximum of 6 months.
- In pregnant or lactating patients with vitiligo, a cautious use of TCS of mild-potency or moderate-potency is indicated.

  HCPs are to be cautious in terms of reduced time and area of treatment.
- Topical tacrolimus can be suggested as a second line agent in pregnant or lactating patients.
- In elderly patients, a combination of topical therapy and phototherapy are recommended.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Vitiligo.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Sort By	Filters	Search Details	Results
(Vitiligo[MeSH Terms]) OR (vitiligo[Title/Abstract])		Guideline, in the last 5 years	("vitiligo"[MeSH Terms] OR "vitiligo"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	1
(Vitiligo[MeSH Terms]) OR (vitiligo[Title/Abstract])		Guideline	("vitiligo"[MeSH Terms] OR "vitiligo"[Title/Abstract]) AND (guideline[Filter])	11
(Vitiligo[MeSH Terms]) OR (vitiligo[Title/Abstract])			"vitiligo"[MeSH Terms] OR "vitiligo"[Title/Abstract]	9,446

Appendix D. Treatment Algorithm