Ruxolitinib Cream (OPZELURA) in Nonsegmental Vitiligo National Drug Monograph Addendum January 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Ruxolitinib is a Janus kinase inhibitor (JAKI) that targets JAK1 and JAK2.
- Ruxolitinib cream was originally approved for the topical treatment of mild to moderate atopic dermatitis.[1]

Indication Under Review in This Document

- Topical treatment of nonsegmental vitiligo in adults

Dosage Regimen and Dosage Form Under Review

- Apply a thin layer twice daily to affected areas of up to 10% body surface area (BSA)
- Cream: 15 mg ruxolitinib per gram (1.5%), 60- and 100-gram tubes

Clinical Evidence Summary

Efficacy Considerations

- There have been no head-to-head trials to inform the place in therapy of ruxolitinib cream in the treatment of nonsegmental vitiligo.
- A 52-week multicenter, concentration- and dose-ranging, phase 2 randomized clinical trial (RCT; N = 157) showed that ruxolitinib cream 1.5% twice daily and 1.5% once daily applied up to 20% of total BSA were significantly better than vehicle in achieving at least 50% improvement in the facial Vitiligo Area Scoring Index (F-VASI50) at Week 24.[2] F-VASI50 response rates were 45% of 33 patients, 50% of 30 patients vs 3% of 32 patients in the twice daily, once daily, and vehicle groups, respectively. At least 75% improvement in the F-VASI occurred in 30% of patients at Week 24 and improved through Week 52. Exploratory subgroup analyses by previous therapy showed F-VASI50 response rates of 66.7% with prior phototherapy, 50.0% with topical corticosteroids, and 42.9% with topical calcineurin inhibitors.[3] Subgroup analyses by disease status showed response rates of 46.2% among patients with stable disease and 45.0% among those with progressive disease. The F-VASI50 response efficacy was higher in patients ≤ 50 years of age than those > 50 years (58.8% vs. 31.3%) and in females than males (60.0% vs. 33.3%, respectively).
- The approval of ruxolitinib cream for nonsegmental vitiligo was mainly based on two, identically designed, 52-week vehicle-controlled randomized clinical trials (RCTs), TRuE-V1 and TRuE-V2.[4] These studies are the focus of this review.

Phase 3 Randomized Clinical Trials

Table 1 Methods of Identically Designed Phase 3 RCTs

Topic	TRuE-V1 and TRuE-V2
Study Design	24-wk multinational DB VC RCT with 2:1 randomization ruxolitinib cream:vehicle conducted in the US, CA or EU Randomization was stratified by geographic region and Fitzpatrick skin type. Multiplicity was controlled using a prespecified fixed sequence of primary and secondary outcome measures.
Major Entry Criteria	Inclusion: Age ≥ 12 years; diagnosis of nonsegmental vitiligo with depigmented areas involving ≤ 10% of total BSA, including ≥ 0.5% facial BSA and ≥ 3% non-facial BSA; F-VASI scores ≥ 0.5 (range 0–3, with higher scores indicating greater area of depigmentation); total VASI scores ≥ 3 (range 0–100). Exclusion: Complete leukotrichia within any facial lesions; previous JAKI therapy; prior biologic or investigational drug within 12 wks or 5 half-lives; phototherapy within 8 wks or during the trial; immunomodulators within 4 wks; topical therapies within 1 wk. The study aimed to including ≥ 10% adolescents (12–17 years old) and ≥ 50% younger than 40 years to ensure a representative population of patients with vitiligo.
Interventions	For 24 Weeks: • Ruxolitinib cream 1.5% twice daily • Vehicle cream twice daily
Maintenance Phase / Long-term Extension	For Additional 28 Weeks, All Patients: • Ruxolitinib cream 1.5% twice daily
Primary Efficacy Measure	Percentage of patients achieving at least 75% improvement in F-VASI75 at Wk 24 (modified intent-to-treat population)
Baseline Patient Characteristics (Pooled data, N = 330)	Mean age 40.2 y (82% 18–64 yr; 7% ≥ 65 y) Males 47% White 82%, Black 5%, Asian 4% Mean affected facial BSA of 1%, total BSA of 7.4% Mean time since diagnosis 14.8 y Fitzpatrick skin types I / very pale (2%), II / pale pink or beige (30%), III / pink or medium-beige (40%), IV / olive or light brown (19%), V / medium to dark brown (7%), or VI / deep dark brown (2%) Stable disease 74%; progressive disease 26% Most common previous therapy: topical calcineurin inhibitors 32%; topical corticosteroids 28%; NB-UVB phototherapy 21%

Results

- Efficacy data are summarized in Table 2.

Table 2 Selected efficacy results at Week 24

Outcome	Study	Ruxolitinib Cream	Vehicle	Relative Risk (95% CI)	Difference (95% CI)
F-VASI75, n/N (%)	TRuE-V1	66/221 (29.8)	8/109 (7.4)	4.0 (1.9, 8.4)	22.5 (14.2, 30.8)
	TRuE-V2	69/222 (30.9)	12/109 (11.4)	2.7 (1.5, 4.9)	16.9 (7.8, 26.0)
F-VASI90, n/N (%)	TRuE-V1	34/221 (15.3)	2/109 (2.2)	7.3 (1.8, 29.5)	13.3 (7.5, 19.1)
	TRuE-V2	36/222 (16.3)	1/109 (1.3)	13.1 (1.9, 90.2)	13.5 (7.7, 19.3)
F-VASI50, n/N (%)	TRuE-V1	113/221 (51.2)	18/109 (16.9)	3.0 (1.9, 4.8)	34.3 (23.9, 43.1)
	TRuE-V2	114/222 (51.4)	23/109 (20.9)	2.5 (1.6, 3.7)	30.5 (19.7, 39.7)
T-VASI50, n/N (%)	TRuE-V1	46/221 (20.6)	6/109 (5.1)	4.1 (1.6, 10.5)	15.5 (7.9, 22.0)
	TRuE-V2	53/222 (23.9)	7/109 (6.8)	3.5 (1.7, 7.5)	17.1 (8.9, 24.0)
VNS response, n/N (%)	TRuE-V1	54/221 (24.5)	4/109 (3.3)	7.5 (2.4, 23.5)	21.2 (13.8, 27.6)
	TRuE-V2	46/222 (20.5)	5/109 (4.9)	4.2 (1.7)10.2)	15.6 (8.1, 22.0)

Source: 4
CFB, Change from baseline; F-VASI75/90, At least 75% or 90% improvement in the Facial Vitiligo Area Scoring Index; Q, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low); VNS, Vitiligo Noticeability Scale, where response was defined as a lot less noticeable or no longer noticeable

- The anticipated absolute effects for achieving F-VASI75 in 24 weeks are presented in Table 3.

Table 3 Absolute Effects for Achieving F-VASI75 Outcome at Week 24

Trial	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
TRuE-V1	220 (66 to 543) more	5 (4, 8)	M[α]
TRuE-V2	187 (55 to 429) more	6 (4, 11)	M[α]

AAE, Anticipated absolute effect for achieving the outcome; **M**, Moderate; **NNT**, Number needed to treat for one additional patient to benefit
[α] Downgraded for imprecision related to fragility.

Subgroup Analyses

- None reported.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest separation between treatment groups) and duration of an adequate therapeutic trial are summarized by outcome measure in Table 4.

Table 4 Onset of Benefit and Adequate Therapeutic Trial (TRuE-V1 and TRuE-V2 Combined)

Outcome Measure	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
F-VASI75	9	≥ 52
T-VASI75	14	46

Source: 1

Durability of Response

- F-VASI75 response rates in TRuE-V1 and TRuE-V2, respectively, were as follows: 91/173 (52.6%) and 85/177 (48.0%) in patients who received ruxolitinib / ruxolitinib for 52 weeks; 22/82 (27%) and 24/81 (30%) who received vehicle / ruxolitinib for 28 / 28 weeks.
- Corresponding T-VASI50 response rates: 92/173 (53.2%) and 87/177 (49.2) in ruxolitinib / ruxolitinib groups; 26/82 (32%) and 18/81 (22%) in the vehicle / ruxolitinib groups.

Evidence Gaps

- Health-related Quality of Life
- Psychological wellbeing (e.g., depression, anxiety)
- Functional ability / Disability
- Patient satisfaction

Network Meta-analyses

- None that included topical ruxolitinib were found.

Safety Considerations

- The safety profile of topical ruxolitinib in nonsegmental vitiligo was generally consistent with that in atopic dermatitis.
- Hematopoietic adverse events: < 1%
- Nonmelanoma skin cancer: Nonmelanoma skin cancers including basal cell and squamous cell carcinoma occurred in 3 patients with vitiligo (0.15%) of 1942 patients involved in the clinical development trials for all indications. Periodic skin assessments during and after treatment as appropriate are recommended.

Other Considerations

- Ruxolitinib plasma concentrations were detectable, with average steady-state concentrations of Weeks 4 and 24 of 55.8 nM and 58.0 nM in TRuE-V1 and TRuE-V2, respectively.

Other Therapeutic Options

- There is no known cure and no effective therapies for limiting the progression of vitiligo.
- Treatment can stimulate inactive melanocytes in unaffected hair follicles to multiply and migrate to the adjacent epidermis, eventually repigmenting vitiligo lesions.[5]
- In 2022 the British Association of Dermatologist (BAD) published the most up-to-date clinical guideline on the management of vitiligo.[6] Topical corticosteroids and topical calcineurin inhibitors were considered first-line drug therapies.
- The BAD guidelines could not recommend **topical vitamin D analogues** because of insufficient evidence. Based on data given in their GRADE evidence tables, ≥ 75% repigmentation was achieved in 70.0% of 30 patients vs 0% of 30 patients with calcipotriene (aka calcipotriol) + PUVA vs calcipotriol, respectively (RR 43.0 (95% CI 2.72, 678.92; anticipated absolute effect [AAE] of 0 [95% CI 0 fewer to 0 fewer]) based on moderate quality evidence. A 2021 meta-analysis showed that the combination of phototherapy (NB-UVB, PUVA, or 308 excimer laser) and topical calcipotriene was more effective in achieving a marked / "apparently effective" response (50%–75% repigmentation) than phototherapy alone (RR 1.50 [95% CI 1.30, 1.73; I^2 = 0%; moderate quality evidence).[7] Study patients had different subtypes of vitiligo, mainly described as *bilateral and symmetrical* or *generalized*.
- The general steps in the treatment of vitiligo according to the BAD guidelines are shown in Table 5.

Table 5 Repigmentation Therapies for Vitiligo Based on the 2021 British Association of Dermatologist (BAD) Guidelines (Published 2022)

Disease Status	Place in Therapy	Treatment Alternatives	Comments
Stable‡ localized disease	1st-line	**Offer high- to super-high potency topical corticosteroids**, (groups 1–3) applied once daily avoiding periocular skin	No vehicle-controlled RCTs found. **Treatment success** (VNS of a lot less noticeable or no longer noticeable) at 9 mos in localized, active nonsegmental vitiligo affecting ≤ 10% BSA: 17% for mometasone furoate ointment 0.1%, 22% for home-based NB-UVB, and 27% for combination.[8] Group 1 topical corticosteroids may be preferred for trunk and extremity lesions. Optimal duration of treatment is unclear. Limited quantities and discontinuous dosage regimens should be used to reduce risks of adverse effects. Associated with skin atrophy, telangiectasias, hypertrichosis, and acneiform eruptions. Mometasone furoate ointment 0.1% (Group 3 / high potency) had no reported adverse events in studies.
		Consider **topical tacrolimus** ointment 0.1% twice daily for **facial** vitiligo	Preferred over topical corticosteroids for the face, intertriginous areas, and genitals. Lacks risk of skin atrophy. Does not seem to be associated with skin or systemic malignancies. **Maintenance of gained repigmentation** at 6 mos with tacrolimus ointment 0.1% vs **placebo**: 89.5% of 19 patients vs 62.5% of 16 patients (RR 1.43 [0.95, 2.16]; AAE 269 more [31 fewer to 725 more]; moderate QE). **CFB in DLQI** to 6 mos, tacrolimus ointment 0.1% vs **placebo**: 19 vs 16 (MD 0.64 higher [2.39 lower to 3.67 higher]; very low QE).
		Consider **topical tacrolimus** 0.1% ointment twice daily **under occlusion** on photoexposed areas	Use only for nonfacial vitiligo.
		Consider **intermittent** regimen of once daily high or super-high **topical corticosteroids ± topical calcineurin inhibitors**	More evidence for tacrolimus. Weigh risks and benefits, especially for areas with thinner skin (e.g., periocular, genitals, intertriginous), and for intermittent regimens that use topical corticosteroids for > 1 wk. Example intermittent regimens: • 1 wk of corticosteroids and ≥ 1 wk off; • 1 wk of corticosteroids alternating with ≥ 1 wk of topical calcineurin inhibitor
	2nd line after inadequate response to topical therapies	Offer **NB-UVB ± topical corticosteroid or ± topical calcineurin inhibitors**	For NB-UVB + topical calcineurin inhibitor, consider theoretical increased risk of skin cancer. For NB-UVB + high potency topical corticosteroid, consider that there is limited evidence. **≥ 75% repigmentation** at 9 mos with hand-

Disease Status	Place in Therapy	Treatment Alternatives	Comments
			held NB-UVB + topical mometasone furoate 0.1% vs hand-held NB-UVB: 10.3% of 175 patients vs 5.3% of 169 patients (RR 1.93 [0.89, 4.18]; AAE 50 more [6 fewer to 169 more]; low QE)
	3rd line	Consider **excimer laser or phototherapy in combination with topical calcineurin inhibitors**	More evidence for tacrolimus. Theoretical increased risk of skin cancer.
	Alternative if other treatments ineffective	Consider **CO_2 laser in combination with topical 5-FU** for nonsegmental vitiligo on the **hands and feet** (high QE)	Not generally feasible in VHA. Apply topical 5-FU once daily for 7 days per month for 5 months. Use CO_2 laser treatments once per month for 5 months. Strength of 5-FU cream was not reported in the study.[9] 5-FU can be associated with application-area hyperpigmentation, inflammation, and ulceration. **≥ 75% repigmentation rates** at 6 mos[6]: • Topical 5-FU + CO_2 laser vs CO_2 laser: 49.8% of 955 patients vs 2.0% of 601 patients (RR 25.0 [14.21, 43.86]; AAE 478 [264, 856] more; high QE). • CO2 laser vs topical 5-FU: 2.0% of 601 patients vs 3.7% of 703 patients (RR 0.54 [0.27, 1.06]; AAE 17 fewer per 1000 [2 more to 27 fewer]; moderate QE)
	Alternative after inadequate response to topical therapies and NB-UVB phototherapy	Surgical transplantation procedures	
	Not included in BAD guidelines	**Topical JAKI** (ruxolitinib cream 1.5% BID)	FDA indication requires no prior therapies, suggesting ruxolitinib cream is a first-line therapy for nonsegmental vitiligo. Dosage is limited to ≤ 10% of BSA. Studied as monotherapy. Safety and efficacy of combination therapy is unclear. Lacks evidence of long-term safety and effectiveness.
Rapidly progressive† lesions	1st-line	**Consider systemic corticosteroids** • Equivalent of betamethasone 0.1 mg/kg 2x/wk on 2 consecutive days for 3 mos then taper by 1 mg/mo for 3 mos in combination with NB-UVB. **Other regimens**[10] • Prednisone 10–20 mg QD x up to 2 wks • Dexamethasone OMP 2.5 mg QD x 2 consecutive days each	Disease typically stabilizes in 1–3 mos. May use in combination with NB-UVB. Evidence: Few uncontrolled studies. Comparative Study: Open-label study showed that betamethasone OMP alone was less effective than in combination with PUVA, NB-UVB, or broadband UVB (15% vs 85%, 81%, or 33%, respectively, at 6 mos).

Disease Status	Place in Therapy	Treatment Alternatives	Comments
		week for an avg of 3 mos • Triamcinolone 40 mg IM x 1 dose; may repeat in 4–6 wks for up to 3 injections	
	Alternative	Offer **NB-UVB phototherapy**	Used when systemic corticosteroids are contraindicated.
Extensive disease	1st line	Offer NB-UVB phototherapy	
	Alternative	Consider depigmentation therapies on visible sites	

Sources: 6,10

AAE, Anticipated absolute effect, shown per 1000 cases [95% CI]; **MD**, Mean difference; **NB-UVB**, Narrow-band ultraviolet B; **OMP**, Oral minipulse; **PUVA**, Psoralen plus ultraviolet A; **QE**, GRADE quality of evidence; **RR**, Relative risk [95% CI]; **VNS**, Vitiligo Noticeability Scale

† **Progressive** disease is defined as new lesions developing or old vitiliginous lesions progressing within the last 12 months. **Rapidly progressive** disease has no international consensus definition but is described as *abrupt* deterioration in developing new lesions or increase in size of old lesions.

‡ **Stable** disease is defined as no new lesions developing within the last 12 months AND lack of progression of old lesions within the last 12 months.

Projected Place in Therapy

- **Epidemiology and Prevalence of Vitiligo**. Vitiligo is a relatively common chronic skin depigmentation disease of unknown causes. Autoimmune destruction of epidermal melanocytes may be involved. Depigmented macules may be localized or generalized over the body and segmental (occurring on one-half of the body) or nonsegmental (occurring on both sides of the body). People with darker skin pigmentation have more noticeable differences in skin coloration between affected and normal areas. Although the disease is physically asymptomatic except for depigmentation, it can be disfiguring and have profound detrimental psychosocial effects on quality of life, social interactions, self-esteem, and discrimination against the patient. The prevalence of vitiligo ranges from 0.5% to 1% worldwide[11] and has been estimated to be about 1.4% based on patient self-reports in the US.[12] Patients who present with disease are aged less than 20 years in 50% of cases and less than 30 years in almost 70% to 80% of cases. There are no sex, racial, or socioeconomic predilections for the disease.
- **Place in Therapy Based on Medical Society Guidelines**. No relevant guidelines.
- **Potential Place in Therapy Based on the Evidence**. No head-to-head trials were available to inform the comparative effectiveness and place in therapy of topical ruxolitinib. In general, topical medications are more effective in combination with phototherapy than either treatment alone and all therapies are only moderately effective, with a possible exception of combination topical 5-fluorouracil plus CO_2 laser, which seems to produce larger effects for vitiligo on the hands and feet. Moderate-quality evidence from two vehicle-controlled trials supports the use of ruxolitinib cream mainly in white patients and patients with Fitzpatrick skin types II to IV who have stable, nonsegmental vitiligo affecting ≤ 10% BSA. The most common prior therapies were topical calcineurin inhibitors, topical corticosteroids, and NB-UVB phototherapy. Inadequate response or intolerance to prior therapies was not required in the clinical trials and is not required in the FDA-approved indication. Overall, facial VASI75 benefits are small and their clinical meaningfulness to patients is uncertain. Several issues need to be considered when selecting treatment. Ruxolitinib cream is the only systematically studied ("pivotal"), FDA-approved therapy for the treatment of vitiligo. It costs 67 to 804 times more than clobetasol cream 0.05% or betamethasone cream 0.05% and 57 times more than tacrolimus ointment 0.1% based on price per gram. Furthermore, the use of topical ruxolitinib in combination with other vitiligo therapies including phototherapy has not been evaluated, and long-term safety and efficacy, such as in sustaining repigmentation, are unknown.

- **Potential Place in Therapy in VHA**. Topical ruxolitinib monotherapy may be used in patients with stable, nonsegmental vitiligo who have tried topical corticosteroids, topical calcineurin inhibitors, and phototherapy unless these therapies are medically inadvisable, not available, or not feasible. Application should be limited to ≤ 10% BSA. The use of topical ruxolitinib concurrently with all other therapies used for vitiligo was not evaluated. Use of topical ruxolitinib in combination with phototherapy, therapeutic biologics, other JAKIs, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

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