Ruxolitinib (OPZELURA) Cream for Atopic Dermatitis National Drug Monograph August 2022

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 bispecific Janus kinase (JAK) inhibitor (JAK1 and JAK2) previously approved in tablet form for the systemic treatment of graft-versus-host disease, myelofibrosis, and polycythemia vera.[1]
- Ruxolitinib cream is the first topical JAK inhibitor (JAKI).

Indication Under Review in This Document

- Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (AD) in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
    - Limitation of Use: Use of ruxolitinib cream in combination with therapeutic biologics, other JAKIs, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

Dosage Regimen and Dosage Form Under Review

- Apply a thin layer twice daily to affected areas up to 20% of body surface area (BSA). Maximum 60 grams per week.
- Stop using when signs and symptoms (e.g., itch, rash, and redness) of AD resolve. If signs and symptoms do not improve within 8 weeks, patients should be re-examined by their health care provider.
- Cream: 15 mg of ruxolitinib per gram (1.5%) in 60-gram tubes.

Clinical Evidence Summary

Efficacy Considerations

- Two identically designed, 8-week, phase 3, double-blind, vehicle-controlled randomized clinical trials (RCTs), TRuE AD1 and TRuE AD2, showed that topical ruxolitinib was efficacious in the treatment of patients with mild to moderate AD and produced rapid reduction in pruritus.[2]
- Results of a multicenter, phase 2, double-blind, dose-, vehicle-, and active-controlled RCT in the US and CA supported the anti-inflammatory and antipruritic efficacy of ruxolitinib cream seen in the phase 3 RCTs and suggested that ruxolitinib 1.5% cream (twice daily) may be better than triamcinolone acetonide cream 0.1% (twice daily) in certain efficacy measures.[3,4]

Phase 2 Active-controlled Trial

- The phase 2 RCT included patients aged 18 to 70 years with active AD, AD diagnosis for ≥ 2 years, Investigator Global Assessment (IGA) score of 2 or 3, and body surface area (BSA) involvement of 3%–20%.
- The RCT consisted of an 8-week double-blind phase and a 4-week follow-on, open-label phase.
- Patients were randomized equally to six interventions, stratified by EASI score (≤ 7 or > 7). The interventions were ruxolitinib cream 1.5% twice daily, 1.5% once daily, 0.5% once daily, and 0.15% once daily; vehicle twice daily or once daily (to maintain the blind); or triamcinolone acetonide cream 0.1% (a medium-potency TCS serving as an active control) twice daily for 4 weeks, then vehicle for 4 weeks.
- Control for multiplicity was not reported.
- Comparisons between ruxolitinib and triamcinolone could only be performed up to Week 4. After Week 4, triamcinolone patients were switched to vehicle. Ruxolitinib cream 1.5% twice daily was nonsignificantly better than triamcinolone cream at Week 4, both in mean percentage improvement from baseline in the Eczema Area and Severity Index (EASI) score (71.6% vs 59.8%, respectively) and IGA response. Ruxolitinib 1.5% twice daily was significantly better than triamcinolone in the mean change in worst Itch Numerical Rating Scale (NRS) score (Table 1).

Table 1 Ruxolitinib vs triamcinolone: Summary of phase 2 RCT efficacy results

Outcome Measure	RUX 1.5% BID N = 50	TACA 0.1% BID N = 51	P-value
Primary Efficacy Measure			
Relative CFB to Week 4 in EASI score, mean	71.6%	59.8%	NSD
Key Secondary Measures			
IGA response at Week 4, n (%)†	19 (38.0)	13 (25.5)	NSD
EASI-90 response at Week 4, n (%)	13 (26.0)	7 (13.7)	—
Worst itch NRS score, mean CFB to Week 4	–4.0	–2.5	0.003
CRI‡ in the worst itch NRS at Week 2, n/N (%)	NR / NR (47.5)	NR / NR (19.4)	< 0.05
CRI‡ in the worst itch NRS at Week 4, n/N (%)	NR / NR (62.5)	NR / NR (32.3)	—
MCID§ in worst itch NRS at ≤ Hour 36 / Day 2, n/N (%)	NR / NR (42.5)	NR / NR (20.5)	< 0.05
Exploratory Measure			
Skindex-16 (QOL), mean relative CFB to Week 4	73.7%	59.7%	0.02

Sources: 4,5

CFB, Change from baseline; CRI, Clinically relevant improvement; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, Not reported; NRS, Numerical rating scale; NSD, No statistically significant difference; QOL, Quality of life; RUX, Ruxolitinib; TACA, Triamcinolone acetonide

† IGA response was defined as achievement of IGA score of 0 to 1 with ≥ 2-point improvement from baseline.

‡ Clinically relevant improvement (CRI) in the worst itch NRS was defined as ≥ 4-point reduction from baseline. The CRI analysis was conducted in patients with baseline itch NRS of ≥ 4 (n = 232).

§ The MCID in itch NRS was defined as a ≥ 2-point reduction on a 0 (No Itch) to 10 (Worst Imaginable Itch) scale. The MCID analysis was performed in patients with baseline itch NRS of ≥ 2 (n = 272).

- Near-maximal improvement in worst Itch NRS scores was seen by Week 4.
- At Week 8, patients were switched to open-label ruxolitinib 1.5% twice daily. Improvements from Week 8 to Week 12 were seen for ruxolitinib 1.5% twice daily in the mean percentage improvement in EASI scores (Week 8 / Week 12: 79.4% of 43 patients / 84.9% of 41 patients, respectively) and in IGA response (55.8% / 58.5%, respectively).[5] The corresponding results for triamcinolone at Week 8 / Week 12 were 59.2% of 40 patients / 86.8% of 39 patients, respectively, for EASI scores and 20.0% / 66.7%, respectively, for IGA response.[5]

Phase 3 TRuE-AD1 and TRuE-AD2 Trials

Study Design

- Two phase 3, multinational, multicenter, double-blind, vehicle-controlled RCTs compared ruxolitinib cream 0.75% and 1.5% with vehicle applied twice daily. Randomization was stratified by baseline IGA score (2 or 3) and region (North America or Europe).
- Patients who completed the first 8 weeks of the trial were eligible to enter an ongoing 44-week blinded safety extension study in which vehicle-treated patients were re-randomized to either ruxolitinib 0.75% or 1.5% cream twice daily. Patients initially randomized to ruxolitinib cream continued the same therapy.
- Inclusion Criteria
    - Age ≥ 12 years
    - AD diagnosis for ≥ 2 years
    - Investigator's Global Assessment (IGA) score of 2 or 3
    - 3% to 20% affected body surface area (BSA) excluding the scalp
- Exclusion Criteria
    - Unstable course of AD
    - Other types of eczema
    - Immunocompromised patients
    - AD biologic therapy within 5 half-lives or within the previous 12 weeks
    - Systemic corticosteroids or other immunomodulating agents for AD within the previous 4 weeks
    - Topical AD therapies within the previous 1 week
- Co-medications
    - No rescue medication was allowed.
- Multiplicity was not controlled.

Primary Efficacy Measures

- Proportion of patients at Week 8 achieving IGA treatment success (IGA-TS), defined as a score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline.

Key Secondary Measures

- Proportion of patients at Week 8 achieving ≥ 75% improvement from baseline in EASI (EASI-75)
- Proportion of patients at Week 8 achieving ≥ 4-point reduction from baseline in worst itch level on the Itch NRS (Itch NRS-4), ranging from 0 (No Itch) to 10 (Worst Imaginable Itch). Reductions ≥ 4 points is considered clinically meaningful.
- Proportion of patients at Week 8 achieving ≥ 6-point (clinically meaningful) improvement from baseline in the Patient-Reported Outcomes Measurement Information System sleep disturbance score (PROMIS-SD-6).

Other Selected Secondary Measures

- Mean change from baseline in Itch NRS
- Proportion of patients at Week 8 achieving ≥ 90% improvement in EASI (EASI-90)

Patient Characteristics

- The study populations mainly consisted of white females with median age 32–33 years who had AD affecting about 10% of BSA (Table 2).

Table 2 Baseline Patient Characteristics

Characteristic	TRuE-AD1	TRuE-AD2
N	631	618
Age, median, y	32	33
Age ≥ 18 y, %	80.5	80.3
Male, %	38	38.5
Race, White / Black / Asian, %	68.6 / 22.2 / 5.1	70.7 / 24.6 / 2.3
Region, North America	69.7	67.2
BSA, mean (%)	9.5	10.0
Itch NRS score	5.1	5.1

- Based on pooled data of the patients' previous AD therapy (N = 1249), TCS therapy had been used in 80.0% of patients, topical calcineurin inhibitor by 22.1%, and systemic therapy by 18.9%. No previous treatment had been received by 10.8% of patients.

Results

- Results reported here focus on ruxolitinib cream 1.5%, the approved cream strength.
- Selected efficacy data are summarized in Table 3.

Table 3 Selected phase 3 RCT efficacy results at Week 8

Outcome	TRuE-AD Trial	RUX 1.5%	Vehicle	Difference vs Vehicle, % (95% CI)
IGA-TS, n/N (%)	1	136/253 (53.8)	19/126 (15.1)	38.7 (29.9, 47.4)
	2	117/228 (51.3)	9/118 (7.6)	43.7 (35.6, 51.8)
Itch NRS-4, n/N (%)	1	84/161 (52.2)	12/78 (15.4)	36.8 (25.7, 47.9)
	2	74/146 (50.7)	13/80 (16.3)	34.4 (23.0, 45.9)
EASI-90, n/N (%)	1	112/253 (44.3)	12/126 (9.5)	38.7 (29.9, 47.4)
	2	99/228 (43.4)	5/118 (4.2)	43.7 (35.6, 51.8)
PROMIS-SD-6	1	53/238 (22.3)	11/116 (9.5)	12.8 (5.3, 20.3)
	2	54/211 (25.6)	21/110 (19.1)	6.5 (–2.9, 15.9)

Sources: 5,6
IGA-TS, Investigator global assessment treatment success (defined as a score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline)

Table 4 Pooled phase 3 RCT efficacy results at Week 8

Outcome	RUX	Vehicle	Relative Risk (95% CL)	Anticipated Absolute Effects per 1,000 patients (95% CL)	NNT (95% CL)	Q
IGA-TS, n/N (%)	253/481 (52.6)	28/244 (11.5)	4.6 (3.2, 6.6)	413 (252, 643) more	3 (3, 3)	H
Itch NRS-4, n/N (%)	158/307 (51.5)	25/158 (15.8)	3.3 (2.2, 4.7)	364 (190, 585) more	3 (3, 4)	H
EASI-90, n/N (%)	211/481 (43.9)	17/244 (6.9)	5.8 (3.6, 9.2)	334 (181, 571) more	3 (3, 3)	H
PROMIS-SD-6, n/N (%)	107/449 (23.9)	32/226 (14.2)	1.7 (1.2, 2.4)	99 (28, 198) more	11 (7, 31)	M[α]

H, High; M, Moderate; Q, GRADE Quality of evidence
[α] Downgraded for inconsistency between trials.

- IGA-TS responses were dependent on time and cream strength.
- *Onset of antipruritic efficacy.* Ruxolitinib 1.5% showed significant benefit in Itch NRS scores within 12 hours of the first application of cream.[2] Ruxolitinib 1.5% also showed significant benefit in the Itch NRS-4 response on Day 2, about 36 hours after the first application.[2]

- *Itch*. In pooled data, ruxolitinib 1.5% showed significant benefit vs vehicle in the percentage of patients achieving Itch NRS scores of 0 or 1 after Week 1 (39.4% of 481 patients vs 14.1% of 244 patients, respectively) and Week 8 (51.5% vs 23.1%, respectively).
- *Functional ability / disability*. Ruxolitinib 1.5% therapy resulted in numerically greater relative improvements from baseline to Week 8 in absenteeism (4.78% vs vehicle 7.41%; no significant difference [NSD]), presenteeism (–19.77% vs –12.31%; $p < 0.0001$), overall work impairment (–15.01% vs –5.73%; $p < 0.0001$), and daily activity impairment (–21.49% vs –10.60%; $p < 0.0001$) (pooled results, paper presentation).[5,7] A lower percentage of ruxolitinib 1.5%-treated patients reported being "A Lot" or "Very Much" affected by AD at Week 8 in shopping, social, and sport activities as measured on the Dermatology Life Quality Index (DLQI); however, differences were not statistically significantly different (pooled results, paper presentation).[5,7]
- Gaps in outcome measures
    - Patient Satisfaction

Subgroup Analyses

- No subgroup response predictors were identified in analyses by sex, age, and race.[5]

Network Meta-analyses

Topical ruxolitinib vs topical CNI or TCS

- A low-quality network meta-analysis of 10 RCTs (N = 4689) compared the efficacy and safety of JAKIs and PDE4 inhibitors in the treatment of patients with mild to severe AD, most of whom had mild to moderate disease.[8] Phase 2 or phase 3 placebo- or active-controlled RCTs were eligible for inclusion. One trial involving tacrolimus and hydrocortisone butyrate was also analyzed as standard therapy for AD. Six of the 10 RCTs were performed in adults.
- Efficacy was based on achieving an IGA-TS at the end of treatment, which was 4 weeks in 7 RCTs, 8 weeks in 2 RCTs, and 6 months in 1 RCT. The quality of evidence was not evaluated.
- Results for the four FDA-approved therapies compared against placebo in phase 3 RCTs are summarized in Table 5.

Table 5 Efficacy and safety of approved topical AD treatments vs placebo

Intervention	K	N	Follow-up (wks)	IGA-TS, OR (95% CrI)	AE Incidence, OR (95% CrI)
Ruxolitinib cream 1.5% BID	2	499	8	13.2 (7.5–25.0)	0.7 (0.5–1.0)
Crisaborole ointment 2% BID	2	1016	4	1.7 (1.2–2.2)	1.2 (0.9–1.6)
Tacrolimus ointment 0.1% BID	1	487	24	3.8 (0.4–28.1)	1.6 (0.7–3.7)
Hydrocortisone butyrate ointment 0.1% BID	1	485	24	2.2 (0.2–17.3)	0.6 (0.3–1.3)

AE, Adverse event; IGA-TS, Investigator Global Assessment treatment success; K, No of RCTs

- In network meta-analyses, twice daily therapy with topical ruxolitinib 1.5% was significantly better in achieving IGA-TS response than crisaborole 2% (OR 7.38; 95% CrI 4.03, 13.52), tacrolimus 0.1% (8.56; 1.21, 60.33) and the lower–mid-potency (group 5) TCS hydrocortisone butyrate 0.1% (12.55; 7.22, 21.80). A limitation of the analyses was variability in assessment time points (range, 4–24 weeks).
- Topical ruxolitinib was not differentiable from the three other approved topical treatments in terms of the incidence of adverse events.

Topical ruxolitinib vs off-label oral JAKIs

- A fair-quality network meta-analysis indirectly compared oral and topical JAKIs based on ≥ 50% improvement from baseline in EASI (EASI-50 response) at Week 4.[9] The meta-analysis included 7

placebo-controlled RCTs (N = 2530) that evaluated 7 JAKIs in 20 different formulations and doses in patients with primarily moderate to severe AD. Of four oral JAKIs evaluated, two (baricitinib and upadacitinib) were available commercially in the US. Of three topical JAKIs, only ruxolitinib was available and the only JAKI approved for AD.

- In pairwise comparisons of the products available in the US, topical ruxolitinib 1.5% twice daily was inferior to oral baricitinib 1 mg daily (OR –2.32; 95% CrI –3.72, –1.09) and 2 mg daily (–1.33; –2.73, –0.12), and undifferentiable from oral baricitinib 4 mg daily (–0.92; –2.31, 0.30) and oral upadacitinib 7.5 mg daily (–0.08; –2.00, 1.82), 15 mg daily (–1.04; –2.99, 0.87), and 30 mg daily (–1.84; –3.89, 0.11).[9]

Safety Considerations

- **Boxed Warnings**: Serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.
- **Contraindications**: None.
- **Other Warnings / Precautions**: The warnings and precautions of topical ruxolitinib are similar to those for oral ruxolitinib (Table 6).

Table 6 Summary of Warnings and Precautions

Warning / Precaution	Considerations Before Initiating Therapy	Pre-treatment Tests or Therapy	Management During Therapy
Serious Infections	Avoid use in patients with active, serious infection, including localized infections. Weigh risk-benefits in patients with chronic or recurrent infection, history of a serious or an opportunistic infection; exposure to TB; residence or travel in areas of endemic TB or endemic mycoses; or underlying conditions that may predispose to infection.	—	Interrupt therapy if patient develops a serious or opportunistic infection or sepsis and do not resume until the infection is controlled.
Tuberculosis (TB)	No cases of active TB were reported during topical ruxolitinib clinical trials. Oral JAKIs used for inflammatory diseases have been associated with active TB.	Consider TB screening.	Monitor patients for signs and symptoms of TB. (No recommendations for regular re-testing for TB.)
Viral Reactivation	Reactivation of viruses including herpes (e.g., herpes zoster) occurred during topical ruxolitinib clinical trials.	—	If a patient develops herpes zoster, consider interrupting therapy until the condition resolves.
Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)	Risk of reactivation of chronic HBV or HCV is unknown. Patients with a history of HBV or HCV infection were excluded from clinical trials.	Initiation of therapy is not recommended in patients with active HBV or HCV infection.	—
Mortality	Oral JAKIs used for inflammatory diseases were associated with increased all-cause mortality. Weigh risk-benefits.	—	—
Malignancy and Lymphoproliferative Disorders	Oral JAKIs used for inflammatory diseases have been associated with malignancies including lymphomas and lung cancer. Weigh risk-benefits, particularly in patients with a known malignancy other than successfully treated non-melanoma	—	Weigh risk-benefits of continuing therapy if a patient develops a malignancy.

Warning / Precaution	Considerations Before Initiating Therapy	Pre-treatment Tests or Therapy	Management During Therapy
	skin cancers and in current or past smokers.		
Non-melanoma Skin Cancers (NMSC)	NMSCs have occurred in patients using topical ruxolitinib.	—	Examine skin periodically.
Major Adverse Cardiovascular Events (MACE)	Weigh risk-benefits, particularly in current or past smokers and patients with other cardiovascular risk factors.	—	—
Thrombosis	Oral JAKIs used for inflammatory diseases increased the risk of thrombosis including deep vein thrombosis, pulmonary embolism, and arterial thrombosis. Thromboembolic events occurred in patients using topical ruxolitinib during clinical trials. Use topical ruxolitinib with caution in patients at increased risk of thrombosis.	—	—
Thrombocytopenia, Anemia, and Neutropenia	These cytopenias occurred during topical ruxolitinib clinical trials. The incidence of neutropenia was < 1%.[1] Incidences of thrombocytopenia and anemia were not reported. Weigh risk-benefits in patients with a known history of these hematologic abnormalities.	—	Monitor CBC as clinically indicated. If clinically significant thrombocytopenia, anemia, or neutropenia occurs, discontinue topical ruxolitinib.
Lipid Elevations	Oral ruxolitinib has been associated with increased lipids including total cholesterol, LDL, and triglycerides.	—	—

Anti-HBc, Antibody to hepatitis B core antigen; **Anti-HBs**, Antibody to hepatitis B surface antigen; **CBC**, Complete blood count; **HBsAg**, Hepatitis B surface antigen

- **Deaths and Serious Adverse Events**: Deaths were not reported. Rates of serious adverse events were similar between ruxolitinib cream 1.5% and vehicle (0.6% and 0.8%, respectively).[2]
- **Withdrawals Due to Adverse Events**: Less frequent on ruxolitinib cream 1.5% vs vehicle (3 [0.6%] vs 8 [3.2%], respectively) based on pooled safety data from TRuE-AD1 and TRuE-AD2.[2]
- **Common Adverse Events (≥ 1%)**: Nasopharyngitis, diarrhea, bronchitis, ear infection, increased eosinophil count, urticaria, folliculitis, tonsillitis, and rhinorrhea.[1] In the phase 3 RCTs, the most common treatment-related adverse events were application site burning and application site pruritus, both of which were more common on vehicle than ruxolitinib cream 1.5%.
- **Other Events of Potential Interest**: Transient, modest increases in platelet count, all within normal reference values, occurred at Week 2 and resolved by Week 4.[11] The mechanism for the increase in platelets is unknown but may not be related to an effect on the bone marrow.[11]

Drug Interactions

- **Strong CYP3A4 Inhibitors**. Avoid concomitant use (could increase systemic exposure of ruxolitinib).

Other Considerations

Absorption

- In a pharmacokinetic (PK) study involving 20 adults and 21 children with AD, plasma concentrations of ruxolitinib were detectable in all patients after topical administration of ruxolitinib cream twice daily for 28 days.[1] The mean dose was about 1.5 mg/cm^2 and the mean affected BSA was 37.5 ± 16.1% (range 25% to 90%, above the recommended maximum BSA of 20%).[1] The dose ranged from 1.2 grams to 37.6 grams per application. The mean ± SD maximum concentration (C_{max}) was 449 ± 883 nM, and the area under the concentration-time curve from 0 to 12 hours ($AUC_{0–12}$) on Day 1 was 3215 ± 6184 nM x h.[1] There was no evidence of drug accumulation with daily application for 28 days in patients with AD.[1]

  PBM Comment: The C_{max} and $AUC_{0–12}$ achieved after topical ruxolitinib application exceeding 20% of BSA were in the range of those observed after oral administration of a single dose of ruxolitinib 5 mg to 200 mg (up to four times the maximum approved total dose of 25 mg twice daily): mean C_{max} 205 nM to 7100 nM; AUC 862 to 30,700 nM x h.[10]

- A published PK study analyzed data from 188 patients in the phase 2 RCT (four ruxolitinib cream treatment groups) and 951 patients in the two phase 3 RCTs (two ruxolitinib cream treatment groups).[11] The mean ± SD (median) topical bioavailability was 5.68% ± 5.58 (4.17) in the phase 2 RCT (application rate, 1.92 mg/cm^2) and 6.22% ± 7.66 (3.64) in the phase 3 RCTs (application rate, 1.47 mg/cm^2) when ruxolitinib cream 1.5% was applied twice daily to ≤ 20% of BSA.[11] Bioavailability was not dependent on dose, strength, or BSA. This low bioavailability after topical application was noted to be substantially lower than the 95% absorption seen with oral administration in healthy volunteers.[10,11]
- The mean ± SD (median) trough C_{ss} resulting from topical application of ruxolitinib 1.5% (twice daily) was 47.7 ± 79.6 (23.1) nM in the phase 2 RCT and 35.7 ± 55.0 (15.4) nM in the two phase 3 RCTs.[11] Less-than-dose / strength-proportional increases in ruxolitinib C_{ss} were observed. Ruxolitinib C_{ss} did not correlate with hemoglobin or absolute neutrophil counts. Ruxolitinib dose- and C_{ss}-dependent increases in platelet count at Week 2 were observed but were small (< 30% change from baseline), remained within normal reference values, and returned to baseline by Week 4. C_{max} values were not reported.

  PBM Comment: These C_{ss} values from the phase 2 RCT and phase 3 RCTs were 13.6% and 10.2%, respectively, of the average C_{ss} of about 350 nM produced with oral ruxolitinib 25 mg twice daily in patients with myelofibrosis.[12]

- The authors of the published PK study noted that the risk of myelosuppression increases when the average drug plasma concentrations repeatedly exceed the whole blood half-maximal inhibitory concentration (IC50) for JAK2 inhibition for several hours to days over a period of ≥ 2 weeks. For ruxolitinib, the IC50 is 281 nM, which is about 6-fold and 7.9-fold higher than the mean C_{ss} in the phase 2 and phase 3 RCTs, respectively. Therefore, the authors concluded that hematologic counts were not expected to change after topical administration of ruxolitinib, and no clinically relevant changes were observed in the PK study.

  PBM Comment: It is noteworthy that the mean ruxolitinib C_{max} of 449 ± 883 nM reported in the prescribing information[1] exceeds the IC50 of 281 nM, although the frequency and duration that C_{max} exceeds the IC50 is not reported.

Other Therapeutic Options

- Low- to medium-potency topical corticosteroids (TCSs) are the mainstay of pharmacotherapy for acute treatment and relapse prevention of mild to moderate AD. TCSs are generally added when patients do not respond adequately to general skin care measures and regular application of emollients alone.[13,14] TCSs improve acute and chronic signs of AD and pruritus.

- The most recent society guideline on the management of AD is the 2020 position paper of the European Task Force on Atopic Dermatitis (ETFAD) of the European Academy of Dermatology and Venerology (EADV).[15] No recent guidelines from American dermatologic societies were available. Table 7 summarizes the alternative topical treatments for mild to moderate AD that are probably at the same level of therapy as topical ruxolitinib.

Table 7 Topical Nonsteroid Pharmacotherapeutic Alternatives for Mild to Moderate Atopic Dermatitis

Topical Product	On VANF	FDA-approved Indications	Safety Considerations	Other Considerations
Janus Kinase Inhibitor (JAKI)				
***Potential place in therapy**: Similar to that of CNIs, based on similar FDA-approved indications.*				
Ruxolitinib Cream 1.5%	TBD	2nd-line tx for short-term and non-continuous chronic tx of **mild to moderate** AD in non-immunocompromised patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Not recommended in combination with biologics, other JAKIs, or potent immunosuppressive txs.	Requires pre-treatment clinical and laboratory assessments that are atypical for topical AD therapies. Does not cause skin atrophy and other TCS class AEs.‡	Has maximum recommended dose (60 g/wk), BSA (20%), and tx duration (till signs and symptoms resolve; re-assess if no improvement after 8 wks).
Calcineurin Inhibitors (CNIs)				
ETFAD / EADV-recommended 1st-line treatment alternative to reactive, moderate-potency TCS therapy for mild AD and 1st-line treatment alternative to moderate- or potent-TCS as proactive therapy for moderate AD [15]				
Tacrolimus (TAC) Ointment 0.03% or 0.1%	Yes	2nd-line tx for short-term and noncontinuous chronic treatment of **moderate to severe** AD in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable	Has boxed warning for rare malignancies (e.g., skin and lymphoma), although the association of CNIs with malignancies has been disputed.[16,17,18,19] Does not cause skin atrophy, epidermal barrier dysfunction, or other TCS class AEs.‡ High rate of application site burning sensation (36%–50%).[20]	TAC 0.03% and 0.1% are better than low-potency TCSs. TAC 0.1% is considered equivalent to medium-potency TCS. Very good antipruritic effects. Tx duration: Till signs and symptoms resolve; re-assess if no improvement after 6 wks. No maximum recommended dose or BSA.
Pimecrolimus (PIM) Cream	No	2nd-line tx for short-term and noncontinuous long-term tx of **mild to moderate** AD in non-immunocompromised pts 2 yrs and older who have failed to respond adequately to other topical prescription txs, or when those txs are not advisable	See TAC. Lower systemic absorption than topical TAC. Seems to have lower rate of burning sensation than TAC (7%–10%).[20]	Same as for TAC except PIM is less effective than lower–mid-potency TCSs.[21] PIM is somewhat less effective than TAC 0.03%[22] but may be preferred over TAC in sensitive areas.[20]

Topical Product	On VANF	FDA-approved Indications	Safety Considerations	Other Considerations
Phosphodiesterase-4 Inhibitor (PDE4I)				
ETFAD / EADV-recommended treatment alternative to reactive, moderate-potency TCS therapy for mild AD.[15]				
Crisaborole Ointment (CRI)	No	**Mild to moderate** AD in adult and pediatric patients 3 months of age and older	Favorable AE profile with no boxed warning. Not immunosuppressive. Does not cause skin atrophy or other TCS class AEs.	No maximum recommended dose, BSA, or tx duration. Limited data and uncertain benefit in adult subgroup May provide resolution of pruritus by Day 6 and improvement in pruritus as early as Day 2.[23]

Sources: 6,15
AE, Adverse events; BSA, Body surface area; TCS, Topical corticosteroid
† Sensitive areas refer to those at increased risk for skin atrophy (e.g., head, face, neck, axilla, and inguinal and genital areas).
‡ TCS class AEs refer to striae, telangiectasia, and hypothalamic-pituitary-adrenal axis suppression.

Projected Place in Therapy

- **Epidemiology and Prevalence of Mild to Moderate AD**. In a population-based cross-sectional study, the prevalence of AD in the US was estimated to be 7.3% (95% CI 5.8, 8.8).[24] More than 80% of patients with AD have mild to moderate disease.[25]
- **Place in Therapy Based on Medical Society Guidelines**. No published dermatologic society guidelines on treatment of AD include topical ruxolitinib. Based on similar FDA-approved indications, topical ruxolitinib could be placed at the same line of therapy as topical pimecrolimus (i.e., second-line after other topical therapies).
- **Potential Place in Therapy Based on the Evidence**. The results of an active-controlled, phase 2 RCT suggested that relative to triamcinolone acetonide cream 0.1% ruxolitinib cream may have significantly better antipruritic effects. No RCTs comparing topical ruxolitinib with topical CNIs or crisaborole were available to further inform place in therapy. However, topical ruxolitinib has more boxed warnings (serious infections, mortality, malignancies, MACE, and thrombosis) than crisaborole ointment (lacks boxed warnings) and the topical CNIs (malignancy). Based on high-certainty evidence from two vehicle-controlled, phase 3 RCTs, short-term (8 weeks) ruxolitinib cream 1.5% significantly improved IGA treatment success (large benefit) in a primarily female, near middle-aged patient population with mild to moderate AD, 90% of whom had received prior therapy (mostly TCSs). Ruxolitinib cream showed large benefits in terms of Itch NRS-4 response (high-certainty evidence), rapid antipruritic effects, and small benefits in achievement of clinically meaningful improvement in sleep disturbance (moderate-certainty evidence). Preliminary data suggested that ruxolitinib cream improved functional ability. Pharmacokinetic studies suggested that about 6% of topically applied ruxolitinib is systemically absorbed and that plasma concentrations resulting from absorption of topically applied ruxolitinib, particularly if it is applied to > 20% of BSA, may fall within the range of plasma concentrations reached with oral ruxolitinib. The warnings and precautions for topical ruxolitinib are similar to those for oral ruxolitinib.
- **Potential Place in Therapy in VHA**. Topical ruxolitinib may be recommended for short-term (up to 8 weeks) and chronic non-continuous (PRN) therapy in non-immunocompromised patients with mild to moderate AD who have intolerance or inadequate response to trials of TCSs and a topical CNI, unless these treatments are medically inadvisable. Use of ruxolitinib cream in combination with therapeutic biologics, other JAKIs, or potent immunosuppressants such as azathioprine or cyclosporine is not

recommended. To ensure safe use, clinicians should consider certain pretreatment tests not typically done for topical AD treatments. Before initiating topical ruxolitinib therapy, clinicians should

- Exclude patients with active, serious infections. (Ruxolitinib may be initiated after the infection is controlled).
- Consider screening for TB. Avoid therapy if patient has untreated latent or active TB infection. Ruxolitinib may be initiated after starting anti-TB therapy.
- Consider screening for hepatitis B: at minimum, HBsAg, total anti-HBc, and anti-HBs. If a patient is HBsAg-positive, topical ruxolitinib may be initiated after starting antiviral prophylaxis, preferably with entecavir or tenofovir. If a patient is HBsAg-negative but anti-HBc-positive, consider consulting a hepatologist or infectious diseases expert for advice on whether to start antiviral prophylaxis to prevent HBV reactivation. HBV antiviral prophylaxis should be continued during ruxolitinib therapy.
- Consider ensuring that the patient has had current or past HCV screening. Topical ruxolitinib may be initiated while waiting for test results. If preemptive monitoring for HCV reactivation is used in patients positive for HCV RNA, check lab tests (e.g., ALT and AST every month and HCV RNA every 3 months) as advised by a hepatologist or infectious diseases expert.
- Consider updating vaccinations including for herpes zoster.

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