Nemolizumab-ilto (NEMLUVIO) in Atopic Dermatitis
National Drug Mini-Monograph

June 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: CFB, change from baseline; EASI-75/-90, at least 75%/90% reduction from baseline in Eczema Area and Severity Index score; IGA, Investigator Global Assessment; LSM, least square mean; PP-NRS, Peak Pruritus Numerical Rating Scale; RCT, randomized clinical trial; TCS, topical corticosteroid; TCI, topical calcineurin inhibitor

AAAAI / ACAAI JTF, American Academy of Allergy, Asthma and Immunology / American College of Allergy, Asthma and Immunology Joint Task Force; AC, active-controlled; CO, crossover; DB, double-blind; DLQI, Dermatology Life Quality Instrument; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; POEM, Patient Oriented Eczema Measure; PP-NRS, peak pruritus numeric rating scale; Pruritus VAS-30, score of <30 mm on pruritus VAS scale; Q, GRADE quality of evidence; RCT, randomized clinical trial; TCS, topical corticosteroids

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Humanized IgG2 monoclonal antibody that is an IL-31 receptor alpha (IL-31RA) antagonist.
Indication Under Review	Treatment of adults and pediatric patients ≥ 12 years of age with moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies.
Dosage Regimen	60 mg (two 30-mg injections) SC then 30 mg SC every 4 weeks. For patients who achieve clear or almost clear skin after Week 16, a dosage of 30 mg every 8 weeks is recommended. Discontinue use of topical therapies after disease has sufficiently improved.
Dosage Forms Under Review	Single-dose, prefilled dual-chamber pen containing 30 mg of nemolizumab-ilto lyophilized powder and diluent.
Pretreatment Procedures	□ Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment. Avoid live vaccines during therapy. □ There are no recommendations for infection, tuberculosis, or hepatitis B virus screening.
Treatment Monitoring	□ Hypersensitivity reactions □ Laboratory Tests: No recommendations
Storage	Should be refrigerated at 2°C to 8°C (36°F to 46°F). May be stored at room temperature up to 77°F (25°C) for up to 90 days.

EFFICACY CONSIDERATIONS	
Trial	**Nemolizumab with concomitant topical therapy in adolescents and adults with moderate-to-severe atopic dermatitis (ARCADIA 1 and ARCADIA 2): results from two replicate, double-blind, randomised controlled phase 3 trials[2]**
Design	Identical 48-week, phase 3, multinational, double-blind, double-dummy, placebo-controlled randomized clinical trials (RCTs), stratified by baseline disease and pruritus severity. Week-16 responders were re-randomized to maintenance regimens. *Coprimary Endpoints at Week 16*: Investigator's Global Assessment (IGA) success defined as score of 0/Clear or 1/Almost Clear with ≥2-point improvement from baseline (IGA success) and ≥75% improvement in Eczema Area and Severity Index from baseline (EASI-75). Either outcome was considered a clinical response.
Population	Adults and adolescents ≥ 12 years who had moderate-to-severe AD with associated pruritus (PP-NRS ≥ 4) and inadequate response to topical corticosteroids (TCSs). *Baseline Characteristics* (N = 1728: 941 ARCADIA 1 and 787 ARCADIA 2): 51% male, 80% White, 79% aged 18–65 years; 5% aged >65 years; PP-NRS score 7.2 (scale 0/None or No Impact to 10/Worst or Worst Impact).
Interventions	*Initial Therapy (Weeks 0–16)*: Nemolizumab 60 mg SC loading dose then 30 mg SC every 4 weeks up to Week 16. *Maintenance Therapy (Weeks 16–48)*: Week-16 responders on nemolizumab were re-randomized (1:1:1) to nemolizumab 30 mg every 4 weeks, nemolizumab 30 mg every 8 weeks, or placebo.
Comparator	Placebo

Background Therapy

TCS with or without topical calcineurin inhibitors (TCI) (TCS-TCI)

Results

16-week Initial Treatment Period

Table 1. Primary and Selected Secondary Endpoints in Overall Population

Outcome	Nemolizumab	Placebo	RR (95% CI)	Adj ARD (95% CI)	Q
ARCADIA 1	N = 620	N = 321			
IGA Success	221 (36)	79 (25)	1.4 (1.16, 1.80)	11.5 (4.7, 18.3)	M[α]
EASI-75 Response	270 (44)	93 (29)	1.5 (1.24, 1.82)	14.9 (7.8, 22.0)	M[α]
PP-NRS-4	265 (43)	57 (18)	2.4 (1.87, 3.10)	24.9 (18.4, 31.5)	M[α]
SD-NRS-4	235 (38)	64 (20)	1.9 (1.49, 2.42)	17.9 (11.3, 24.5)	H
ARCADIA 2	N = 522	N = 265			
IGA Success	197 (38)	69 (26)	1.4 (1.15, 1.83)	12.2 (4.6, 19.8)	L[αβ]
EASI-75 Response	220 (42)	80 (30)	1.4 (1.13, 1.72)	12.5 (4.6, 20.3)	L[αβ]
PP-NRS-4	214 (41)	48 (18)	2.3 (1.72, 2.98)	23.2 (16.1, 30.3)	L[αβ]
SD-NRS-4	175 (34)	43 (16)	2.1 (1.53, 2.79)	17.5 (10.8, 24.3)	M[β]

Adj ARD, adjusted absolute risk difference; PP-NRS-4, Peak Pruritus Numerical Rating Scale score improvement of ≥4 points; SD-NRS-4, reduction of ≥4 points on the Sleep Disturbance Numerical Rating Scale

[α] Downgraded for indirectness (surrogate for a final clinical outcome)

[β] Downgraded for imprecision (optimal information size not met or confidence interval is wide)

Table 2. Primary and Selected Secondary Endpoints in the Severe Pruritus Subpopulation (Baseline PP-NRS ≥7)

Outcome	Nemolizumab	Placebo	RR (95% CI)	Adj ARD (95% CI)	Q
ARCADIA 1	n = 406	n = 210			
IGA Success	144 (35)	45 (21)	1.7 (1.24, 2.21)	14.3 (6.1, 22.5)	L[αβ]
EASI-75 Response	169 (42)	50 (24)	1.8 (1.34, 2.29)	18.1 (9.6, 26.6)	L[αβ]
PP-NRS-4	187 (46)	39 (19)	2.5 (1.83, 3.35)	20.3 (13.8, 26.8)	L[αβ]
SD-NRS-4	171 (42)	47 (22)	1.9 (1.43, 2.48)	19.7 (11.2, 28.2)	M[β]
ARCADIA 2	n = 316	n = 164			
IGA Success	116 (37)	36 (22)	1.7 (1.21, 2.31)	14.9 (5.6, 24.3)	L[αβ]
EASI-75 Response	130 (41)	41 (25)	1.6 (1.22, 2.21)	16.3 (6.6, 26.0)	L[αβ]
PP-NRS-4	153 (48)	35 (21)	2.3 (1.66, 3.11)	27.1 (17.5, 36.6)	L[αβ]
SD-NRS-4	135 (43)	34 (21)	2.1 (1.49, 2.85)	21.9 (12.5, 31.4)	M[β]

See footnotes for Table 1.

- EASI-90 was not assessed.
- PP-NRS-4 response showed a significant treatment difference as early as Week 1.

Weeks 16–48 Maintenance Treatment Period: No publication found as of 4/9/2025.

Onset of Significant Effects: Week 1 based on PP-NRS-4 response; earlier time points were not reported.

Duration of an Adequate Therapeutic Trial: Unable to determine because of insufficient data.

Authors' Conclusions

Nemolizumab with background topical therapy was efficacious in adults (and adolescents) with moderate-to-severe AD, showing significant, clinically relevant improvements in inflammation and pruritus. The safety profile of nemolizumab was similar to that of placebo.

JP01 and JP02 Trials

Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus[3]

Nemolizumab plus topical agents in patients with atopic dermatitis (AD) and moderate-to-severe pruritus provide improvement in pruritus and signs of AD for up to 68 weeks: results from two phase III, long-term studies[4]

Nemolizumab Improves Patient-Reported Symptoms of Atopic Dermatitis with Pruritus: Post Hoc Analysis of a Japanese Phase III Randomized Controlled Trial[5]

Design

16-week phase 3, multicenter, double-blind RCT followed by a 52-week extension, performed in Japan

Primary Efficacy Endpoint: Percent change in weekly mean VAS score for pruritus at Week 16.

Population

Age ≥ 13 years; confirmed diagnosis of AD with pruritus, inadequate antipruritic response to medium-potency TCS or TCI at stable doses for ≥ 4 weeks and oral antihistamines at stable doses for ≥ 2 weeks (or inability to use these therapies). Pruritus Visual Analogue Scale (VAS) score of ≥ 50 (range, 0 to 100); EASI score ≥ 10 (range, 0 to 72).

Baseline Characteristics (N = 215): 66% male, median age 40 years; 100% on topical therapy (97% medium-potency TCS; 40% TCI)

Interventions

Nemolizumab 60 mg SC every 4 weeks vs Placebo

Co-therapies

Medium-potency TCS, TCI, oral antihistamines at stable doses.

Lower potency TCSs and moisturizers or protectants and higher-potency TCSs (rescue therapy) were allowed.

Results

Table 3. Primary and Selected Secondary Endpoint at Week 16

Outcome	NMLZ 60 mg Q4W	Placebo	RR (95% CI)	Adj ARD (95% CI)	Q
CFB in Pruritus VAS Score [N]	–42.8 [143]	–21.4 [72]	NA	–21.5 (–30.2, –12.7)	L[α,β]
DLQI-4, n/N (%)	89/133 (67)	34/68 (50)	1.3 (1.03, 1.75)	17 (3, 31)	M

CFB, change from baseline; DLQI-4, at least 4-point improvement on the Dermatology Life Quality Index (DLQI-4), considered the minimal clinically important difference; L, low; M, moderate; Q, GRADE quality of evidence
[α] Downgraded for indirectness to a final clinical outcome
[β] Downgraded for imprecision due to suboptimal information size and wide confidence interval)

Long-term Extension Studies: Continuation of nemolizumab after Week 16 resulted in further improvements in pruritus VAS, EASI, and QoL up to 68 weeks. The change from baseline in the pruritus VAS was about –45% at Week 16 and –65.9% at Week 68 on nemolizumab / nemolizumab in Study JP01. The corresponding values for EASI scores were about –45% at Week 16 to –78.2% at Week 68, respectively.

Duration of an Adequate Therapeutic Trial: 40 weeks based on pruritus VAS and EASI scores.

Authors' Conclusions

When used with topical therapies, nemolizumab was significantly better than placebo in reducing pruritus in patients with AD. Injection-related reactions were more frequent on nemolizumab. Safety and durability of therapy was not assessed beyond 16 weeks.

PBM Notes

In Japan, the manufacturer pursued an indication of moderate-to-severe pruritus with AD.**Error! Bookmark not defined.** Therefore, the primary efficacy endpoint was the pruritus VAS score.

XCIMA Trial

Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis[6]

Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study[7]

Design

Phase 2, 12-week, double-blind, double-dummy, dose- and placebo-controlled RCT (Part A) with double-blind, treat-through long-term extension (Part B) conducted in the US, EU, and JP; stratified by region

Primary Efficacy Endpoint: Percentage improvement/reduction in the pruritus VAS at Week 12

Population

Adults with moderate-to-severe AD inadequately controlled by topical therapy (TCS or TCI)

Baseline Characteristics: 51% male; mean age 35 years; 22% from US.

Intervention

Part A (Weeks 0–12): Nemolizumab 0.1, 0.5, or 2.0 mg/kg SC every 4 weeks or an exploratory dose of 2.0 mg/kg every 8 weeks for 12 weeks

Part B (Weeks 12–64): Nemolizumab 0.1, 0.5, or 2.0 mg/kg SC every 4 weeks or 2.0 mg/kg every 8 weeks for 52 weeks

Comparator

Part A: Placebo every 4 weeks or at Week 4 for the exploratory (every-8-week) dose

Part B: No placebo group

Co-therapies

Part A: Emollients

Part B: Emollients and mild/lowest potency TCS or TCI PRN

Results

Table 4. Primary and Selected Secondary Endpoints at Weeks 12 and 64

		Nemolizumab (mg/kg)				
Outcome	Time (wks)	0.1 Q4W	0.5 Q4W	2.0 Q4W	2.0 Q8W	Placebo
Pruritus VAS, LSM CFB [N]	12	–43.7 [33]	–59.8 [35]	–63.1 [32]	–60† [39]	–20.9 [26]
	64‡	–73.0 [29]	–89.6 [26]	–74.7 [28]	–79.1 [18]	—
sIGA-0/1, n/N (%)	12	3/45 (7)	9/46 (20)	8/46 (17)	3/37 (8)	—
	64	11/31 (35)	9/28 (32)	11/29 (38)	6/19 (32)	—
EASI Score, mean %CFB [N][6]	12	–23.0 [33]	–42.3 [35]	–40.9 [32]	Not reported	–26.6 [26]
EASI Score, mean % CFB [N][7]	12	–35.1 [45]	–47.8 [46]	–46.8 [46]	–42.1 [37]	Not reported
	64‡	–68.5 [31]	–75.8 [28]	–78.9 [29]	–69.3 [19]	—
Sleep Disturbance VAS, CFB [N]	12	–56.9 [45]	–67.8 [44]	–62.0 [46]	–66.9 [39]	—
	64‡	–81.5 [29]	–92.2 [26]	–72.5 [28]	–79.5 [18]	—
DLQI-4, n/N (%)	12	31/43 (72)	27/44 (61)	34/44 (77)	25/37 (68)	—
	64‡	28/30 (93)	22/27 (81)	25/28 (89)	15/18 (83)	—

† Estimated from figure 2A of reference 7.
‡ ITT population who received nemolizumab in Part A; includes data after rescue therapy.

Duration of an Adequate Trial: 24 weeks based on the time of maximal reduction in pruritus VAS-30 score and 44 weeks using EASI scores, using nemolizumab 0.5 mg/kg every 4 weeks.

Authors' Conclusions	*Part A*: Nemolizumab given on a monthly basis reduced pruritus in patients with moderate-to-severe AD. These phase 2 results support further studies of the role of IL-31 inhibition in antipruritic effects. *Part B*: In patients with moderate-to-severe AD inadequately controlled on topical therapy, nemolizumab administered for up to 64 weeks was efficacious in reducing pruritus and dermatitis and well tolerated with no new safety concerns during long-term therapy.

Dose-controlled Trial	**Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus[8]**
	This 24-week study determined that nemolizumab 30 mg every 4 weeks on a background of TCSs was significantly better than 10 mg and 90 mg in EASI-50/75/90 responses, IGA success, PP-NRS, and sleep improvement. Significant improvements (vs placebo) in DLQI were seen as early as Week 2 and were similar in magnitude across doses. However, this study used an inclusion criterion of EASI ≥ 12 rather than the more current threshold of ≥ 16 to define moderate-to-severe AD.
Subgroup Analysis and Onset	**Nemolizumab is associated with a rapid improvement in atopic dermatitis signs and symptoms: subpopulation (EASI ≥ 16) analysis of randomized phase 2B study[9]**
	This was a subgroup analysis of patients from the phase 2B study who had baseline EASI scores ≥ 16, a baseline disease severity similar to that of patients in current AD studies. It evaluated the effects of nemolizumab 30 mg vs placebo at Week 16 to be comparable with assessment time points used in current studies. The onset of significant PP-NRS effects of nemolizumab was as early as Day 2.
Network Meta-analysis	**Systemic treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials[10]**
(4 trials; total N not reported)	Nemolizumab was assessed as being • among the most effective agents for reducing sleep disturbance, • among the intermediate (inferior) effective agents based on itch NRS, and • not clearly different from placebo in AD severity (EASI), patient-reported severity, and eczema-related quality of life.

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	Known hypersensitivity
Other Warnings	Hypersensitivity Vaccinations: Avoid use of live vaccines during treatment.
Top 5 AEs (≥ 1%)	Headache/migraine, arthralgia, urticaria, myalgia
Drug Interactions	*Cytochrome P450 (CYP450) Substrates*: Nemolizumab-ilto may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes. After initiating or discontinuing nemolizumab-ilto in patients taking CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., warfarin) or drug concentration (e.g., cyclosporine) and modifying the dosage of the CYP450 substrate.
Pregnancy	Insufficient data. Nemolizumab-ilto may be transferred from the mother to the fetus. In monkey studies using doses 36 times higher than the maximum recommended human dose, rates of early postnatal death increased. Weigh potential risks vs benefits before administering live vaccines to infants exposed to nemolizumab-ilto in utero. Based on the half-life of the drug (18.9 days), consider delaying live virus immunizations in infants exposed to nemolizumab-ilto in utero by a minimum of 3 months post-birth.
Lactation	Insufficient data. Weigh potential risks vs benefits.
Geriatric Use	No age-related pharmacokinetic differences.[1] An insufficient number of patients ≥ 65 years was included in the clinical trials to determine whether they respond differently to younger adults.
Hepatic or Renal Impairment	*Mild to Moderate Impairment*: No clinically significant pharmacokinetic differences. *Severe Impairment*: Unknown pharmacokinetic effects.
Body Weight	Higher body weight can reduce systemic drug exposure. There was a 1.7-fold lower drug exposure for body weight above 87 kg vs below 62 kg, and this reduction had a clinically meaningful impact on Investigator Global Assessment of skin lesion response but not pruritus improvement.

Trial Safety Results

Most treatment-emergent adverse events (AEs) were mild to moderate in intensity.

Table 5. ARCADIA 1 and ARCADIA 2 Selected Safety Results

	ARCADIA 1		ARCADIA 2	
Adverse Event	NMLZ 30 Q4W (N = 616)	Placebo (N = 321)	NMLZ 30 Q4W (N = 519)	Placebo (N = 263)
Serious AE	6 (1)	4 (1)	13 (3)	3 (1)
Discontinuation due to AE	11 (2)	13 (4)	18 (3)	3 (1)
Severe AE	18 (3)	8 (2)	21 (4)	7 (3)

Values denote n (%)

Serious AEs Assessed as Possibly Causally Related to Nemolizumab

- None in ARCADIA 1.
- Five (1%) patients (10 events) in ARCADIA 2:
  - Abdominal adhesion and small bowel obstruction (n = 1)
  - Herpes simplex and superinfection bacterial (n = 1)
  - Herpes zoster and ophthalmic herpes zoster (n = 1)
  - Peripheral edema, atopic dermatitis, and lymphadenopathy (n = 1)
  - Eosinophilic colitis (n = 1)

Table 6. Phase 3 RCT in Japan Selected Safety Results[3]

Adverse Event	NMLZ 60 Q4W (N = 143)	Placebo (N = 72)
≥1 Serious AE	3 (2)	2 (3)
Discontinuation due to AE	3 (2)	0
≥1 AE	101 (71)	51 (71)
Injection-related reaction	12 (8)	2 (3)
Worsening of AD	34 (24)	15 (21)

Values denote n (%)

Table 7. Phase 2 Dose-controlled, Long-term Extension Selected Safety Results[7]

	Nemolizumab (mg/kg)			
Adverse Event	0.1 Q4W (N = 53)	0.5 Q4W (N = 54)	2.0 Q4W (N = 52)	2.0 Q8W (N = 52)
≥1 Serious AE, n (%)	3 (6)	3 (6)	4 (8)	9 (17)
Related to study treatment	0	0	2 (4)	3 (6)
Discontinuation due to AE, n (%)	7 (13)	3 (6)	5 (10)	6 (12)
≥1 AE, n (%)	47 (89)	46 (85)	45 (87)	43 (83)
Exacerbation of AD	15 (28)	13 (24)	14 (27)	11 (21)
Increased blood CPK	5 (9)	3 (6)	9 (17)	6 (12)
Peripheral edema	2 (4)	3 (6)	6 (12)	2 (4)

Most Common Serious AE (no. of events): exacerbation of AD (5).

Other Notable Serious AEs (no. of events): herpes simplex (1), herpes zoster (1)

OTHER CONSIDERATIONS

Storage	The prefilled pen should be stored in a refrigerator at 36°F to 46°F (2°C to 8°C) or may be stored at room temperature (up to 77°F [25°C]) for up to **90 days**. Nemolizumab-ilto has a longer maximal storage duration at room temperature than dupilumab and tralokinumab-ldrm (14 days for each) and lebrikizumab-lbkz (7 days).
FDA Review	Not available for AD
ICER Review	Not available
NICE Review	Draft guidance under review as of 4/9/2025.

THERAPEUTIC ALTERNATIVES FOR MODERATE-TO-SEVERE AD AND THEIR PLACE IN THERAPY

Table 8. Place in Therapy of Therapeutic Alternatives

DRUG	VANF	CFU	FDA (ADULT INDICATIONS)	AAD GUIDELINES (2024)[11]	2023 AAAAI/ACAAI JTFPP GUIDELINES[12]
Anti-Interleukin-4/13					
Dupilumab (DUPIXENT)	No	Moderate-to-severe AD refractory to ≥2 classes of topical therapies for ≥12 weeks total unless medically inadvisable or not tolerated. If patient weighs <100 kg, consider tralokinumab prior to dupilumab	Treatment of adults with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable. Can be used with or without TCS.	Strong recommendation (moderate certainty evidence)	Recommend adding; consider if refractory, intolerant, or unable to use mid-to-high–potency topical treatment (strong in favor, high certainty evidence)
Anti-IL-13					
Tralokinumab-ldrm (ADBRY)	No	Same as for dupilumab	Same as for dupilumab	Strong recommendation (moderate certainty evidence)	Same as for dupilumab
Lebrikizumab-lbkz (EBGLYSS)	TBD	TBD	Same as for dupilumab	Not mentioned	Not mentioned
Anti-IL-31					
Nemolizumab-ilto (NEMLUVIO)	TBD	TBD	Treatment of adults with moderate-to-severe AD in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies	Not mentioned	Not mentioned
Janus Kinase Inhibitors					
Abrocitinib (CIBINQO)	No	Prior dupilumab or tralokinumab-ldrm (NO response after 12 wks or inadequate response after 16 wks) unless contraindicated, not tolerated, or otherwise medically inadvisable	Treatment of adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Limitation of Use: Not recommended for use in combination with other JAKis, biologic immunomodulators, or with other immunosuppressants.	Strong recommendation (moderate certainty evidence)	Suggest adding a JAKi; consider if refractory, intolerant or unable to use mid-to-high–potency topical treatment and systemic treatment inclusive of a biologic recommended above (conditional in favor; low certainty evidence)
Upadacitinib (RINVOQ)	No	Same as for abrocitinib	Same as for abrocitinib	Strong recommendation (moderate certainty evidence)	Same as for abrocitinib
Baricitinib (	No	NA	Off label	Strong recommendation (moderate certainty evidence)	Same as for abrocitinib. Recommend against using dose of 1 mg daily.
Antimetabolite					
Methotrexate	Yes	NA	Off label	Conditional recommendation (low certainty evidence)	Suggest against adding (conditional against, low certainty evidence)

DRUG	VANF	CFU	FDA (ADULT INDICATIONS)	AAD GUIDELINES (2024)[11]	2023 AAAAI/ACAAI JTFPP GUIDELINES[12]
Immunosuppressants					
Corticosteroids, Systemic	Yes	NA	Anti-inflammatory or immunosuppressive agent for a variety of certain conditions including dermatologic	Conditional recommendation against; use should be reserved exclusively for acute, severe exacerbations and short-term bridge therapy to other systemic, corticosteroid-sparing therapy (low certainty evidence)	Suggest against systemic corticosteroids for all patients with AD (conditional against, low certainty evidence)
Azathioprine	Yes	NA	Off label	Conditional recommendation (low certainty evidence)	Suggest against adding (conditional against, low certainty evidence)
Cyclosporine	Yes	NA	Off label	Conditional recommendation for limited-term use with proper monitoring (low certainty evidence)	Suggest adding; shared decision-making should determine whether to start therapy at high dose (5 mg/kg) or low dose (3 mg/kg) (conditional in favor, low certainty evidence)
Mycophenolate mofetil	Yes	NA	Off label	Conditional recommendation (very low certainty evidence)	Suggest against adding (conditional against, low certainty evidence)

POTENTIAL PLACE IN THERAPY	
Evidence Summary	• There were no active-controlled trials to inform the place in therapy of nemolizumab-ilto among other targeted systemic therapies for moderate-to-severe AD. Nemolizumab plus topical therapy (TCS with or without TCI) showed significant antiinflammatory and antipruritic efficacy in patients with moderate-to-severe AD including those with severe pruritus. The treatment effect of nemolizumab relative to placebo, each therapy given concomitantly with topical therapy, was small with a relatively high response to placebo plus topical co-therapy. Somewhat larger effects were observed for itch than AD area and severity, and antipruritic effects occurred as early as 1 week. It should be noted that the design of the ARCADIA 1 and ARCADIA 2 trials did not allow a comparison of nemolizumab against topical therapy. Further studies are needed to determine whether nemolizumab outperforms topical corticosteroids with or without topical calcineurin inhibitors and to compare nemolizumab with other targeted systemic immunotherapies for AD. Additional studies are needed to further characterize the risks of long-term therapy, including peripheral edema and elevated creatine phosphokinase blood levels. • Information is lacking on the relative efficacy and safety of extending the dosing interval of nemolizumab-ilto to every 8 weeks versus using the marketed 4 weeks for maintenance therapy. A maintenance trial evaluating every 8 week dosing was unpublished at the time of this review. • Treatment with nemolizumab monotherapy has only been supported by results of a small phase 2 trial.[6,7] • Non-white races and patients >65 years were underrepresented in clinical trials. Comorbidities were not reported. It is uncertain to what extent the results can be extrapolated to the VHA patient population.
Potential VHA Place in Therapy	• Nemolizumab-ilto with concomitant topical therapy may be used in patients with moderate-to-severe AD who have an inadequate response to topical prescription therapy (corticosteroids with or without calcineurin inhibitors). Its potential advantages over other targeted systemic monoclonal antibody therapies (dupilumab, tralokinumab-ldrm, and lebrikizumab-lbkz) include a novel anti-IL-31 mechanism that may be useful in patients who experience an inadequate response or intolerance to the anti-IL-4/-13 or anti-IL-13 agents. Nemolizumab-ilto lacks the ocular adverse effects (e.g., conjunctivitis, keratoconjunctivitis) and risk of helminth (parasitic) infections seen with dupilumab, tralokinumab-ldrm, and lebrikizumab-lbkz. Nemolizumab-ilto offers a better safety profile than JAK inhibitors, which carry boxed warnings for potential increased risks of mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. • Some patients may find the less frequent dosing (every 4 or 8 weeks) with nemolizumab-ilto to be more convenient than those for dupilumab and tralokinumab-ldrm (both administered every 2 weeks). The initial dosing regimen of nemolizumab-ilto may also be easier for some patients than that of lebrikizumab-lbkz since nemolizumab is dosed every 4 weeks from initiation, whereas lebrikizumab-lbkz is given every 2 weeks initially then changed to every 4 weeks for maintenance. Nemolizumab-ilto also has a long maximal storage duration at room temperature (90 days) that some patients may find useful. • Although the labeling recommends an every-8-week maintenance frequency, the product web site seems to market the 4-week dosing interval.[13] The cost of nemolizumab-ilto will be twice as high if the maintenance dose is kept at every 4 weeks rather than the recommended frequency of every 8 weeks. At a dosage of 30 mg every 8 weeks, nemolizumab-ilto has the lowest cost for maintenance therapy of the other targeted systemic therapies except for tralokinumab-ldrm 300 mg every 4 weeks, an alternative dosage that may be considered for patients <100 kg who respond at Week 16. Dosed every 4 weeks, nemolizumab-ilto has the highest drug cost of the AD biologics.

Contact: Francine Goodman, National Program Manager, VA Pharmacy Benefits Management Services – Formulary Management (12PBM)

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