Tralokinumab-ldrm (ADBRY) in Atopic Dermatitis
National Drug Monograph
October 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

- First-in-class human IgG4 monoclonal antibody against interleukin-13, a cytokine involved in the Type 2 immune response.[1,2] The drug inhibits the interaction of the cytokine with the IL-13 receptor α1 and α2 subunits.

Indication(s) Under Review in This Document

- Treatment of moderate to severe atopic dermatitis (AD) in adults whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- Tralokinumab can be used with or without topical corticosteroids (TCSs).

Pre-treatment Assessments

- Update vaccinations.
- Treat patients with pre-existing helminth infections before initiating therapy. (In clinical trials, patients were excluded if a helminth parasitic infection within the previous 6 months had not been treated with or had failed to respond to standard of care therapy.)[3]
- No recommendations for pretreatment screening of tuberculosis, hepatitis B, hepatitis C, or HIV.

Dosage Regimen and Dosage Form Under Review

- Tralokinumab-ldrm 600 mg (four 150-mg injections) then 300 mg (two 150-mg injections) SC every 2 weeks (Q2W). A less frequent dose of 300 mg every 4 weeks (Q4W) may be considered for patients who weigh less than 100 kg who achieve clear or almost clear skin after 16 weeks of treatment.
- Injection: 150 mg/mL in a single-dose prefilled syringe (PFS); pack sizes of two cartons (multipack) containing 4 PFSs and one carton containing 2 PFSs.

Clinical Evidence Summary

Efficacy Considerations

- No active-controlled trials were available to inform the place in therapy of tralokinumab-ldrm.
- The FDA approval of tralokinumab-ldrm for the treatment of moderate to severe AD was mainly based on three phase 3 randomized clinical trials (RCTs): two monotherapy trials (ECZTRA 1 and ECZTRA 2)[3,4] and one combination therapy trial (ECZTRA 3)[5,6,7] in which tralokinumab-ldrm was used concomitantly with a mid-potency TCS (mometasone furoate 0.1% cream). The ECZTRA 1, ECZTRA 2, and ECZTRA 3 RCTs showed that tralokinumab-ldrm, with or without TCS, significantly improved skin and pruritus outcomes vs placebo at Week 16 in patients who had inadequate response or medical inadvisability to TCS or

systemic therapy.[3,5] The two monotherapy trials showed partial maintenance of responses with tralokinumab-ldrm Q2W or Q4W from Week 16 to Week 52.[3] ECZTRA 3 showed higher maintenance of response with tralokinumab-ldrm plus TCS but for a follow-up period of only up to Week 32.

- Supplementary efficacy and safety data were provided in ECZTRA 5, a study that evaluated the effect of tralokinumab-ldrm on immune responses to vaccination.[8]
- Tralokinumab-ldrm was compared with placebo, each given with as-needed TCS, in a 26-week, phase 3 RCT (ECZTRA 7) that involved European patients who had an inadequate response, intolerance, or contraindication to cyclosporin A (CSA).[9] This study showed that tralokinumab-ldrm Q2W with as-needed TCS significantly improved skin outcomes and inconsistently improved itch outcomes in patients with severe AD. Durability of response in this patient subpopulation was not reported.
- A 12-week, dose-ranging, phase 2b, placebo-controlled RCT that evaluated tralokinumab-ldrm plus TCS provided supportive efficacy, health-related quality of life, and safety evidence.[10,11]
- An open-label, 5-year extension trial (ECZTEND) is ongoing. This trial evaluates the long-term safety of tralokinumab-ldrm therapy and the efficacy of tralokinumab-ldrm continuous treatment, re-treatment, and initial treatment, including the ability to regain response after interrupting, then reinitiating, tralokinumab-ldrm therapy. Interim results of these trials have been presented at dermatologic conferences[12,13] and published online.[14]

Randomized Clinical Trials

Table 1 Methods of Phase 3 RCTs

Topic	ECZTRA 1 and ECZTRA 2	ECZTRA 3	ECZTRA 7
Study Design	52-wk MN DB PC RCT Randomization was 3:1 and stratified by region and baseline IGA of 3 or 4. Definition of Response: IGA0/1 or EASI-75 at Wk 16 without receiving rescue therapy. Hierarchical multiplicity control.	Same as ECZTRA 1 and 2 except randomization was 2:1	26-wk MC DB PC RCT Post Hoc Subgroup Analyses: EASI75 response in CSA failures (defined as IR after > 12 wks or AE related to CSA) and EASI ≤ 7 from Week 16 to Week 26. Hierarchical multiplicity control.
Major Entry Criteria	Adults (≥ 18 y), AD diagnosis for ≥ 1 y, moderate to severe AD with IR within ≤ 1 yr to topical therapies or topical therapies medically inadvisable. IGA ≥ 3, EASI ≥ 16, BSA ≥ 10%, average Worst Pruritus NRS score ≥ 4. Excluded live attenuated vaccines within 30 days before randomization and during trial.	Adults (≥ 18 y), AD diagnosis for ≥ 1 y, IR to topical therapies or systemic therapy for AD in past 1 y. IGA ≥ 3, EASI ≥ 16, BSA ≥ 10%, average Worst Pruritus NRS score ≥ 4. Excluded live attenuated vaccines within 30 days before randomization and during trial.	Adults (≥ 18 y) with **severe AD**, diagnosis of AD x ≥ 1 y, inadequate response to topical or systemic therapies in the past year, and not adequately controlled with CSA or had contraindication. IGA ≥ 3; EASI ≥ 20, BSA ≥ 10%, and Worst Pruritus NRS ≥ 4. Excluded live attenuated vaccines within 30 days before randomization and during trial.
Interventions	**Monotherapy x 16 wks**: • TRA 600 mg SC on Day 0 then 300 mg SC Q2W • PBO Rescue Therapy: At investigator discretion.	**With TCS and PRN TCI x 16 wks**: • TRA 600 mg SC on Day 0 then 300 mg SC Q2W • PBO Rescue Therapy: Topical or systemic therapies at investigator discretion.	**With PRN TCS x 26 wks**: • TRA 600 mg on Day 0 then 300 mg SC Q2W • PBO Rescue Therapy: Topical or systemic therapies at investigator discretion.
Maintenance Phase or Long-term Extension	Responders on TRA were re-randomized (2:2:1) to tx w/TRA Q2W, Q4W, or PBO Q2W x 36 wks. Responders on PBO continued on PBO Q2W x 36 wks. Nonresponders at Week 16 and patients who lost response during maintenance were given open-label TRA Q2W plus optional TCS.	Responders on TRA + TCS were re-randomized 1:1 to tx w/TRA Q2W + TCS or TRA Q4W + TCS x 16 wks (up to Week 32). Placebo responders at Week 16 continued placebo + TCS Q2W x 16 wks. Week-16 nonresponders on TRA received TRA Q2W for another 16 wks.	Long-term Extension Trial: ECZTEND
Primary Efficacy Measure(s)	IGA0/1 response at Week 16 EASI75 response at Week 16	IGA0/1 response at Week 16 EASI75 response at Week 16	EASI75 response at Week 16

Topic	ECZTRA 1 and ECZTRA 2	ECZTRA 3	ECZTRA 7
Baseline Patient Characteristics	Median Age 34 y, White 66%, Male 61%, From US 23.1%[4] IGA of 4 (severe) 50%. Previous AD therapies mostly TCS (99%), systemic CS (63%), TCIs (49%), and phototherapy (46%). Previous CSA 34%, MTX 17%, AZP 9%, MMF 6%, other IST 5%. In US patients, CSA, MTX, AZP, and MMF were used by < 11% each.	Median Age 36 y, White 76%, Male 55% IGA of 4 (severe) 46% Previous AD therapies mostly TCS (98%), systemic CS (62%)	Median Age 34 y, White 98%, Male 60%. IGA of 4 (severe): not reported Median BSA 52% Previous AD therapies mostly TCS (> 99%), CSA (75%; IR 34%; AE 31%), systemic CS (68%), and phototherapy (59%). Previous MTX 18%, AZP 13%, DUP 5%, MMF 3%.

AE, Adverse effect; **AZP**, Azathioprine; **BSA**, Body surface area of involvement; **CS**, Corticosteroid; **CSA**, Cyclosporine A; **DUP**, Dupilumab; **EASI-75**, At least 75% improvement from baseline on the Eczema Area and Severity Index (scale 0–72); **IGA0/1**, Achievement of 0 (clear) or 1 (almost clear) on the Investigator Global Assessment score (scale 0–4); **IR**, Inadequate response; **IST**, Immunosuppressive therapy; **MMF**, Mycophenolate; **MTX**, Methotrexate; **NRS**, Numerical rating scale; **PBO**, Placebo; **TCS**, Topical corticosteroid (mid-potency mometasone furoate 0.1% cream once daily or lower potency TCS or TCI to sensitive areas based on investigator discretion) from Week 0 to Week 32 and discontinued when control was achieved; **PRN**, Pro Re Nata (as needed); **TRA**, Tralokinumab-ldrm.

Results

- Efficacy results are summarized in Table 2.

Table 2 Key efficacy results by outcome measure from phase 3 trials

Outcome Measure	Time (Wks)	Trial	TRA Q2W‡	PBO‡	Relative Risk (95% CI)	Absolute Difference (95% CI)
EASI75, n/N (%)	16	ECZTRA 1	150/601 (25.0)	25/197 (12.7)	2.0 (1.3, 2.9)	**12.1 (6.5, 17.7)**
	16	ECZTRA 2	196/591 (33.2)	23/201 (11.4)	2.9 (1.9, 4.3)	**21.6 (15.8, 27.3)**
	16	Pooled 1 + 2	346/1192 (29.0)	48/398 (12.1)	2.4 (1.8, 3.2)	**16.9 (12.5, 20.8)**
	16	ECZTRA 3	141/252 (56.0)	45/126 (35.7)	1.6 (1.2, 2.0)	**20.2 (9.8, 30.6)**
	16	ECZTRA 7	88/138 (64.2)	69/137 (50.5)	1.3 (1.0, 1.6)	**14.1 (2.5, 25.7)**
	26	ECZTRA 7	95/138 (68.8)	76/137 (55.3)	1.2 (1.0, 1.5)	**14.1 (2.9, 25.3)**
IGA0/1, n/N (%)	16	ECZTRA 1	95/601 (15.8)	14/197 (7.1)	2.2 (1.3, 3.8)	**8.6 (4.1, 13.1)**
	16	ECZTRA 2	131/591 (22.2)	22/201 (10.9)	2.0 (1.3, 3.1)	**11.1 (5.8, 16.4)**
	16	Pooled 1 + 2	226/1192 (19.0)	36/398 (9.0)	2.1 (1.5, 2.9)	**10.0 (6.1, 13.4)**
	16	ECZTRA 3	98/252 (38.9)	33/126 (26.2)	1.5 (1.1, 2.1)	**12.4 (2.9, 21.9)**
Worst Pruritus NRS4	16	ECZTRA 1	119/594 (20.0)	20/194 (10.3)	1.9 (1.2, 3.0)	**9.7 (4.4, 15.0)**
	16	ECZTRA 2	144/575 (25.0)	19/200 (9.5)	2.6 (1.7, 4.1)	**15.6 (10.3, 20.9)**
	16	Pooled 1 + 2	263/1169 (22.5)	39/394 (9.9)	2.3 (1.7, 3.1)	**12.6 (8.5, 16.2)**
	16	ECZTRA 3	113/249 (45.4)	43/126 (34.1)	2.3 (1.7, 3.1)	**11.3 (0.9, 21.6)**
	16	ECZTRA 7	61/134 (45.5)	48/135 (35.6)	1.3 (1.0, 1.8)	9.7 (–2.0, 21.4)

Sources: 3,5,9

Bold blue text indicates statistically significant difference.

‡ Study drug was used in combination with topical corticosteroids in ECZTRA 3 and ECZTRA 7.

- The anticipated absolute effects for achieving EASI75, IGA0/1, and Worst Pruritus NRS4 responses in 16 weeks are presented in Table 3.

Table 3 Absolute Effect for Achieving Skin and Itch Outcomes for Tralokinumab-ldrm Q2W vs Placebo at Week 16

Outcome Measure	Trial	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
EASI75 response	ECZTRA 1 + 2	169 more (96, 265 more)	6 (5, 9)	H
	ECZTRA 3	214 more (71, 357 more)	5 (4, 11)	M[α]
	ECZTRA 7	166 more (0 fewer, 333 more)	8 (4, 56)	M[α]
IGA0/1 response	ECZTRA 1 + 2	99 more (45, 172 more)	11 (8, 18)	H
	ECZTRA 3	262 more (26, 288 more)	8 (5, 39)	M[α]
Worst Pruritus NRS4 response	ECZTRA 1 + 2	129 more (69, 208 more)	8 (6, 13)	H
	ECZTRA 3	444 more (239, 717 more)	9 (5, 133)	M[α]
	ECZTRA 7	107 more (0 fewer, 284 more)	10 (NSD)	M[α]

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit

Q, GRADE quality of evidence (H = High, M = Moderate)-

[α] Downgraded for imprecision (wide CIs or optimal information size not met).

  - In ECZTRA 7 (patients with cyclosporine A [CSA] inadequate response or intolerance), the 95% CIs for the anticipated absolute effects include a worst case of no incremental EASI75 benefit or Worst Pruritus NRS4 benefit versus placebo.

- Secondary efficacy results
  - Tralokinumab-ldrm Q2W was consistently significantly better than placebo in
    - EASI90 response at Week 16 across the four phase 3 RCTs;
    - Change from baseline (CFB) in Worst Pruritus numerical rating scale (NRS) at Week 1 (ECZTRA 1 and 2), Week 16 (ECZTRA 3 and 7) and Week 26 (ECZTRA 7), where Worst Pruritus was assessed as the weekly average of worst daily pruritus;
    - CFB in Dermatology Life Quality Index (DLQI) at Week 2 (ECZTRA 1 and 2), Week 16 (ECZTRA 1, 2 and 3), and Week 26 (ECZTRA 7);
    - DLQI score improvement by ≥ 4 points (DLQI-4 response) at Week 16 in ECZTRA 3;
    - CFB in POEM at Week 16 (ECZTRA 1, 2 and 7) and Week 26 (ECZTRA 7); and
    - CFB in AD-related sleep at Week 16 (ECZTRA 1, 2 and 7) and Week 26 (ECZTRA 7).

Rescue Therapy

- The need for rescue therapy was consistently numerically lower on tralokinumab-ldrm than placebo:
  - 35.8% vs 46.2%, respectively, in ECZTRA 1 and 22.8% vs 44.3%, respectively, in ECZTRA 2,[3]
  - 2.8% vs 10.2%, respectively, in the ECZTRA 3 combination therapy trial,[5] and
  - 5.7% vs 13.9%, respectively, in the ECZTRA 7 combination therapy trial.[9]

TCS Sparing Effects

- In ECZTRA 3, cumulative TCS use (g ± SE) at Weeks 15–16 was lower with tralokinumab-ldrm than placebo: 134.9 ± 11.7 (N = 229) vs 193.5 ± 16.7 (N = 108), respectively; difference–58.6 (–98.7, –18.5).
- However, measurement of cumulative TCS use assumed that no TCS was used from nonreturned tubes. Therefore, TCS use may have been underestimated (and TCS sparing effects overestimated).

Subgroup Analyses (Post Hoc)

- In the US subpopulation of ECZTRA 1 and 2, EASI75 response at Week 16 was 39.9% of 273 tralokinumab-ldrm patients and 24.2% of 95 placebo patients (abstract of conference presentation).[4,15] IGA0/1 response was achieved at Week 16 in 24.9% and 20.0% of patients in the tralokinumab-ldrm and placebo groups, respectively. [15]
- For the US subpopulation of ECZTRA 3 (combination therapy) tralokinumab-ldrm was also numerically better than placebo. EASI75 response at Week 16 was 56.3% vs 21.4% for tralokinumab-ldrm (n = 72) and

placebo (n = 28), each with TCS, respectively.[6,15] IGA0/1 response at the same time point was 40.8% vs 10.7% for combination therapy with tralokinumab-ldrm and placebo, respectively.[6,15]

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

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

Table 4 Onset of Benefit and Adequate Therapeutic Trial

Trial	Outcome Measure	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
ECZTRA 1	EASI75 / IGA0/1 / EASI90	6 / 6 / 6	10 / ≥ 16 / ≥ 16
ECZTRA 2	EASI75 / IGA0/1 / EASI90	2 / 4 / 6	12 / ≥ 16 / ≥ 16
ECZTRA 3	EASI75 / IGA0/1	6 / 10	10 / ≥ 16
ECZTRA 7	EASI75	10	≥ 26

- Depending on the study population and treatment, onset of benefit ranged from 2 to 10 weeks for achievement of EASI75, 4 to 10 weeks for IGA0/1, and 6 weeks for EASI90. Overall, the average onset of benefit was 6 weeks.
- The duration of an adequate trial seems to be at least 16 weeks and may be longer (≥ 26 weeks) in patients with severe AD. However, in severe AD, it would be reasonable to allow switching to another therapy if there was no response by 16 weeks.

Durability of Response

- In ECZTRA 1 and 2, durability of response with tralokinumab-ldrm Q2W / Q2W or Q2W / Q4W was higher than with tralokunumab-ldrm Q2W / PBO but statistically significant differences were inconsistent (Table 5).

Table 5 Durability of Response in Maintenance Phase

Outcome Measure Maintained†	Trial	Time (Wks)	TRA Q2W / Q2W‡	TRA Q2W / Q4W‡	TRA Q2W / PBO	Diff (95% CI): TRA Q2W / Q2W vs TRA Q2W / PBO	Diff (95% CI): TRA Q2W / Q4W vs TRA Q2W / PBO
EASI75	ECZTRA 1	16–52	28/47 (60%)	28/57 (49%)	10/30 (33%)	21.2 (–0.2, 42.6)	11.7 (–8.7, 32.0)
EASI75	ECZTRA 2	16–52	43/77 (56%)	38/74 (51%)	9/42 (21%)	**33.7 (17.3, 50.0)**	**30.0 (13.7, 46.4)**
EASI75	ECZTRA 3	16–32	62/67 (92.5%)	59/65 (90.8%)	—	—	—
IGA0/1	ECZTRA 1	16–52	20/39 (51%)	14/36 (39%)	9/19 (47%)	6.0 (–21.8, 33.7)	–9.5 (–37.1, 18.0)
IGA0/1	ECZTRA 2	16–52	32/54 (59%)	22/49 (45%)	7/28 (25%)	**34.1 (13.4, 54.9)**	19.9 (–1.2, 40.9)
IGA0/1	ECZTRA 3	16–32	43/48 (89.6%)	34/49 (77.6%)	—	—	—

† Response maintained without rescue medication including topical corticosteroids.
‡ Study drug was used in combination with topical corticosteroids in ECZTRA 3. Maintenance of response was not associated with an increased use of topical corticosteroids.

  - Differences in response rates favored tralokinumab-ldrm but did not reach the level of significance for the Q2W and Q4W maintenance dosages vs placebo in ECZTRA 1 using either EASI75 or IGA0/1, and in ECZTRA 2 for IGA0/1 (Table 5).
  - Continuation of tralokinumab-ldrm Q2W was significantly better than placebo in durability of response only in ECZTRA 2 using IGA0/1 or EAS75.
  - Carryover effects of active treatment after switching to placebo at Week 16 was unlikely to have remained after Week 31 (15 weeks or 5 half-lives after Week 16).

- In ECZTRA 3, higher rates of durable response were observed with tralokinumab-ldrm + TCS combination therapy up to Week 32, ranging from 89.6% to 92.5% with continuation of Q2W dosing and 77.6% to 90.8% with de-escalation to less frequent Q4W maintenance dosing (Table 5).
- Interim 2-year efficacy results from ECZTEND (N = 345) showed that open-label tralokinumab-ldrm Q2W (plus "mild or moderate" / class ≥ 4 topical corticosteroids or calcineurin inhibitors in about one-third of patients) maintained EASI-75 responses in 82.5%, EASI-90 in 59.8%, and IGA0/1 in 48.1% of patients.[14] Mild AD (EASI ≤ 7) was maintained in 83 (77.6%) of 107 patients. The median improvement in EASI from the parent trial baseline to Week 56 of ECZTEND (Year 2 of therapy) was 92.5%. Maintenance therapy improved itch and sleep interference. The impact of AD on quality of life was small (DLQI 2.0, n = 274) at Year 2 of therapy.

Evidence Gaps

- Hospitalization or readmission
- Patient Satisfaction

Network Meta-analyses (NMAs)

- Four NMAs have included tralokinumab-ldrm trials.[16,17,18,19] Drucker (2022) and Pereyra-Rodriguez (2021) did not include ECZTRA 7. Silverberg (2021) and Sawangjit (2020) only included the phase 2b trial of tralokinumab-ldrm.
- Assessment time points were 8–16 weeks for the NMA by Drucker (2022), 12–16 weeks for the NMAs by Pereyra-Rodriguez, et al. (2021) and Silverberg, et al. (2021), and ≤ 16 weeks (short-term) and > 16 weeks (long-term, specifically, 6–13 months) for the Cochrane NMA by Swangjit, et al. (2020).
- Selected findings of the network meta-analyses are presented in Table 6 to Table 8.

Table 6 Summary of Network Meta-analyses Comparing Tralokinumab-ldrm with Other Targeted AD Therapies

Comparison	NMA Estimate			
	Efficacy Outcomes		Safety Outcomes	
Drucker (2022)	**CFB in EASI,† MD (95% CrI) Q**	**CFB in Signs,† SMD (95% CrI) Q**	**SAE,† OR (95% CrI) Q**	**DAE,† OR (95% CrI) Q**
ABR100 vs TRA300, ± TAI	–1.4 (–3.9, 1.1) M	–0.2 (–0.4, 0.0) H	1.7 (0.7, 4.7) VL$^{\gamma}$	0.8 (0.3, 2.0) VL$^{\gamma}$
ABR200 vs TRA300, ± TAI	–5.7 (–8.2, –3.2) H	–0.6 (–0.8, –0.4) H	0.9 (0.3, 2.7) VL$^{\gamma}$	0.8 (0.3, 1.9) VL$^{\gamma}$
BAR2 vs TRA300, ± TAI	1.7 (–1.0, 4.3) M	0.2 (0.0, 0.4) M$^{\alpha}$	0.7 (0.2, 1.7) VL$^{\gamma}$	0.9 (0.3, 2.6) VL$^{\gamma}$
BAR4 vs TRA300, ± TAI	–0.3 (–3.0, 2.4) H	0.1 (–0.1, 0.3) H	1.0 (0.4, 2.6) VL$^{\gamma}$	1.7 (0.6, 4.7) VL$^{\gamma}$
DUP300 vs TRA300, ± TAI	–3.5 (–5.8, –1.3) H	–0.3 (–0.5, –0.1) H	0.7 (0.3, 1.6) VL$^{\gamma}$	1.1 (0.4, 2.6) VL$^{\gamma}$
TRA300 vs UPA15, ± TAI	3.7 (1.4, 6.1) H	0.6 (0.4, 0.7) H	1.0 (0.4, 2.5) VL$^{\gamma}$	1.6 (0.7, 3.9) VL$^{\gamma}$
TRA300 vs UPA30, ± TAI	6.3 (3.9, 8.6) H	0.8 (0.6, 1.0) H	1.0 (0.4, 2.6) VL$^{\gamma}$	1.2 (0.5, 3.0) VL$^{\gamma}$
AZP vs TRA300, ± TAI	NE	0.0 (–0.5, 0.4) M$^{\beta}$	NE	NE
CSAhd vs TRA300, ± TAI	NE	–0.5 (–1.1, 0.2) L$^{\alpha}$	NE	NE
CSAld vs TRA300, ± TAI	NE	–0.2 (–0.8, 0.5) L$^{\alpha}$	NE	NE
MTX vs TRA300, ± TAI	NE	–0.1 (–0.7, 0.6) M$^{\beta}$	NE	NE
Pereyra-Rodriguez (2021)	**EASI75, OR (CI NR) Q**	**IGA0/1, OR (CI NR) Q**	**Severe AE OR (CI NR) Q**	**Any AE OR (CI NR) Q**
ABR100 vs TRA300, + TCS / – TCS	1.69 / 1.74 NE	1.92 / 1.79 NE	NR	NR
ABR200 vs TRA300, + TCS / – TCS	**2.68 / 3.82** NE	**3.23 / 3.39** NE	NR	NR
BAR2 vs TRA300, + TCS / – TCS	0.93 / 0.94 NE	1.00 / 1.06 NE	NR	NR
BAR4 vs TRA300, + TCS / – TCS	1.12 / 1.24 NE	1.40 / 1.56 NE	NR	NR
DUP300 vs TRA300, + TCS / – TCS	**2.23 / 2.12** NE	**2.29 / 2.51** NE	NR	NR
TRA300 vs UPA15, + TCS / – TCS	**0.44 / 0.27** NE	**0.34 / 0.22** NE	NR	NR
TRA300 vs UPA30, + TCS / – TCS	**0.24 / 0.16** NE	**0.16 / 0.12** NE	NR	NR
Silverberg (2021)	**EASI75, OR (95% CrI) Q**	**IGA0/1, OR (95% CrI) Q**	**TEAE**	**DAE**
TRA300 vs BAR2, + TCS	NR	1.21 (0.29, 5.47) NR	NE	NE
TRA300 vs BAR4, + TCS	NR	0.96 (0.23, 4.22) NR	NE	NE
TRA300 vs DUP300	NR	0.59 (0.16, 3.27) NR	NE	NE
Sawangjit (2020)	**EASI75, RR (95% CI) Q**	**IGA0/1, RR (95% CI) Q**	**Short-term SAE, RR (95% CI) Q**	**—**
DUP vs TRA, ± TCS	1.20 (0.56, 2.58) NR	**2.22** (0.96, 5.13) NR	**0.26** (0.04, 1.78) NR	
ABR vs TRA, ± TCS	NE	**2.06** (0.58, 7.36) NR	0.56 (0.04, 7.70) NR	
APR vs TRA, ± TCS	NE	NE	**2.06** (0.11, 40.05) NR	
BAR vs TRA, ± TCS	NE	NE	**2.76** (0.07, 104.00) NR	
TRA vs UST, ± TCS	**2.80** (0.69, 11.31) NR	1.61 (0.71, 3.66) NR	NE	

Bold blue text indicates at least a moderate effect based on point estimates of the MD or SMD (see cutoffs under abbreviations below) or RR or OR of < 0.50 or > 2.0 (commonly considered to be clinically important).[20]

There were no reported direct comparisons between tralokinumab-ldrm and active comparators and therefore no direct estimates. The network meta-analysis estimates (which combine direct estimates and indirect estimates) are the same as the indirect estimates except that GRADE quality of evidence could be lower for the NMA than the indirect estimate.

ABR100 (ABR200), Abrocitinib 100 mg (200 mg) QD; **APR**, Apremilast; **AZP**, Azathioprine 1–2.5 mg/kg/d; **BAR2 (BAR4**), Baricitinib 2 mg (4 mg) QD (off-label for AD in the US to date); **CI**, Confidence interval; **CFB**, Change from baseline; **CrI**, Credible interval; **CSAhd**, Cyclosporine higher dose (300 mg/d, 4–5 mg/kg/d); **CSAld**, Cyclosporine lower dose (150 mg/d, ≤ 3 mg/kg/d); **CrI**, Credibile interval; **CS**, Corticosteroid; **DUP(300)**, Dupilumab (300 mg Q2W); **EASI**, Eczema Area and Severity Index (MCID, 6.6); **MCID**, Minimal clinically important difference; **MD**, Mean difference (definitions of the effect size of the MD: < 1, little or no difference; > 1 but < MCID, small effect of uncertain importance / "reduces slightly"; > MCID, moderate effect; > 2x MCID, large effect[16]); **MTX**, Methotrexate 10–22.5 mg/week; **NE**, Not evaluated; **NR**, Not reported; **Q**, GRADE quality of evidence as reported by the authors (H = High, M = Moderate, L = Low, VL = Very low); **SMD**, Standardized mean difference (definitions of the effect size of the SMD: < 0.2, little or no difference; 0.2–0.8, small effect of uncertain importance; and > 0.8 moderate effect / "reduces"; no SMD equivalent for large effect[16] **SUCRA**, Surface under the cumulative ranking score; **TRA300**, Tralokinumab 300 mg Q2W; **UPA(15)(30)**, Upadacitinib 15 mg (30 mg) QD; **UST**, Ustekinumab

† Negative effect estimates favor the intervention (drug listed first). Positive effect estimates favor the comparator (drug listed second).

‡ Rated moderate in indirect estimate (different rating from that in the NMA estimate) with no change in the estimate size (downgraded to moderate for significant risk of bias).

α Downgraded for imprecision.

β Downgraded for significant risk of bias.

γ Double downgraded for imprecision (the upper and lower ends 95% CrI for the estimate would suggest different conclusions and CrIs very wide).

δ Downgraded for imprecision (the upper and lower ends 95% CrI for the estimate would suggest different conclusions).

Table 7 Summary of SUCRA cluster rank plot for combined efficacy and safety outcomes

	Pereyra-Rodriguez (2021)	Sawangjit (2020)
Plot Position†	**EASI75 and Any AE**	**EASI75 and SAEs**
Upper rank efficacy / Upper rank safety	DUP300 DUP300 + TCS UPA15 + TCS ABR100 + TCS	DUP‡§
Upper rank efficacy / Lower rank safety	UPA30 UPA30 + TCS ABR200 ABR200 + TCS UPA15 ABR100	**TRA**‡§
Lower rank efficacy / Upper rank safety	**TRA300 + TCS**	
Lower rank efficacy / Lower rank safety	BAR4 **TRA300** BAR2	

Drucker, et al. (2022) and Silverberg, et al. (2021) did not provide SUCRA cluster rank plots.

Drug abbreviations: See Table 6 footnotes. **±**, With or without (results pooled regardless of whether concomitant topical therapy was used)

† For monograph purposes, upper / lower rank efficacy and upper / lower rank safety were arbitrarily described using SUCRA rank cutoffs of ≥ / < 0.50 and as defined in each network meta-analysis based on cluster rank plots. Specifically, in the Pereyra-Rodriguez (2021) review, upper / lower rank efficacy corresponded to efficacy outcome SUCRA rank ≥ / < 0.50, respectively, vs placebo; upper / lower rank risks corresponded to safety outcome SUCRA rank **< / ≥** 0.50, respectively. In the Sawangjit (2020) review, both upper / lower rank efficacy and upper / lower rank safety corresponded to SUCRA rank ≥ / < 0.50, respectively.

‡ Despite apparently different placements in the cluster rank plot, tralokinumab-ldrm and dupilumab were categorized in the same group and assumed to have similar performance when the two outcomes were considered jointly.

§ In the Cochrane network meta-analysis, 81.1% of RCTs allowed co-therapy, mainly emollients / TCS.

Table 8 Other Considerations About the Network Meta-analyses

Consideration	Drucker (2022)	Pereyra-Rodriguez (2021)	Silverberg (2021)	Sawangjit (2020)
Heterogeneity Among Trials	Evaluated but not reported	Substantial	Little evidence of detectable heterogeneity	Some heterogeneity in trial designs (widely varying placebo responses possibly related to variable use of concomitant therapies)
Inconsistency Among Trials	Not mentioned	Significant disagreement between direct and indirect estimates	Could not be assessed	None
Evidence of Violation of Transitivity Assumptions	Not mentioned	Not mentioned	Not mentioned	None
Limitations	Included ECZTRA 1, 2, 3 and 5 but not 7. Questionable GRADE quality assessments of evidence for indirect comparisons between two active therapies (e.g., rated as high in the absence of direct comparisons).	Included phase 2b and phase 3 ECZTRA 1, 2 and 3 trials but did not include ECZTRA 7. No GRADE quality of evidence assessment; only assessed risk of bias. No long-term trials.	Included only the phase 2b trial. No GRADE quality of evidence assessment; only assessed risk of bias. No long-term trials.	Included only the phase 2b trial. No long-term data (> 16 wks) for TRA. Pooled data for monotherapy and combination therapy (81.1% of RCTs allowed co-therapy, mainly emollients / TCS).
Funding by mfr	No	No (Not funded)	Yes – Pfizer (abrocitinib)	No
Author(s) Conflict of Interest with LEO Pharma	Yes	Yes	Yes	No

TCS, Topical corticosteroids; TRA, Tralokinumab-ldrm

- Results from the limited network meta-analyses collectively suggest (inconclusively) that, in terms of EASI75, IGA0/1, CFB in EASI, and CFB in clinical signs, tralokinumab-ldrm is negligibly to moderately less effective than dupilumab and the JAK inhibitors abrocitinib and upadacitinib, and could be similar in efficacy to baricitinib. This trend was generally supported by other efficacy assessments not shown in this monograph review, such as EASI90 response,[16,18] EASI50 response,[18] and Worst Pruritus NRS4.[18] The certainty of the evidence differed by efficacy measure, being reportedly moderate to high for CFB in EASI and CFB in clinical signs, and indeterminate for EASI75 and IGA0/1 responses.
- There was reportedly low to moderate certainty evidence that tralokinumab-ldrm is similar to conventional immunomodulators (azathioprine, cyclosporine, and methotrexate) in CFB in clinical signs.
- Results of analyses that combined relative efficacy and safety ratings (surface under the cumulative ranking curve [SUCRA] cluster rank plots) suggest that tralokinumab-ldrm might be less effective and more likely to cause adverse events or serious adverse events than dupilumab. However, the comparative safety of tralokinumab-ldrm was of very low or undetermined certainty, and did not allow inferences about the relative usefulness of the drug based on likelihood of harms.

Institute for Clinical and Economic Review (ICER) Network Meta-analyses

- ICER's network meta-analyses of JAK Inhibitor and monoclonal antibody treatments of moderate to severe AD[21] included the three phase 3 RCTs of tralokinumab. The findings were similar to those of the other published network meta-analyses (Table 9).

Table 9 ICER Comparative Clinical Effectiveness* of Systemic Agents

Drug(s)	Net Health Benefit	Comparator	ICER Evidence Rating
Abrocitinib Baricitinib **Tralokinumab** Upadacitinib	Small or substantial benefit (moderate certainty), with a small but nonzero likelihood of a negative net health benefit	Topical therapies	Promising but inconclusive
Abrocitinib Upadacitinib	Higher doses somewhat superior (low certainty)	Dupilumab	Insufficient
Baricitinib **Tralokinumab**	Likely somewhat inferior (moderate certainty)	Dupilumab	Comparable or inferior
Abrocitinib Baricitinib **Tralokinumab** Upadacitinib	May range from negative to substantial net benefit (low certainty)	Each other	Insufficient

*Outcomes: Improvements in severity of atopic dermatitis, itch and sleep

Safety Considerations

- **Boxed Warnings:** None
- **Contraindications**: Hypersensitivity
- **Other Warnings / Precautions**: Conjunctivitis and keratitis; parasitic / helminth infections; risk of infection with live vaccines.
- **Deaths and Serious Adverse Events**: Serious adverse events included hypersensitivity reactions such as anaphylaxis, conjunctivitis and keratitis.
- **Discontinuations Due to Adverse Events**: Rates of discontinuations due to adverse events through Week 16 in patients on tralokinumab-ldrm 300 mg Q2W vs placebo were 0.7% vs 0%, respectively, as monotherapy and 0.8% vs 0%, respectively, as combination therapy with TCSs. The most common adverse events leading to discontinuation of treatment were injection site reaction and eosinophilia with monotherapy and injection site reaction and conjunctivitis with combination therapy.
- **Common Adverse Events (≥ 1%)**: Upper respiratory tract infections, conjunctivitis, injection site reactions, eosinophilia (transient).
- **Safety of Tralokinumab-ldrm vs Placebo**: Overall, tralokinumab-ldrm and placebo were similar in the frequency and intensity of adverse events.
    - In an analysis of data up to 16 weeks from five RCTs, the incidence of **conjunctivitis** was higher with tralokinumab-ldrm than placebo (7.5% vs 3.2%, respectively).[22] Most cases of **conjunctivitis** were mild and transient. **Conjunctivitis** led to discontinuation of therapy in 2 patients on tralokinumab-ldrm (1.4%).[22]
- **Long-term Safety**: In the 2-year interim safety analysis of ECZTEND (N = 1174, Patient-Years of Exposure [PYE] 1235.7), 71.9% of patients treated with tralokinumab-ldrm Q2W (± TCS / TCNI) experienced ≥ 1 adverse event (59.2% mild, 37.1% moderate, 5.3% severe). Serious adverse events occurred in 4.7% of patients and led to discontinuation of therapy in 1.6%. The top three most frequently reported adverse events (≥ 2.0% of patients) were viral upper respiratory tract infection (21.3%, 29.3 events per 100 PYE), atopic dermatitis (13.5%, 20.6), and upper respiratory tract infection (7.1%, 9.1). Conjunctivitis occurred in 3.8% (4.5 events per 100 PYE), injection site reaction in 2.4% (3.9), herpes simplex in 2.1% (2.9), oral

herpes in 2.0% (2.6), and allergic conjunctivitis in 2.0% (2.3). For adverse events of special interest, eye disorders occurred in 6.6% (7.8 events per 100 PYE), skin infections requiring systemic treatment in 1.8% (2.2), eczema herpeticum in 0.9% (0.8), and malignancies diagnosed after dosing in 0.8% (0.7).

- **Comparative Harms in Network Meta-analyses**. In the ICER network meta-analyses, rates of discontinuation due to adverse events and incidence of serious adverse events were low and generally similar among the systemic agents for moderate to severe AD.[21]

Other Considerations

- **Geriatric Use:** Insufficient data to determine whether there is an age-related difference in efficacy or safety.
- **Immunogenicity**: The overall incidence of antidrug antibodies in tralokinumab-ldrm–treated patients was 4.6%, including 1.0% with neutralizing antibodies. No clinically meaningful differences in safety, efficacy, or pharmacokinetics of tralokinumab-ldrm were observed.
- **Dose-Exposure Relationship**: There was a clear relationship between tralokinumab-ldrm exposure and efficacy responses.[2] Body weight > 100 kg can be expected to reduce the systemic exposure of tralokinumab-ldrm (dosed at 300 mg Q4W) by 1.46-fold compared with body weight < 100 kg. Because tralokinumab-ldrm has linear pharmacokinetics, the mean trough concentration decreased by about one-half at Week 28 vs Week 16 after switching from Q2W to Q4W dosing.[2]

Other Therapeutic Options

- Mild to moderate AD is generally treated with topical therapies, which consist of TCS, TCI, crisaborole, or ruxolitinib. Patients with mild to moderate AD who do not respond to topical therapies are candidates for systemic therapies (pharmacotherapy or phototherapy).
- In moderate to severe AD, topical therapies are mainly used as adjuncts to systemic therapies.
- The general steps in systemic drug therapy of moderate to severe AD are shown in Table 10.

Table 10 Systemic Pharmacotherapies for Moderate to Severe AD by Conventional Steps in Therapy and Labeled Indications

Step in Therapy	Treatment Alternatives	Comments
Conventional Immunomodulators	Azathioprine	Can be used long-term.[23]
	Alitretinoin	May be used for AD of the hand when TCSs are inadequate.[23]
	Corticosteroids	Outdated systemic therapy.[23]
	Cyclosporine A	Considered first-line therapy for severe AD as acute flare intervention.[23] Continuous use should be restricted to a maximum of 2 years.[23]
	Methotrexate	May be used for long-term maintenance.[23]
	Mycophenolate	May be used if CSA is inadequate or not indicated; little toxicity.[23]
Non-JAK targeted systemic therapies	Dupilumab	FDA-approved treatment of adults and children ≥ 6 years with moderate to severe AD when topical prescription therapies are inadequate or not advisable. EU guideline-recommended when topical therapy is inadequate and other systemic therapies are not advisable; for long-term maintenance.[23]
	Tralokinumab-ldrm	FDA-approved for treatment of adults with moderate to severe AD when topical prescription therapies are inadequate or not advisable.
JAK targeted systemic therapies	Abrocitinib Upadacitinib	FDA-approved for treatment of adults with refractory, moderate to severe AD when other systemic drug therapies are inadequate or inadvisable.

- Table 11 summarizes alternative treatments for moderate to severe AD in patients who had an inadequate response to prescription topical therapies or for whom these therapies are medically inadvisable. JAK inhibitors are not included in this table because they are recommended at a subsequent

step in therapy; i.e., in patients with refractory AD who have an inadequate response to other systemic therapies or when they are inadvisable.

Table 11 Targeted Therapies for Moderate to Severe AD After Unsuccessful Prescription Topical Antiinflammatory Therapy

Drug	Formulary	CFU Place in Therapy	Safety Considerations	Other Considerations
IL-13 Inhibitor				
Tralokinumab-ldrm	TBD	TBD	• Parasitic helminth infections • Conjunctivitis / keratitis • Avoid live vaccines. • Injection site reactions are common (requires > 1 injection per dose). • No recommended laboratory monitoring.	• Available as 150 mg/mL in 150-mg PFSs to date. Therapy will require twice the number of injections as dupilumab despite having the same dosage. • Potential cost savings from option to reduce maintenance dose from Q2W to Q4W.
IL-4/13 Inhibitor				
Dupilumab	NonF CFU	For severe AD after Rx topicals, phototherapy if available and feasible, induction therapy with CSA or SCS if needed, and TWO csIMMs	• Parasitic helminth infection • Conjunctivitis / keratitis • Arthralgia • Avoid live vaccines. • No recommended laboratory monitoring.	• Also approved for asthma and chronic rhinosinusitis with nasal polyposis. • Available as 150 mg/mL in 300-, 200-, and 100-mg PFSs. • Q4W and Q8W dosing were studied but not approved.[24]

Sources: FDA Multi-discipline Review[2]

CFU, Criteria for use; **csIMM**, Conventional synthetic immunomodulator; **NonF**, Nonformulary; **PFS**, Prefilled syringe; **SCS**, Systemic corticosteroid; **TBD**, To be decided

Projected Place in Therapy

- **Place in Therapy Based on Medical Society Guidelines**. No guidelines on the management of AD include tralokinumab-ldrm.
- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available to inform place in therapy, moderate- to high-quality evidence from placebo-controlled trials supports the use of tralokinumab-ldrm in patients with moderate to severe AD who have had an inadequate response to topical or systemic therapies, or when those therapies are medically inadvisable. Short-term results also support the use of tralokinumab-ldrm in patients with severe AD who have an inadequate response or contraindication to cyclosporine A, although improvement in itch outcomes were inconsistent. Overall, skin and itch benefits were small but clinically meaningful. Indirect comparisons from network meta-analyses suggested that abrocitinib, upadacitinib, and dupilumab might be more effective and dupilumab might have a safety advantage relative to tralokinumab-ldrm; however, the quality / certainty of the effect estimates were indeterminate and could be low or very low. In patients less than 100 kg who achieve clear or almost clear skin after 16 weeks of treatment, clinicians may consider decreasing the frequency of tralokinumab-ldrm maintenance doses from Q2W to Q4W after weighing a potential risk of loss of response, and considering that there is a lack of information on whether response can be recaptured with return to Q2W dosing. The FDA-approved option to extend the dosing interval to Q4W in responders is a potential dosing convenience or cost-saving advantage of tralokinumab-ldrm over dupilumab.

- **Potential Place in Therapy in VHA**. Tralokinumab-ldrm may be used in patients with severe AD who have an inadequate response or intolerance to prescription topical therapies, phototherapy (only if available, feasible, and not medically inadvisable), and/or conventional synthetic immunomodulators, unless these therapies are medically inadvisable.

Prepared October 2022. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

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