CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

tralokinumab (Adtralza)

(LEO Pharma Inc.)

Indication: Adtralza (tralokinumab injection) is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adtralza can be used with or without topical corticosteroids.

November 30, 2023

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0787-000
Brand name (generic)	Tralokinumab (Adtralza)
Indication(s)	Adtralza (tralokinumab injection) is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adtralza can be used with or without topical corticosteroids.
Organization	Eczema Society of Canada
Contact information[a]	Amanda Cresswell-Melville Executive Director

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Eczema Society of Canada (ESC) does not agree with the draft recommendation regarding the reimbursement of Adtralza. There is a significant gap in treatments for patients suffering with moderate to severe atopic dermatitis (AD), and Adtralza is proven to be both safe and effective and allows patients who are suffering a chance of significant disease improvement. Through ESC's patient input submission, it was also demonstrated that this medication can significantly improve the disease and quality of life for sufferers.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

Eczema Society of Canada (ESC) is disappointed to review this draft recommendation and learn that the recommendation was not to reimburse this medication. As demonstrated in our patient input submission, Adtralza can be a life-changing medication for patients, and our submission revealed the significant benefit that this medication can offer the patient community, including for patients who have failed other available systemic medications.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

The draft recommendation indicated that there is uncertainty about Adtralza's value to the patient community. Our patient input submission clearly demonstrated the value that the medication brings to patients.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

The draft recommendation indicated:

CDEC could not determine whether tralokinumab would adequately meet this need due to the uncertainty around the magnitude of treatment effect, and the benefit of tralokinumab versus appropriate comparators and in patients who received prior dupilumab or JAKi treatment.

As demonstrated in our original patient input submission, Adtralza provides an opportunity for disease management for patients who have failed other treatments, including other systemic options, as named above. Our submission clearly illustrated that for the patients interviewed, Adtralza was a life-changing medication and offered patients the opportunity for disease management and clear skin when nothing else has worked to manage their atopic dermatitis (AD).

If the CDEC or CADTH teams would like additional patient input or perspectives, we would happily provide this. AD is a complex disease to treat, and we believe patients need various treatment options. We hope that this draft recommendation is only a draft recommendation and that with this feedback from the patient and health care provider community there could be a path forward to make additional treatment options available to patients.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	Amanda Cresswell-Melville
Position	Executive Director, Eczema Society of Canada
Date	November 21st, 2023
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Leo Pharma	☐	☐	☒	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0787-000
Brand name (generic)	Adtralza (tralokinumab)
Indication(s)	Moderate-to-severe atopic dermatitis in adults and adolescents
Organizations	Joint submission from: (i) Dermatology Association of Ontario (DAO) + (ii) Atlantic Specialist Group Managing Atopic Dermatitis + (iii) Canadian Dermatology Association (CDA)
Contact information[a]	(i): Dr. David N. Adam, DAO, [redacted] (ii): Dr. Ian Landells, Atlantic Specialist Group Managing Atopic Dermatitis, [redacted] (iii): Dr. Monica Li, CDA, [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

We are disappointed by the recommendation to not reimburse Adtralza and ask that the committee reconsider its recommendation. Over the past 2 years, we have observed the meaningful impact of Adtralza in patients fortunate enough to have private insurance. It is undeniable that patients who rely on public insurance coverage – including those suffering from disabilities and needing social assistance – are not eligible to receive the same level of care as those who have private insurance.

1. The committee notes one of its reasons for the recommendation is "**the magnitude of treatment effect was uncertain**" in reference to week 16 data from the RCTs (page 3, "Rationale for the Recommendation"). Consider:
   - Clinical experts consulted by CADTH and clinician input from our organizations all note that it takes approximately 6 months for Adtralza to demonstrate optimal treatment effect. Maintenance treatment period data from the RCTs validate clinical expert and clinician input demonstrating that patients see continued improvement past 16 weeks (i.e., ECZTRA 3 post-hoc analysis by Silverberg et al. (2022) shows continued improvements in EASI scores, pruritus NRS, sleep NRS, and DLQI over 32 weeks across all patients randomized to Adtralza regardless of their response at 16 weeks).[1]
   - The open-label extension trial ECZTEND provided further evidence that patients who elected to continue treatment with Adtralza appeared to continue to maintain response and be free from significant adverse events for up to 2, 3, or 4 years of total treatment. While there are limitations with open-label trials, the committee must appreciate that there is data from nearly 500 adult patients (in the case of the 3-year data) and just over 100 adolescent patients (in the case of the 2-year data) that, at a minimum, indicates long-term control and safety with Adtralza is not a chance outcome.
   - Reviewing this depth of data and concluding that no conclusions can be drawn beyond 16 weeks is disheartening as it suggests there is no value in any data collected after the primary endpoints of the RCTs. The promising evidence observed in the RCTs and long-term extension trial corroborate the input our organizations provided at the outset of the review – that Adtralza produces a clinically meaningful treatment effect, typically closer to the 6 month timeframe, and that it is capable of producing long-term response without safety concerns.

- A committee of 12 Canadian dermatologists with extensive experience in managing atopic dermatitis recently developed a consensus treat-to-target recommendation for moderate-to-severe atopic dermatitis.[2] The committee agreed that assessment targets for 12-16 weeks are more appropriately set as EASI 50 or IGA/PGA ≤2 and one of either an improvement in pruritus NRS of ≥3, DLQI ≥4, or POEM ≥3 versus baseline. Targets including EASI 75 and IGA/PGA 0/1 are more appropriate targets at 6-8 months or 12 months. We previously indicated in our input at the outset of the review that EASI 50 is the threshold for meaningful improvement at earlier timepoints (i.e., 16 weeks) – the magnitude of treatment effect as measured by EASI 50 at 16 weeks is far more pronounced when looking at the RCTs. And as noted above, the EASI 75 response rates at later timepoints also become far more apparent.

2. The committee notes that there was uncertainty in the benefit of Adtralza in "**patients who received prior dupilumab or JAKi treatment**" (page 3, "Rationale for the Recommendation"). Consider:
   - The collective data from the real-world studies reviewed by CADTH, while limited by sample size and duration of study are emerging evidence that mirrors what we have previously conveyed in our input at the outset of the review – that patients who have previously been treated with dupilumab or JAKi can be reasonably treated with Adtralza where we have seen treatment success in Canadian practice.
   - We ask the committee to consider what a reasonable alternative course of action is for patients who failed to respond to or were unable to tolerate dupilumab and JAKi. Based on the prior treatment criteria previously recommended by CDEC, patients cannot be managed with topicals alone and have already trialed or could not tolerate phototherapy and off-label systemics such as methotrexate and cyclosporine. With no other treatment options available, reinitiating these other therapies is ill advised nor is it supported by robust Phase 3 RCTs.

3. The committee also notes that there was uncertainty in "**the benefit of tralokinumab versus appropriate comparators**".
   - From a safety perspective, it is certain that there is favourable benefit with Adtralza compared to comparators as it does not have black box warnings or laboratory monitoring requirements (where JAKi do). Moreover, compared to dupilumab, rates and severity of conjunctivitis and facial erythema are far less common with Adtralza.
   - From an efficacy perspective, indirect evidence is challenging to interpret given differences in trial designs and statistical analyses across trials. The combined indirect evidence CADTH has reviewed does not suggest that there are apparent significant differences between therapies. This would be aligned with the input we provided at the outset of the review where our clinical experience has been that these therapies generally appear similar in terms of efficacy outcomes beyond 16 weeks.

4. In closing:
   - It appears the meaningful input and evidence provided by clinicians, clinical experts, and patient organizations has not been fully utilized to help address some of the uncertainties identified by CDEC.
   - There is promising, collective evidence that suggests reimbursing Adtralza provides another reasonable treatment option to patients where there continues to be an unmet need. The combined evidence from the RCTs, open-label extension studies, and now years' worth of treatment experience conveyed in our input to CADTH, all suggest Adtralza can address this need for patients.
   - On top of the promising data and clinical experiences – Adtralza was noted by CADTH as having the potential to produce $7 million in savings.

- We encourage the committee to consider if a denial to reimburse a promising therapy for a difficult-to-treat condition is equitable and sensible considering the emerging real world (Canadian) experiences with the therapy.
- We also encourage the committee to consider if there is an opportunity to consider real world data collection to address the highlighted uncertainties (e.g., recommend a pay-for-performance or outcomes-based agreements, which was recently highlighted by CADTH as an area being considered to enhance drug reviews)[3], as that allows further development of emerging data while putting patients at the center of everything (particularly those who rely on public insurance coverage).

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
It does not appear our input was considered to help address the uncertainties cited by the committee as the reasons for the recommendation on Page 3 (re: Rationale for the Recommendation) make no mention of the clinician input submitted. Our collective input reflects years of experience with Adtralza and complements the clinical trial data which can help address the identified uncertainties. For example, our input on the characterization and impression of the clinical trial results – namely, that the efficacy outcomes at week 16 across the trials are clinically meaningful (especially in the context that EASI 50 is the more appropriate benchmark at this earlier timepoint), was not noted.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
The recommendation is based on "uncertainty" with regards to i) magnitude of treatment effect ii) comparative effect vs comparators and iii) effect in patients previously treated with dupilumab/JAKi. As there is promising evidence through the RCTs, open-label extension trial, and evidence/feedback provided by clinicians, clinical experts, and patients i.e., Adtralza exerts a treatment effect, has no significant safety signals, and per the CADTH analysis, produces savings for drug plan budgets – the recommendation to "Do not reimburse" appears at odds with the totality of evidence reviewed.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
As noted, a "Do not reimburse" recommendation creates further inequity between patients who are fortunate enough to have private insurance coverage. Patients who rely solely on public coverage, will be ineligible for optimal therapy compared to those with private coverage. Moreover, for patients who did not respond to or could not tolerate dupilumab and JAKi, there are no other appropriate treatment options to direct patients to as the criteria recommended by CADTH, and adopted by public drug plans, means these patients have already failed to achieve response with topical therapies, phototherapy, and off-label systemics.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
Not applicable		

[a] CADTH may contact this person if comments require clarification.

References

1. Silverberg JI, Adam DN, Zirwas M, et al. Tralokinumab Plus Topical Corticosteroids as Needed Provides Progressive and Sustained Efficacy in Adults with Moderate-to-Severe Atopic

Dermatitis Over a 32-Week Period: An ECZTRA 3 Post Hoc Analysis. Am J Clin Dermatol. 2022;23(4):547-559. doi:10.1007/s40257-022-00702-2

2. Yeung J, Gooderham MJ, Hong HC, et al. Treat-to-target in the management of moderate-to-severe atopic dermatitis in adults: A Canadian perspective. J Am Acad Dermatol. 2023;89(2):372-375. doi:10.1016/j.jaad.2023.01.053

3. Canadian Agency for Drugs and Technologies in Health. Upcoming Improvements to the CADTH Reimbursement Review Process. https://www.cadth.ca/news/upcoming-improvements-cadth-reimbursement-review-process. 2023.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. David Adam • Dr. Wei Jing Loo • Dr. Salvatore Cammisuli • Dr. Sameh Hanna • Dr. Carrie Lynde • Dr. Maxwell Sauder • Dr. John Kraft • Dr. Perla Lansang • Dr. Paul Adam • Dr. Patrick Fleming • Dr. Caroline Horgan-Bell • Dr. Geeta Yadav • Dr. Fiona Lovegrove • Dr. Jennifer Lipson • Dr. Lyn Giroux • Dr. Denise Wexler • Dr. Monica Li		

- Dr. Ian Landells
- Dr. Wayne Gulliver
- Dr. Martin Leblanc
- Dr. Katherine Rodriguez
- Dr. Bolu Ogunyemi
- Dr. Nicole Maillet-Lebel
- Dr. Irina Turchin

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1 – Dr Monica Li	
Name	Dr. Monica Li
Position	Chair, Pharmacy and Therapeutics Advisory Board, Canadian Dermatology Association
Date	22-11-2023
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0787
Name of the drug and Indication(s)	Tralokinumab (Adtralza) For the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older 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.
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.