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CADTH Reimbursement Recommendation

Tralokinumab (Adtralza)

Indication: For the treatment of moderate to severe atopic dermatitis in adult patients 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.

Sponsor: Leo Pharma Inc.

Final recommendation: Do not reimburse

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Adtralza?

CADTH recommends that Adtralza should not be reimbursed by public drug plans for the treatment of atopic dermatitis (AD).

Why Did CADTH Make This Recommendation?

- Evidence from 3 clinical trials showed that after 16 weeks of treatment, Adtralza was only modestly effective in reducing AD symptoms, including eliminating (or almost eliminating) skin lesions, alleviating itchy skin, and improving quality of life. These modest effects were shown when Adtralza was used alone or in combination with a topical corticosteroid.
- In another clinical trial in patients with severe AD, Adtralza in combination with topical corticosteroids effectively improved the Eczema Area and Severity Index (EASI) score (a tool used to measure the extent and severity of disease), but this effect was modest. In this same study, treatment with Adtralza in combination with topical corticosteroids did not significantly improve itchy skin than placebo in combination with topical corticosteroids.
- Results from indirect evidence are inconsistent: 1 indirect comparison suggested that Adtralza is less effective than dupilumab, while the indirect evidence submitted by the sponsor suggested that Adtralza [redacted] dupilumab.
- There is a need for more treatment options for patients whose AD is not controlled despite the use of existing treatments; however, the evidence reviewed did not show that Adtralza would meet this need.

Additional Information

What Is Atopic Dermatitis?

AD is a condition that affects the skin. People with AD have dry, red skin that is extremely itchy. Constant scratching can cause the skin to split and bleed, which can cause skin infections. Oozing and weeping sores can also occur in more severe forms of AD. Severe dermatitis can be physically disabling or incapacitating and cause anxiety or depression. The lifetime prevalence of AD is estimated to be up to 17% in the Canadian population.

Unmet Needs in Atopic Dermatitis

There is no cure for AD, and treatment aims to provide symptom relief and control symptoms in the longer term. Although many treatments are approved in Canada to treat AD, symptoms may not be controlled with existing drugs in some patients. Other treatment options are needed for these patients.

How Much Does Adtralza Cost?

Treatment with Adtralza is expected to cost approximately $22,802 per patient per year in the first year of use and $21,633 in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tralokinumab not be reimbursed for the treatment of moderate to severe atopic dermatitis (AD) in adult patients.

Rationale for the Recommendation

Three phase III, randomized, placebo-controlled trials (ECZTRA 1, ECZTRA 2, and ECZTRA 3) in adults with moderate to severe atopic dermatitis demonstrated that treatment with tralokinumab resulted in statistically significant improvements in AD severity, symptoms, and health-related quality of life (HRQoL) compared with placebo; however, the clinical importance of the magnitude of the treatment effect was uncertain. The ECZTRA 1 and ECZTRA 2 trials evaluated the efficacy of tralokinumab as monotherapy and the ECZTRA 3 trial evaluated the efficacy of tralokinumab in combination with topical corticosteroids (TCS). The percentage of patients who achieved a 75% or greater improvement from baseline in the Eczema Area and Severity Index (EASI75) score at week 16 was 25.0% in the tralokinumab treatment group and 12.7% in the placebo group in the ECZTRA 1 trial (between-group difference of 12.1%; 95% confidence interval [CI], 6.5 to 17.7; P < 0.001), 33.2% in the tralokinumab treatment group and 11.4% in the placebo group in the ECZTRA 2 trial (between-group difference = 21.6%; 95% CI, 15.8 to 27.3; P < 0.001), and 56.0% in the tralokinumab treatment group and 35.7% in the placebo group in the ECZTRA 3 trial (between-group difference = 20.2%; 95% CI, 9.8 to 30.6; P < 0.001). The percentage of patients who achieved an Investigator's Global Assessment (IGA) score of 0 or 1 at week 16 was 15.8% in the tralokinumab treatment group and 7.1% in the placebo group in the ECZTRA 1 trial (between-group difference = 8.6%; 95% CI, 4.1 to 13.1; P = 0.002), 22.2% in the tralokinumab treatment group and 10.9% in the placebo group in the ECZTRA 2 trial (between-group difference = 11.1%%; 95% CI, 5.8 to 16.4; P < 0.001), and 38.9% in the tralokinumab treatment group and 26.2% in the placebo group in the ECZTRA 3 trial (between-group difference = 12.4%; 95% CI, 2.9 to 21.9; P = 0.015).

A fourth study (ECZTRA 7) evaluated the efficacy and safety of tralokinumab as a combination therapy with TCS compared to placebo plus TCS in adults with severe AD who were not adequately controlled with, or had contraindications to, oral cyclosporine A. Although a statistically significant improvement in EASI75 score was achieved in ECZTRA 7 when tralokinumab was compared with placebo, the outcome daily pruritus numerical rating scale (NRS), which was tested first in the hierarchy, did not demonstrate a statistically significant difference between treatment groups. Hence it is not known whether tralokinumab would achieve statistically significant results for other efficacy outcomes of importance to patients in ECZTRA 7.

Direct comparative evidence for tralokinumab against other systemic agents was not available for this review. [redacted]. In addition, results from a published indirect treatment comparison (ITC) suggested that tralokinumab may be inferior to dupilumab 300 mg in terms of most efficacy outcomes when used as monotherapy or in combination with TCS.

Patient input received for this review identified a need for additional treatments for patients whose AD is not controlled despite the use of existing treatments. Based on the evidence reviewed, CDEC determined that tralokinumab might not adequately meet this need due to the uncertainty around the clinical importance of the magnitude of the treatment effect and the benefit of tralokinumab versus appropriate comparators.

Discussion Points

- CDEC noted that for patients with AD who do not achieve disease control with appropriate skin care measures (TCS and/or topical calcineurin inhibitors or phototherapy), current approaches to treatment consist of intermittent courses of immunosuppressive drugs (methotrexate, cyclosporine, azathioprine, or mycophenolate mofetil). The committee noted that tralokinumab would likely be used as an alternative treatment option for patients whose AD is not adequately controlled with immunosuppressive drugs or who have contraindications to such drugs. However, the committee concluded that the potential advantages of using tralokinumab in this population are questionable given the uncertain comparative efficacy and safety against dupilumab, a drug that is already available and has a similar mechanism of action. CDEC also noted that the potential benefit of tralokinumab in patients with severe AD who are not adequately controlled with, or have contraindications to, oral cyclosporine A remains unknown. In the ECZTRA 7 trial, it was uncertain whether tralokinumab improved AD symptoms and HRQoL. In addition, tralokinumab was not statistically significantly different from placebo in improving pruritus.
- Although CDEC recognized the value that both patients and clinicians place in having a choice of treatment options, CDEC and the clinical experts noted that results from the published indirect treatment comparison(ITC) suggested that tralokinumab may be inferior to dupilumab in terms of most efficacy outcomes; hence, it is uncertain whether tralokinumab would address the unmet need for treatment options that are more effective in reducing AD symptoms and severity and improving HRQoL.
- CDEC noted that AD is a chronic, relapsing condition in which patients often experience episodes of worsening symptoms throughout their lives. The primary outcomes were measured at 16 weeks, and available evidence from the maintenance phase of the studies is limited to 56 weeks in duration; therefore, there are limited data on the long-term safety and efficacy of tralokinumab.
- CDEC discussed the results of the cost-minimization analysis, which was specific to the sponsor's reimbursement request and not the broader Health Canada indication. CDEC agreed that a cost-minimization analysis was unlikely to be sufficient to assess the cost-effectiveness of tralokinumab in comparison with dupilumab because the available clinical evidence suggests tralokinumab may not be clinically equivalent to dupilumab; therefore, the cost-effectiveness of tralokinumab in comparison with dupilumab is uncertain as a result.

Background

Tralokinumab has a Health Canada indication for the treatment of moderate to severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Tralokinumab can be used with or without TCS. Tralokinumab is a fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptor alpha 1 and alpha 2 subunits (of the type II receptor). The recommended dosage of tralokinumab for adult patients is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week as a subcutaneous injection. At the prescriber's discretion, dosing every 4 weeks may be considered for some patients who achieve clear or almost clear skin after 16 weeks of treatment.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 4 phase III, placebo-controlled randomized trials in adult populations with moderate to severe AD
- patient perspectives gathered by 2 patient groups: the Eczema Society of Canada (ESC) and a joint submission from the Canadian Skin Patient Alliance (CSPA) and Eczéma Québec
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with AD
- input from 2 clinician groups: Canadian Dermatology Association and the Origins Dermatology Centre
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 2 patient group submissions for the review of tralokinumab for AD from ESC and a joint submission from the CSPA and Eczéma Québec. ESC conducted a survey and interviews covering topics of how AD affects quality of life, experiences with symptoms and treatments, and the patient journey. The group received more than 3,000 responses from adults living with AD as well as their caregivers and family. CSPA and Eczéma Québec created a web-based survey. A total of 26 adults (22 patients and 2 caregivers) responded to the CSPA and Eczéma Québec survey, and the joint submission also included information from 56 Canadians with AD and caregivers who participated in health technology assessment surveys and interviews regarding Janus kinase inhibitor treatments.

Patients described numerous symptoms associated with their AD including itching, pain, redness of the skin, repeated rashes, frequent scratching, dry or rough skin, cracked skin, flaking, bleeding, and thickening of the skin. From the CSPA and Eczéma Québec submission, nearly all of those with AD experienced itching (98%), skin redness (91%), repeated rashes (87%), frequent scratching (87%), cracked skin (87%), and dry and rough skin (81%). Of these symptoms, persistent itching is clearly the most burdensome for patients; it increases with the severity of the disease and carries an intensity and drive to scratch the skin that is described as overwhelming and uncontrollable. In the ESC survey, 72% and 95% of patients with moderate and severe AD, respectively, reporting feeling itchy multiple times a day. Moreover, 44% of respondents with severe disease were itchy all the time, and more than half of respondents described being unable to control the urge to scratch their skin and that it could be overwhelming and uncontrollable. Flares of worsening symptoms such as extreme itching and pain frequently led to loss of sleep. For instance, 63% and 86% of patients with moderate and severe AD, respectively, noted sleep disruptions; half of respondents with severe AD had lost sleep at least 8 nights per month. Patients also described AD as having a significant impact on many aspects of their quality of life. The ESC submission also noted that the unpredictable pattern of flares and the chronic and uncontrollable nature of the disease causes stress and carries a negative mental health impact.

Patients were interested in new therapies that could reduce their symptoms (particularly itching), clear their skin, reduce the frequency of flares, and improve quality of life. Those with moderate or severe AD noted the importance of having a medication that provided long-term relief and tolerable side effects. Respondents also felt that new treatments should be covered by insurance or be affordable, allow them to stop using topical therapies, be easy to use, and not be very time-consuming. From the CSPA and Eczéma Québec surveys, 64% felt it was important that AD treatments not require injections, while the other 34% were indifferent or felt it was not important.

From the ESC submission, some patients had accessed tralokinumab through a clinical trial and many felt it had significantly improved their pain, itching, discomfort, and the frequency of flares. Some patients felt improvements in 4 weeks to 6 weeks while others noted that changes took a few months. According to patients who were interviewed by ESC, they generally felt that an injectable medication was simpler and more convenient than other skincare routines and topicals that could be messy in nature and done with great care and thoroughness. Some patients raised concerns over the fear of needles, although they felt they would be able to overcome this challenge.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts with expertise in the diagnosis and management of AD consulted by CADTH indicated that some patients with moderate-severe AD respond to the current therapies; however, there is a need for additional therapies for patients with inadequate access to phototherapy or patients who have experienced side effects with systemic therapies like methotrexate and cyclosporine A. The clinical experts also stated that tralokinumab would complement other therapies and can be added to other treatments (excluding dupilumab because both treatments act on similar receptors) such as TCS. The clinical experts indicated a trial of appropriate topical therapy should be considered first before considering therapies like tralokinumab, particularly because of the cost associated with tralokinumab. The place in therapy of tralokinumab was variable among the clinical

experts, with 1 clinical expert indicated that tralokinumab may offer a safer and more effective treatment option than the off-label systemic therapies currently available. The other clinical expert disagreed with that statement due to the lack of long-term evidence of safety and that results from the trials were not encouraging. The clinical experts indicated that patients who would be best suited for treatment with tralokinumab are those with moderate to severe AD who have not responded to an adequate trial of topical therapies and an adequate trial of phototherapy. In terms of assessing response to treatment, the clinical experts were not aware of good predictors of a good response to tralokinumab but suggested that a clinically meaningful response would include improvements in quality-of-life scores, itch scores, and clinical scores (IGA or EASI). One clinical expert indicated that the treatment response should be assessed monthly early on in treatment, and every 3 months to 6 months later on in the course of treatment, while another clinical expert noted that response to tralokinumab should not be assessed earlier than 16 weeks and that responders should be assessed every 6 months. According to the clinical experts, the factors to consider for discontinuation would be lack of efficacy and adverse effects (e.g., severe conjunctivitis unresponsive to treatment measures). The clinical experts indicated that it would be reasonable to have a dermatologist diagnose, treat, and monitor patients receiving tralokinumab. The clinical experts indicated that tralokinumab is not expected to cause a dramatic shift in the current treatment paradigm but may present an additional therapy in the class of biologic therapies. Dupilumab has already established a precedent in this class of therapies.

Clinician Group Input

Two individual clinician inputs were received for the review of tralokinumab. One clinician input was received on behalf of the Canadian Dermatology Association from a dermatologist practising in British Columbia and the other clinician input was provided by a dermatologist who practices at the Origins Dermatology Centre in Saskatchewan. One clinician advised that tralokinumab would be used in the first-line setting, whereas the other clinician advised that topicals should be used as a first-line therapy followed by phototherapy and then systemics, including biologics. According to the clinician input, tralokinumab would be relevant to clinical practice because two-thirds of patients treated with dupilumab do not achieve clear skin; therefore, there is a need for additional systemic medications with different mechanisms of action. Additionally, both clinicians emphasized that there is a need for treatments that are convenient for patients with long-lasting effect. One clinician specifically voiced this concern for Indigenous populations living in remote areas. These patients are often have limited access to health care and can be hard to reach virtually, which makes it extremely difficult to monitor patient safety while on treatment with traditional systemic immunosuppressants. The clinician emphasized that traditional immunosuppressants can lead to side effects such as worsening of infection, cytopenia, and liver damage, for which many people living on reserves or in remote areas may not be able to receive adequate follow-up care. Both clinicians stated that patients with moderate to severe AD who do not respond to topical drugs and phototherapy have a high unmet need for this drug. Additionally, a clinician noted that women of childbearing age also have an unmet need because most off-label systemics are teratogenic.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The drug plans noted that there is limited access to phototherapy across Canada, particularly for patients living in rural areas.

The clinical experts consulted by CADTH were asked questions related to the implementation of tralokinumab into current provincial drug plans. Overall, most implementation questions related to therapies required to be used before becoming eligible for tralokinumab, dosing schedule, the eligible patient population, and renewal of therapy.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The evidence for this review was derived from a systematic literature review of pivotal and phase III studies that was supplemented with additional studies to address important gaps in the evidence from randomized controlled trials. The systematic review included 4 double-blind, phase III, randomized controlled trials.

ECZTRA 1 (N = 802) and ECZTRA 2 (N = 794) were randomized, double-blind, placebo-controlled, identically designed 52-week, trials that evaluated the efficacy and safety of tralokinumab as a monotherapy compared with placebo in adults with moderate to severe AD. The studies had 3 key phases: initial treatment phase (0 weeks to 16 weeks), maintenance treatment phase (16 weeks to 52 weeks), and safety follow-up (52 weeks to 66 weeks). All patients used an emollient twice daily (or more, as needed) for at least 14 days before randomization and were to continue this treatment throughout the trial. Patients were randomized in the initial treatment phase in a 3:1 ratio to either the biweekly 300 mg tralokinumab injections (following the baseline 600 mg loading dose on day 0) group or to the placebo administered every 2 weeks group. At week 16, patients who achieved a clinical response (defined as IGA score of 0 or 1 or an EASI75 score) and were assigned to the tralokinumab group in the initial treatment phase were re-randomized in a 2:2:1 ratio to biweekly 300 mg tralokinumab injections, tralokinumab 300 mg every 4 weeks (alternating biweekly dosages of placebo and 300 mg tralokinumab injections), or placebo. The primary outcomes were the percentage of patients achieving an IGA response of 0 (clear skin) or 1 (almost clear skin) and the percentage of patients achieving an EASI75 score at week 16, with secondary end points addressing symptom scores and extent of AD (SCORAD), itch severity (worst daily pruritus NRS), and an HRQoL measure related to AD. Of the participants enrolled in the ECZTRA 1 trial, the mean age at baseline was 38.8 years and 59.1% of the trial population were men. The mean body surface area involvement with AD was 53.1%, [redacted] and the mean duration of AD was 28.3 years. Of the participants enrolled in the ECZTRA 2 trial, the mean age at baseline was 36.7 years and 59.6% of the total trial population were men. At baseline, the mean body surface area involvement with AD was 52.7%, [redacted] and the mean duration of AD was 28.1 years.

ECZTRA 3 (N = 380) was a randomized, double-blind, placebo-controlled, 32-week trial that evaluated the efficacy and safety of tralokinumab as a combination therapy with TCS compared to placebo plus TCS in adults with moderate to severe AD. All patients used an emollient twice daily (or more, as needed) for at least 14 days before randomization and were to continue this treatment throughout the trial. The trial had a 16-week initial treatment period followed by an additional 16-week continuation period. On day 0 of the initial treatment period, patients received a loading dose of 600 mg tralokinumab or placebo. In the initial treatment period, 380 patients were randomized in a 2:1 ratio to receive subcutaneous doses

of tralokinumab or placebo every second week during the 16-week initial treatment period. At baseline, all patients were instructed to initiate treatment once daily with a supplied TCS (mometasone furoate 0.1% cream) on lesional skin and continue as needed throughout the trial. Patients randomized to the tralokinumab group in the initial treatment period who had a clinical response (defined as IGA score of 0 or 1 or EASI75 score from baseline) at week 16 were re-randomized into the continuation treatment period in a 1:1 ratio, stratified by region (Europe and North America) and IGA response at week 16 (IGA 0 or 1 or IGA > 1): tralokinumab 300 mg every 2 weeks or tralokinumab 300 mg every 4 weeks (alternating dose administrations of tralokinumab 300 mg and placebo). The trial evaluated the percentage of patients achieving IGA response of 0 (clear) or 1 (almost clear) and the percentage of patients achieving at EASI75 at week 16 (primary end points). The mean age of participants at baseline was 39.1 years. In the tralokinumab every 2 weeks plus TCS group, men and women were equally distributed. In the placebo plus TCS group, there was a higher proportion of men than women (66.1% vs. 33.9%). Most participants were White (75.8% patients). The mean body surface area involvement with AD was 48.1%, [redacted] and the mean duration of AD was 28.2 years.

ECZTRA 7 (N = 277) was a randomized, double-blind, placebo-controlled, 26-week, trial that evaluated the efficacy and safety of tralokinumab as a combination therapy with TCS compared to placebo plus TCS in adults with severe AD who were not adequately controlled with, or had contraindications to, oral cyclosporine A. Participants were randomized in a 1:1 ratio to receive tralokinumab 300 mg plus TCS or placebo plus TCS. The randomization was stratified by prior cyclosporine A use (yes or no), country (Germany: yes or no), and baseline disease severity (IGA: 3 or 4). All patients were instructed to use a supplied TCS (mometasone furoate 0.1% cream) once daily, as needed, on lesional skin during the treatment period. Each patient received a loading dose of 600 mg tralokinumab or placebo. At subsequent visits in the treatment period, patients received either tralokinumab 300 mg every 2 weeks or placebo every 2 weeks. The trial evaluated the percentage of patients achieving EASI75 score at week 16 (primary end point). The median age of participants at baseline was 34 years. There was a higher proportion of men than women (59.6% vs. 40.4% patients). Most participants were White (98.2%). The median body surface area involvement with AD was 52%, [redacted] and the median duration of AD was 26 years.

Efficacy Results

Treatment with tralokinumab elicited a statistically significant improvement in markers of AD severity, such as IGA and EASI, at 16 weeks in adults with moderate to severe AD. For participants who achieved an IGA score of 0 or 1 at week 16, the percent difference between tralokinumab and placebo was 8.6% in ECZTRA 1 (95% CI, 4.1 to 13.1; P = 0.002), 11.1% in ECZTRA 2 (95% CI, 5.8 to 16.4; P < 0.001), 12.4% in ECZTRA 3 (95% CI, 2.9 to 21.9; P = 0.015), all favouring tralokinumab. In the ECZTRA 7 trial, for participants who achieved an IGA score of 0 or 1 at week 16, the percent difference between tralokinumab and placebo was [redacted]; however, due to the insignificant difference between tralokinumab and placebo in the reduction of worst daily pruritus NRS outcome, which was first in the testing hierarchy, statistical testing was not conducted for this outcome.

For participants who achieved an EASI75 score at week 16, the percent difference between tralokinumab and placebo was 12.1% in ECZTRA 1 (95% CI, 6.5 to 17.7; P < 0.001), 21.6% in ECZTRA 2 (95% CI, 15.8 to 27.3; P < 0.001), 20.2% in ECZTRA 3 (95% CI, 9.8 to 30.6; P < 0.001), and 14.1% in ECZTRA 7 (95% CI, 2.5 to 25.7; P < 0.018). These differences were statistically significantly in favour of tralokinumab in all 4 trials.

The adjusted mean change from baseline in SCORAD was statistically significantly larger in the tralokinumab group compared with the placebo group at week 16 in the ECZTRA 1, ECZTRA 2, and ECZTRA 3 trials, in which the difference between tralokinumab and placebo was −10.4 in ECZTRA 1 (95% CI, −14.4 to −6.5; P < 0.001), −14.0 in ECZTRA 2 (95% CI, −18.0 to −10.1; P < 0.001), and −10.9 in ECZTRA 3 (95% CI, −15.2 to −6.6; P < 0.001). The difference between tralokinumab and placebo in ECZTRA 7 was −8.6 (95% CI, −13.0 to −4.2); however, due to the insignificant difference between tralokinumab and placebo in the reduction of worst daily pruritus NRS outcome, which was first in the testing hierarchy, statistical testing was not conducted for this outcome.

The adjusted mean change from baseline in patient-oriented eczema measure (POEM) scores also favoured tralokinumab when compared to placebo at week 16, in which the difference between tralokinumab and placebo was −4.6 in ECZTRA 1 (95% CI, −6.0 to −3.1; P < 0.001), −5.1 in ECZTRA 2 (95% CI, −6.5 to −3.6; P < 0.001), −4.0 in ECZTRA 3 (95% CI, −5.6 to −2.4; P < 0.001), and −3.4 in ECZTRA 7 (95% CI, −5.0 to −1.8; P < 0.001) studies. However, this outcome was exploratory and was not adjusted for multiple testing in any of the included trials.

In terms of symptom reduction, for participants who achieved an improvement of at least 4 points in weekly average of daily pruritus NRS at week 16, the percent difference between tralokinumab and placebo was 9.7% in ECZTRA 1 (95% CI, 4.4 to 15.0; P = 0.002), 15.6% in ECZTRA 2 (95% CI, 10.3 to 20.9; P < 0.001), 11.3% in ECZTRA 3 (95% CI, 0.9 to 21.6; P = 0.037), and 9.7% in ECZTRA 7 (95% CI, −2.0 to 21.4; P = 0.106) study. The between-group difference was statistically significant in favour of tralokinumab in ECZTRA 1, ECZTRA 2, and ECZTRA 3, but not ECZTRA 7.

Participants who received tralokinumab also experienced improvement in how much the eczema interfered with the sleep at week 16 based on the eczema-related sleep NRS, in which the difference between groups in the adjusted mean change from baseline at week 16 was −0.7 in ECZTRA 1 (95% CI, −1.2 to −0.2; P = 0.007), −1.4% in ECZTRA 2 (95% CI, −1.9 to −0.9; P < 0.001), −1.3% in ECZTRA 3 (95% CI, −1.8 to −0.8; P < 0.001), and −0.8% in ECZTRA 7 (95% CI, −1.3 to −0.2; P = 0.005) in favour of tralokinumab. The minimal important difference has not been identified for the eczema-related sleep NRS in populations with AD; this outcome was exploratory and was not adjusted for multiple testing in any of the included trials.

Treatment with tralokinumab also elicited a statistically significant improvement in HRQoL at week 16 based on the DLQI measure in the ECZTRA 1, the ECZTRA 2, and the ECZTRA 3 trials. For instance, the between-group difference in the adjusted mean change from baseline in DLQI was statistically significantly larger in the tralokinumab group compared with the placebo group at week 16, where the in the ECZTRA 1 (−2.1; 95% CI, −3.4 to −0.8; P = 0.002), ECZTRA 2 (−3.9; 95% CI, −5.2 to −2.6; P < 0.001), and ECZTRA 3 (−2.9; 95% CI, −4.3 to −1.6; P < 0.001) trials. Treatment with tralokinumab also elicited a improvement in HRQoL at week 16 based on the DLQI measure in the ECZTRA 7 trial, in which between-group difference in the adjusted mean change in DLQI was larger in the tralokinumab group compared with the placebo group (−1.5; 95% CI, −2.6 to −0.4); however, this outcome was ranked after the hierarchical analysis failed and was stopped; thus, no appropriate statistical comparisons can be made. [redacted] The minimal important differences have yet to be identified in populations with AD for the DLQI, SF-36, and EQ-5D-5L outcome measures; the SF-36 and

EQ-5D-5L outcomes were exploratory and were not adjusted for multiple testing in any of the included trials.

Harms Results

In the ECZTRA 1 trial, adverse events (AEs) were reported in 76.4% (n = 460) of patients treated with tralokinumab and 77.0% (n = 151) of patients treated with placebo at week 16; serious adverse events (SAEs) were reported in 3.8% (n = 23) of patients treated with tralokinumab and 4.1% (n = 8) of patients treated with placebo. Treatment-emergent AEs leading to permanent discontinuation of the study drug were reported in 3.3% (n = 20) of patients treated with tralokinumab and 4.1% (n = 8) of patients treated with placebo at week 16. At week 52, AEs were reported in 79.4% (n = 54) of patients in the tralokinumab every 2 weeks group, 69.7% (n = 53) in the tralokinumab every 4 weeks group, and 71.4% (n = 25) of patients in the placebo group. [redacted]

In the ECZTRA 2 trial, AEs were reported in 61.5% (n = 364) of patients treated with tralokinumab and 66.0% (n = 132) of patients treated with placebo at week 16; SAEs were reported in 1.7% (n = 10) of patients treated with tralokinumab and 2.5% (n = 5) of patients treated with placebo. Treatment-emergent AEs leading to permanent discontinuation of the study drug were reported in 1.5% (n = 9) of patients in the tralokinumab group and 1.5% (n = 3) of patients in the placebo group. At week 52, AEs were reported in 68.1% (n = 62) of patients in the tralokinumab every 2 weeks group, 62.9% (n = 56) in the tralokinumab every 4 weeks group, and 69.6% (n = 32) of patients in the placebo group. [redacted]

In the ECZTRA 3 trial, AEs were reported in 71.4% (n = 180) of patients treated with tralokinumab every 2 weeks plus TCS and 66.7% (n = 84) of patients treated with placebo plus TCS at week 16; SAEs were reported in 0.8% (n = 2) of patients treated with tralokinumab every 2 weeks plus TCS and 3.2% (n = 4) of patients treated with placebo plus TCS. Treatment-emergent AEs leading to permanent discontinuation of the study drug were reported in 2.4% (n = 6) of patients treated with tralokinumab every 2 weeks plus TCS and 0.8% (n = 1) of patients treated with placebo plus TCS patients at week 16. At week 32, AEs were reported in 69.6% (n = 48) of patients in the tralokinumab every 2 weeks plus TCS group and 59.4% (n = 41) in the tralokinumab every 4 weeks plus TCS group. [redacted]

In the ECZTRA 7 trial, AEs were reported in 77.5% (n = 107) of patients treated with tralokinumab every 2 weeks plus TCS and 78.8% (n = 108) of patients treated with placebo plus TCS at week 26; SAEs were reported in 0.7% (n = 1) of patients treated with tralokinumab every 2 weeks plus TCS and 3.6% (n = 5) patients treated with placebo plus TCS. Treatment-emergent AEs leading to permanent discontinuation of the study drug were reported in 0.7% (n = 1) of patients in the tralokinumab every 2 weeks plus TCS group and 2.2% (n = 3) of patients in the placebo plus TCS group at week 26. There were no deaths reported in the ECZTRA 7 trial.

Harms of special interest at week 16 included AD, which occurred in 25.9% (n = 156) of patients treated with tralokinumab and 38.3% (n = 75) of patients treated with placebo in the ECZTRA 1 trial and 16.6% (n = 98) of patients treated with tralokinumab and 33.5% (n = 67) of patients treated with placebo in the ECZTRA 2 trial, and viral upper respiratory tract infection,

which occurred in 23.1% (n = 139) of patients treated with tralokinumab and 20.9% (n = 41) of patients treated with placebo in the ECZTRA 1 trial and 8.3% (n = 49) of patients treated with tralokinumab and 18.5% (n = 17) treated with placebo in the ECZTRA 2 trial. In the ECZTRA 3 and ECZTRA 7 trials, the most common AE was viral upper respiratory tract infection, which occurred in 19.4% (n = 49) of patients treated with tralokinumab plus TCS and 11.1% (n = 14) of patients treated with placebo plus TCS in the ECZTRA 3 trial and 26.8% (n = 37) of patients treated with tralokinumab plus TCS and 25.5% (n = 35) of patients treated with placebo plus TCS in the ECZTRA 7 trial. Among notable harms at week 16, pruritus occurred in 5.3% (n = 32) of patients treated with tralokinumab and 5.1% (n = 10) of patients treated with placebo in the ECZTRA 1 trial, upper respiratory infraction occurred in 10.0% (n = 59) of patients treated with tralokinumab and 8.5% (n = 17) of patients treated with placebo in the ECZTRA 2 trial, conjunctivitis occurred in 11.1% (n = 28) of patients treated with tralokinumab plus TCS and 3.2% (n = 4) of patients treated with placebo plus TCS in the ECZTRA 3 trial, and headache occurred in 15.2% (n = 21) of patients treated with tralokinumab plus TCS and 9.5% (n = 13) of patients treated with placebo in the ECZTRA 7 trial.

Critical Appraisal

Although the analyses were appropriate and investigators accounted for multiplicity, there are several limitations associated with the design of the trials. First, for the ECZTRA 1, ECZTRA 2, and ECZTRA 3 trials, there was a 2-week to 6-week washout period during which no topical corticosteroid use was allowed. As noted by Wollenberg et al., the patient population being studied had significant disease and high levels of prior medication use. Therefore, the washout period may have been long enough to exacerbate AD leading to patients being labelled as "non-responders" early in the studies. Second, the duration of the initial treatment period (16 weeks) in the ECZTRA 1, ECZTRA 2, and ECZTRA 3 trials may not have been sufficient. Further, a limitation affecting assessment of longer-term efficacy and safety in the ECZTRA 1, ECZTRA 2, and ECZTRA 3 trials is that only patients who achieved a clinical response at week 16 were eligible to be re-randomized. As a result, the estimates of effect in the maintenance phase are uncertain; the analyses in the maintenance phase also were not powered, which signifies that the long-term efficacy and safety of tralokinumab is uncertain. Another limitation is the absence of a comparator with a similar mechanism of action (e.g., dupilumab). Within the context of the trials, there were statistically significant improvement with tralokinumab on the primary and secondary end points compared with placebo; however, the intervention is not compared to another biologic that is currently available to patients. Finally, pauses in dosing or the use of rescue medication in situations in which the intervention was not available due to COVID-19 during the ECZTRA 7 trial may have affected results.

In terms of external validity, the ECZTRA 3 and ECZTRA 7 trials are more reflective of real-world practice because tralokinumab was combined with TCS as the intervention. In the ECZTRA 1 and ECZTRA 2 trials, patients who used rescue medication were considered "non-responders"; this does not align with real-world use of biologics which, as per the clinical experts consulted by CADTH for this review, are initiated as add-on therapy to TCS for active lesions.

Indirect Comparisons

Description of Studies

CADTH summarized and appraised 2 ITCs: 1 matched-adjusted indirect comparison (MAIC) submitted by the sponsor and a published network meta-analysis (NMA) by the Institute for

Clinical and Economic Review (ICER). The ICER NMA compared tralokinumab with dupilumab (the only drug approved for use in the treatment of AD at the time of this review); upadacitinib and abrocitinib (currently under review by Health Canada and CADTH for use in the treatment of AD), and several drugs that were not listed as under review by Health Canada or CADTH at the time of this review (e.g., nemolizumab, lebrikizumab, and baricitinib). The sponsor-submitted MAIC [redacted].

Efficacy Results

Results from the ICER NMA showed that tralokinumab was generally superior to placebo, although inferior to upadacitinib (both 15 mg and 30 mg), abrocitinib 200 mg, and dupilumab 300 mg. These results were consistent when these treatments were used as monotherapy or in combination with topical therapies.

The sponsor-submitted MAIC reported that [redacted].

Harms Results

Results from the sponsor-submitted MAIC indicate that [redacted].

Critical Appraisal

Neither ITC commented on their methods of study selection, data extraction, or quality assessment. [redacted]

Conclusions regarding the long-term efficacy of tralokinumab compared with the active comparators relevant to this review cannot be drawn from the ICER NMA because the NMA used study results collected over a relatively short duration in contrast to the chronic nature of AD. There is also uncertainty due to the inherent heterogeneity across trials in the networks. The robustness of the comparative efficacy was further compromised by the lack of precision in some of the findings, hence results from the ICER NMA must be interpreted with caution.

Other Relevant Evidence

Description of Studies

One on-going, open-label, single-arm, long-term extension study (ECZTEND) has been summarized to provide additional evidence on the safety and efficacy of tralokinumab in patients with AD who have previously participated in clinical trials for tralokinumab (i.e., ECZTRA 1 to ECZTRA 8 and TraSki). The ECZTEND study has a 2-week screening period (which is expected to overlap with the end of the parent trial for most patients), a 6-month to 5-year treatment phase, and 14 weeks of follow-up beginning 2 weeks after the final dose. At the time of data cut-off, 1,174 patients were included in the ECZTEND trial. The primary outcome is safety or the number of AEs experienced during the study. The secondary outcomes are for drug efficacy, including achieving an IGA score of 0 or 1 and achieving an EASI75 score at weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 during the treatment

phase relative to baseline. Blinding of treatment allocation was maintained for patients who continued from a blinded parent trial and entered the open-label extension study.

Efficacy Results

Responders were defined as achieving an IGA score of 0 or 1 or an EASI75 score. [redacted]

Harms Results

Overall, 844 (71.9%) patients experienced at least 1 AE, with the 3 most common AEs being viral upper respiratory tract infection (21.3%), AD (13.5%), and upper respiratory tract infection (7.1%). Other harms of special interest that were identified in CADTH's systematic review protocol include [redacted]. There were 19 (1.6%) patients who withdrew due to AE, and no deaths were reported.

Critical Appraisal

The ECZTEND trial lacked a comparator, which made it difficult to adjust for natural changes in the course of AD or the effects of potential confounders. Additionally, the open-label design may have influenced the perception of improvement by patients and clinicians which could impact the reporting of harms and efficacy measures. The number of patients screened from the parent trials was not reported nor were the reasons for screening failures. Moreover, patients were recruited exclusively from the parent trials of tralokinumab, and only those who could tolerate the treatments were able to enrol in the ECZTEND study. No formal sample size or power calculations were performed, no control for multiplicity was described in the report, and there was no imputation of missing safety data. Most patients in the study were White (71.3%), which may be a result of the regions where the study took place (mainly Europe and North America). Although the clinical experts CADTH consulted with on this review were uncertain if race would bias the outcomes, it may limit how the results can be interpreted in the context of a broader patient population in Canada. Treatment history was not described in this report, and it is unknown if patients were treatment-naive or which medications they had experience with (e.g., topical, systemic, biologic), which limits the generalizability of the results to other patients with AD and prevents comparisons with other treatments.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-minimization analysis

Component	Description
Target population	Adult patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and have had an adequate trial or are ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.
Treatment	Tralokinumab
Comparator	Dupilumab
Submitted price	Tralokinumab, 150 mg, subcutaneous injection: $422.26 per syringe
Treatment cost	At the recommended dose of 600 mg as an initial dose and 300 mg every 2 weeks thereafter; the annual cost of treatment with tralokinumab is $22,802 in the first year of treatment and $21,633 in subsequent years of treatment
Perspective	Canadian publicly funded health care payer
Key data source	Sponsor-submitted matching adjusted indirect comparison
Costs considered	Drug acquisition costs
Time horizon	2 years (induction period and 1 maintenance year)
Key limitations	• The assumption of similar clinical efficacy for tralokinumab and dupilumab to support the conduct of a cost-minimization analysis is highly uncertain because the indirect treatment comparisons appraised by the CADTH clinical review team suggest for most efficacy analyses, the true difference between dupilumab and tralokinumab ranges from [redacted]. There were limitations identified with the indirect treatment comparisons, which introduces uncertainty in the findings. • The use of an alternative maintenance dosing schedule applied at week 16 onward for a proportion of the target population on tralokinumab is not reflective of likely Canadian clinical practice and underestimates total costs associated with tralokinumab. • A prior CDEC recommendation for dupilumab included a submitted price for dupilumab lower than the current publicly available list price of dupilumab used in the sponsor's analysis. Additionally, CDEC recommended a significant price reduction for dupilumab was necessary for it to be cost-effective. Because CADTH is not aware of the confidential negotiated prices, the price of dupilumab is uncertain and significant reductions in its price may limit or eliminate the cost savings associated with tralokinumab.
CADTH reanalysis results	• CADTH conducted a reanalysis using the standard maintenance dose suggested in the product monograph for all patients to reflect the expected maintenance dosing schedule in Canadian clinical practice. • Based on the CADTH reanalysis, tralokinumab was associated with a per patient savings of $7,060 over a 2-year time horizon. • CADTH considered scenario analyses exploring the cost of dupilumab. Should a 54% reduction in price as per the CADTH pharmacoeconomic report for a prior dupilumab submission be negotiated, tralokinumab would be associated with an incremental per patient cost of $21,201 over the 2-year time horizon. • CADTH was unable to address the uncertainty associated with the comparative efficacy of tralokinumab compared with dupilumab. Should tralokinumab be considered clinically inferior to dupilumab, a cost-minimization analysis is not appropriate to assess the cost-effectiveness of tralokinumab, and the cost-effectiveness of tralokinumab would be unknown.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The parameters used to derive the size of the population eligible for treatment with tralokinumab are uncertain.
- The proportion of patients assumed to follow an alternative maintenance dosing schedule (every 4 weeks) with tralokinumab did not reflect expected Canadian clinical practice, with patients expected to follow the standard maintenance dosing schedule (every 2 weeks).

Due to limitations with the sponsor's model programming which prevented CADTH from deriving results at the pan-Canadian level, CADTH programmed a corrected base case which approximated the sponsor's results before conducting any reanalyses. CADTH's reanalyses included the following changes to the sponsor's approximated base case: revising several epidemiological inputs to address the uncertainty in the total population size eligible for tralokinumab and revising the proportion of patients expected to receive the standard maintenance dosing. Based on CADTH reanalyses, the budget impact from the introduction of tralokinumab would result in an estimated budget savings of $5,184,103 in year 1, $9,041,398 in year 2, and $11,396,269 in year 3, for a total budget savings of $25,621,769, over the 3-year time horizon. The magnitude of budget savings from the introduction of tralokinumab varies with the price of dupilumab. The budget impact from reimbursing tralokinumab in the broader Health Canada indicated population, as well as situations where tralokinumab is expected to displace treatments other than dupilumab, is unknown.

CDEC Information

Initial Meeting Date: September 22, 2021

Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: February 24, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Regrets: None

Conflicts of interest: None