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Reimbursement Recommendation

Lebrikizumab (Ebglyss)

Indication: For the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without topical corticosteroids.

Sponsor: Eli Lilly Canada Inc.

Final recommendation: Do not reimburse

Summary

What Is Canada's Drug Agency Reimbursement Recommendation for Ebglyss?

Canada's Drug Agency (CDA-AMC) recommends that Ebglyss should not be reimbursed by public drug plans for the treatment of moderate to severe atopic dermatitis (AD) in adults and adolescents aged 12 years and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 3 clinical trials demonstrated that, in the short-term, Ebglyss treatment improved the severity of AD and reduced itch symptoms compared with placebo in adults and adolescents with moderate to severe AD. However, based on the evidence reviewed in the initial meeting and the reconsideration meeting, the Canadian Drug Expert Committee (CDEC) could not determine whether lebrikizumab would address the unmet needs of patients because of the uncertainty around the benefit of lebrikizumab versus appropriate comparators and in patients who received prior dupilumab or Janus kinase (JAK) inhibitor treatment.
- No evidence was submitted that directly compared Ebglyss to currently available treatments for AD. The indirect evidence submitted had limitations that impacted the certainty of the evidence, and it was unclear if the estimates were valid.
- The safety of Ebglyss relative to other treatments for AD is unknown because no comparative evidence was submitted. In addition, longer-term safety and efficacy was uncertain because of limitations of the study designs and analysis with the available evidence.

Additional Information

What Is AD?

AD is a condition that affects the skin and causes dry, red skin that is extremely itchy. Constant scratching causes the skin to split and bleed, which can lead to infections. Oozing and weeping sores occur in more severe forms. Severe AD can be physically incapacitating and cause anxiety or depression. AD affects around 20% of children, and up to 10% of adults in high-income countries.

Summary

Unmet Needs in AD

There is a potential need for additional treatment options that effectively reduce the severity and symptoms of AD, particularly in patients whose disease did not adequately respond to, or were deemed unsafe to receive, other biologics or JAK inhibitors.

How Much Does Ebglyss Cost?

Treatment with Ebglyss is expected to cost approximately $35,657 per patient in the first year and approximately $24,397 per patient in subsequent years.

Recommendation

CDEC recommends that lebrikizumab not be reimbursed for the treatment of moderate to severe AD in adults and adolescents aged 12 years and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Rationale for the Recommendation

CDEC acknowledged the need for additional treatment options that effectively reduced the severity and symptoms of AD; however, input from patients and clinicians indicated that there is unmet need among those with AD that was not adequately controlled by biologic therapy and are concerned about the safety profile of JAK inhibitors, or for those who have exhausted currently available treatment options. Based on the submitted evidence, CDEC could not determine whether lebrikizumab would adequately meet this need.

Three phase III randomized controlled trials (RCTs) (ADvocate 1, N = 424; ADvocate 2, N = 427; and ADhere, N = 211) in adults and adolescents with moderate to severe AD that was not adequately controlled with topical therapies provided evidence of lebrikizumab compared with placebo. The ADvocate 1, ADvocate 2, and ADhere trials demonstrated that lebrikizumab induction therapy (with or without topical corticosteroids [TCS]) provided a clinically relevant improvement in physician assessed Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA), and reduced patient-reported symptoms of itch relative to placebo at 16 weeks.

Dupilumab, upadacitinib, and abrocitinib were identified as comparators of interest for lebrikizumab. There was no direct evidence comparing lebrikizumab to other biologics or JAK inhibitors used to treat AD. One network meta-analysis (NMA) provided indirect evidence for the comparisons of interest; however, the results of the NMA were inconclusive for lebrikizumab relative to dupilumab and abrocitinib, with most estimates affected by serious imprecision that limits the interpretability of the treatment effect of lebrikizumab relevant to other comparators. Further, because of heterogeneity, it was unclear whether the transitivity assumption was met and if the estimates were valid.

The NMA did not assess any safety end points and in the absence of direct comparative evidence, the comparative safety of lebrikizumab is unknown. The clinical trial evidence suggests lebrikizumab may increase the short-term risk of conjunctivitis relative to placebo. The longer-term safety and efficacy of lebrikizumab from the RCTs and extension study is uncertain because of limitations with the data which included an enriched population and carry-over effects for the 52-week data in the pivotal trials, and the lack of comparator group for the extension study.

Patient input received for this review identified a need for additional treatments for patients that can reduce severity and symptoms of AD, improve sleep quality and health-related quality of life (HRQoL), have sustained benefits, and are safe. As described above, the evidence does not suggest that lebrikizumab meets this need relative to other available treatments.

Discussion Points

- **Sponsor request for reconsideration:** The sponsor requested a reconsideration of the initial draft recommendation to not reimburse lebrikizumab for treatment of moderate to severe AD in adults and adolescents aged 12 years and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. There were 3 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. Briefly, the sponsor indicated that the place in therapy for lebrikizumab is as a first-line advanced treatment for AD, the sponsor also suggested that the indirect evidence demonstrates a comparable clinical benefit with lebrikizumab relative to dupilumab, and that the sponsor requests that CDEC reconsider the broad unmet need for patients with moderate to severe AD.
- **Interpretation of indirect evidence:** During the initial meeting and the reconsideration meeting, CDEC discussed the availability of other treatments for AD, and the challenge of a comprehensive assessment of lebrikizumab in the absence of direct comparative evidence. Based on the NMA included in the initial submission, there was no evidence to suggest lebrikizumab offered a benefit over other advanced therapies for AD, namely, dupilumab, upadacitinib, and abrocitinib. It was also noted that findings that are not statistically significant cannot be interpreted as equivalence. Moreover, the NMA signals that there may be differences in some outcomes, such as EASI response at week 16 and the Pruritus Numerical Rating Scale (NRS) response at week 16, that suggests lebrikizumab may not be as effective as upadacitinib and abrocitinib.
- **Use of lebrikizumab following other advanced therapies is uncertain**: During the initial meeting and the reconsideration meeting, CDEC acknowledged that lebrikizumab (with or without TCS) appears more efficacious than placebo in important EASI and IGA end points as well as patient-reported Pruritis NRS for itch. The committee also discussed the use of lebrikizumab in patients who are refractory to or do not tolerate current biologic therapy (i.e., dupilumab), which was identified as an unmet need by patients and clinician groups and where additional treatment options are needed most. This area of unmet need was also noted by the clinical expert supporting this submission. Although some patients had exposure to other systemic therapies, the study populations were not required to have AD that did not adequately respond to treatment with, or have experienced intolerance to other immunomodulator therapies, biologics or JAK inhibitors, which is the population identified as having an unmet need. Therefore, whether treatment with lebrikizumab is an effective treatment for patients with AD that was previously unsuccessfully treated with dupilumab or a JAK inhibitor (i.e., as a second- or subsequent-line therapy) remains uncertain.
- **Certainty of the systematic review evidence (GRADE)**: CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of outcomes selected for the review of lebrikizumab. The GRADE assessment applied to relevant outcomes included in placebo-controlled ADvocate 1, ADvocate 2, and ADhere trials, which demonstrated that lebrikizumab (with or without TCS) increased the proportion of patients with an IGA 0 or 1 response, EASI 75 response, or at least a 4-point improvement in the Pruritus NRS, relative to placebo with moderate to high certainty. The treatment effects for all 3 outcomes were considered clinically

relevant; however, the relevance was based on clinical expert input in the absence of evidence for a minimally importance difference and therefore subject to some uncertainty. Also of note, outcomes related to HRQoL and safety, both of which were identified as outcomes that are important to patients, were assessed as having low to very low certainty.

- **Lack of comparative data for safety and HRQoL:** During the initial meeting and the reconsideration meeting, CDEC recognized the value that both patients and clinicians place in having a choice of treatment options, but the absence of comparative safety data as well as HRQoL outcomes preclude assessment of all factors necessary to balance all outcomes and unmet needs (including improved safety).

Background

AD is a chronic, relapsing, inflammatory, and noncontagious skin disease, which is commonly associated with other atopic expressions such as asthma, allergic rhinitis, and food allergy. The burden of disease and its impact on quality of life may be profound, particularly in case of moderate to severe AD. Itch or pruritus; soreness, pain, or tenderness; and skin dryness were the signs and symptoms that were most frequently cited as having a clinical impact. Itch is the major symptom which has negative impact on quality of life and is associated with mental distress and increased risk for suicidal ideation. Depression, anxiety, and sleep disturbance are frequently reported comorbidities. Moreover, AD can result in embarrassment from appearance, and negative impact on self-esteem, and social life. Patients with AD are at an increased risk of skin infections because of excessive rubbing or scratching. Exacerbations or flares are an integral part of the disease course and generally indicate a worsening of AD that requires escalation or intensification of treatment.

AD impacts approximately 15% to 20% of children and 1% to 3% of adults worldwide, and in high-income countries, AD affects around 20% of children, and up to 10% of adults. Most of the adult patients with AD have mild disease, and approximately 50% have moderate to severe disease based on clinical disease severity scales.

Initial treatment for most patients with AD is emollients (moisturizers) plus topical anti-inflammatory therapy, including TCS and topical calcineurin inhibitors. For patients with more severe AD or with AD that is refractory to topical therapy, advanced treatments including phototherapy and systemic treatment are considered. According to the American Academy of Dermatology and American Academy of Allergy, Asthma and Immunology clinical practice guidelines, biologics, and particularly dupilumab, are considered first-line systemic therapy. Other options include tralokinumab (another biologic) and oral JAK inhibitors (upadacitinib and abrocitinib). According to the clinical expert consulted, off-label immunomodulators (cyclosporine, methotrexate, mycophenolate, and azathioprine) are generally only used when mandated by a medication payer as step-through therapy or if the previously mentioned biologic and JAK inhibitor treatments are unsuccessful or are contraindicated. These drugs were not listed as first-line systemic therapies in the 2023 American Academy of Dermatology clinical practice guidelines because of their lower certainty of evidence

relative to newer drugs, the potential for serious adverse events (SAEs), the need for stringent laboratory monitoring, and lack of regulatory approval for use in AD.

Lebrikizumab was approved by Health Canada for the treatment of moderate to severe AD in adults and adolescents aged 12 years and older with a body weight of at least 40 kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without TCS. Lebrikizumab is available as a 250 mg per 2 mL solution in a prefilled pen or prefilled syringe with needle shield for subcutaneous (SC) injection. The recommended initial dose is 500 mg (two 250 mg injections) at week 0 and week 2, followed by 250 mg (1 injection) every 2 weeks until week 16. Once clinical response is achieved, the recommended maintenance dose is 250 mg every 4 weeks starting at week 16. The product monograph states that continued therapy beyond 16 weeks should be carefully considered in a patient who does not show treatment benefit during this time.

Sources of Information Used by the Committee

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

- a review of 3 RCTs in adults and adolescents with moderate to severe AD
- patients' perspectives gathered by patient groups, Eczema Quebec, Canadian Skin Patient Alliance, and the Eczema Society of Canada
- input from public drug plans that participate in the CDA-AMC review process
- 1 clinical specialist with expertise diagnosing and treating patients with moderate to severe AD
- input from 2 clinician groups, including the Canadian Dermatology Association and the Dermatology Association of Ontario (DAO)
- supporting evidence from 1 long-term extension study, and 4 other clinical trials addressing gaps in the systematic review evidence
- appraisal of a sponsor-submitted NMA
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from the clinical expert we consulted for the purpose of this review.

Patient Input

Three patient groups provided input to this submission. Eczema Quebec gathered information through review of scientific literature, informal conversations with patients, *The Skin I'm In, 2022 Update* (a joint report by Eczema Quebec and Canadian Skin Patient Alliance), expert opinion from McGill University Health Centre's Centre of Excellence for Atopic Dermatitis, 9 written patient testimonials, interviews with 14 patients, and feedback from 3 patient group discussions. The Canadian Skin Patient Alliance gathered information from previous submissions to CDA-AMC, data from the Canadian Institute for Health Information on AD-related emergency department visits, and hospitalizations from 2016 to 2020 as reported in the *The Skin I'm In* report, and guidelines. Eczema Society of Canada gathered information through a survey, and 1-on-1 interviews from more than 3,000 patients with AD and their caregivers who live in Canada.

According to the input from patient groups, symptoms of patients with AD include inflamed, painful, dry, and itchy skin that cracks, oozes, bleeds and in some cases involves thickening and/or infections of the skin. Conditions associated with AD include asthma, seasonal and environmental allergies, food intolerances, sleep disorders, anxiety, and depression. Patient groups stated that physical manifestations and visibility of the disease contribute to psychological distress through stigmatization which impacts self-esteem, professional commitments, and social engagements.

Based on input from patient groups, the stress of AD also extends to caregivers and family members. Caregivers reported feelings of anxiety, depression, helplessness, guilt, frustration, and a lack of control over the situation. Caregivers and family members also shared that their own health and emotional wellness, lifestyle, sleep, intimacy, social activities, and family dynamics were affected by the disease. Further, the cost of treatment and other skincare products can place financial stress not only on the patients but also on the family.

Important desired outcomes reported by patient groups included: better, fast and long-term control of the disease, reduction of flares, relief from itch, reduction of skin symptoms, pain and discomfort relief, improved psychological status, improved daily and social activities, increased productivity, improved emotional well-being, improved sleep quality, maintained intimate relationships, treatments covered by insurance or to be affordable, and treatments that are easy to use (i.e., those that are not administered by injection or topically).

Access to health care presents another challenge to patients with AD, with Canada's low ratio of dermatologists to the population, making specialized care difficult to obtain, particularly in remote areas. Additionally, 36% of caregivers reported feeling a lack of support from the health care system and 30% reported financial challenges related to managing their child’s disease.

Clinician Input

Input From Clinical Expert We Consulted

According to the clinical expert we consulted, there is an unmet need for more treatment options for people who are refractory to or do not tolerate current biologic treatments for AD, as well as for people who are concerned about the safety profile of oral JAK inhibitors, particularly people with comorbidities and who are older.

Patients with moderate to severe AD refractory to topical therapy are most likely to respond to treatment with lebrikizumab, according to the clinical expert. The clinical expert anticipates lebrikizumab's use will be similar to other systemic medications with concomitant use of emollients and topical anti-inflammatory treatments (e.g., corticosteroids). Given the clinical experience with, and evidence supporting the use of dupilumab, the expert anticipated that lebrikizumab would be considered a second-line biologic after dupilumab, and it may be chosen for patients for whom dupilumab is contraindicated, ineffective, or not tolerated.

In clinical practice, the clinical expert stated that clinicians generally use a gestalt assessment of improvement in clinical signs and patients' history of change in symptoms (e.g., itch) and quality of life. Clinicians only use the tools used in clinical trials (e.g., EASI score) if mandated by a medication payer to obtain coverage. According to the clinical expert, a meaningful response to treatment would be an approximately 50% to 75% improvement in signs and symptoms; the specific proportion likely differs by clinician and by patient. The improvement should include a reduction in the severity and frequency of symptoms and is often accompanied by an improvement in quality of life and ability to perform household and work or school activities. A reduction in skin infections and disease flares are also important.

The clinical expert indicated that lebrikizumab would be discontinued if it is inadequately effective, if the patient experiences intolerable adverse effects, or the patient wishes to interrupt or discontinue therapy. The clinical expert noted that in most instances, a specialist (dermatologist, allergist, or pediatrician) would be required to treat AD with a biologic, although in areas where access to specialty care is difficult, some family physicians could gain comfort with biologics for AD.

Clinician Group Input

We received inputs from 2 clinician groups for this review. The Canadian Dermatology Association submitted input from 3 clinicians from their pharmacy and therapeutics advisory board, and the DAO submission included input from 11 clinicians.

Clinician groups and the clinical expert we consulted agreed that lack of adequate response to treatment, incomplete effectiveness, adverse effects of treatments, lack of feasibility of some of the treatments, and relapses are unmet needs of patients with AD. One of the clinician groups added that challenges in access to care, multitiered treatment regimens, treatment intolerance or contraindications, and comorbid bacterial skin infections are unmet needs as well.

The Canadian Dermatology Association and the clinical expert we consulted agreed that the goals of treatment are improving quality of life and maximizing efficacy and safety. Regarding the place of lebrikizumab in therapy, the DAO and the clinical expert believe that lebrikizumab will not cause a shift in the treatment paradigm and would be considered another treatment option. The Canadian Dermatology Association stated lebrikizumab contributes to an important shift in the current treatment paradigm toward a new era of focus on novel disease mechanism targeting and disease modification with favourable safety and efficacy profiles.

According to the DAO, adult patients with moderate to severe AD who have had unsuccessful treatment using phototherapy or topical therapies and those that do not have access to phototherapy would be best

suited for the treatment with lebrikizumab. The Canadian Dermatology Association stated that patients best suited for treatment with lebrikizumab would be those with uncontrolled moderate to severe AD who are candidates for systemic therapy or meet criteria for biologic therapy. They also noted that dupilumab is indicated for patients with other severe forms of atopic or allergic conditions such as severe asthma or eosinophilic esophagitis, thus dupilumab may be chosen for these patients instead of the IL-13 inhibitors, such as lebrikizumab, which are not approved for use in these conditions.

The DAO noted that a patient's response to treatment would be assessed using the IGA, EASI, Pruritus NRS, and Dermatology Life Quality Index (DLQI) score systems at 4 to 6 months and then annually thereafter. The Canadian Dermatology Association stated that assessment of a patient's response would be based on clinical exam, patient's history, physician-reported clinical scoring systems (EASI, body surface area [BSA], and IGA,) and patient-reported outcomes (DLQI, children's DLQI [CDLQI], and Pruritus NRS). They added that in clinical practice, because of time limitations, only some of the scoring systems are used.

Clinician groups reported adverse events (AEs) and poor efficacy of treatment as factors that should be considered when deciding to discontinue the treatment.

Based on clinician groups input, treatment and monitoring of patients on lebrikizumab should be limited to specialists trained in this area which would include dermatology, allergy, immunology, or pediatrics.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process. The following were identified as key factors that could potentially impact the implementation of our recommendation for lebrikizumab:

- considerations for relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- system and economic issues.

The clinical expert we consulted provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

Three double-blind RCTs met the inclusion criteria for systematic review (ADvocate 1, ADvocate 2, and ADhere studies). The objective of ADvocate 1 (N = 424) and ADvocate 2 (N = 427) studies were to evaluate

the safety and efficacy of lebrikizumab as monotherapy in patients with moderate to severe AD. Eligible patients were adults or adolescents (aged 12 to younger than 18 years and weighing more than 40 kg) who had a diagnosis of chronic AD that was rated as moderate to severe based on an EASI score of at least 16, IGA score of at least 3, and AD covering a BSA of 10% or more. All patients had history of inadequate response to topical therapies for AD. Both studies included a 16-week induction period (parallel design), followed by a 36-week maintenance period (randomized withdrawal design). The studies randomized patients in a ratio of 2:1 to receive double-blind lebrikizumab 500 mg SC loading dose at week 0 and 2, and then 250 mg SC every 2 weeks or placebo for the 16-week induction period. At week 16, patients in the lebrikizumab group who responded to treatment (i.e., with an IGA score of 0 or 1, or at least a 75% reduction in EASI 75, and who did not receive rescue therapy) were randomly reassigned in a ratio of 2:2:1 to double-blind lebrikizumab 250 mg every 2 weeks, lebrikizumab 250 mg every 4 weeks, or placebo for the 36-week maintenance period.

The objective of the ADhere study was to evaluate the safety and efficacy of lebrikizumab in combination with low-to-midpotency TCS, compared with placebo + TCS in patients with moderate to severe AD. The study was a 16-week randomized, double-blind, parallel design trial (N = 211). Adults or adolescents (aged 12 to younger than 18 years weighing more than 40 kg) with moderate to severe AD (EASI ≥ 16, IGA score ≥ 3, AD covered a BSA of ≥ 10%) were eligible to enrol. Patients were randomized 2:1 to receive lebrikizumab 500 mg SC loading dose at week 0 and 2 then 250 mg SC once every 2 weeks in addition to TCS, or placebo + TCS for the 16-week treatment period.

In all trials the coprimary outcomes were the proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline to week 16, and the proportion of patients with an EASI 75 response at week 16. The IGA measures the investigator's global assessment of the patient's overall severity of AD at that visit, based on a static, numeric 5-point scale ranging from 0 (clear) to 4 (severe). The EASI is a composite index, based on the physician's assessment of 4 clinical signs of the disease (erythema, infiltration and/or papulation, excoriation, and lichenification) and the extent of BSA involved at that visit. It is scored from 0 to 72 with higher scores indicating greater disease severity and/or extent of disease. Other key outcomes reported were the proportion of patients with a Pruritus NRS score of at least 4 points at baseline who reported a at least a 4-point reduction from baseline at week 16, and the change from baseline to week 16 in the Patient Oriented Eczema Measure (POEM) score, the DLQI total score, or the CDLQI total score.

Patients enrolled in the trials had a mean age that ranged from 34.2 years (standard deviation [SD] = 16.4) to 37.5 years (SD = 19.9) per treatment group. In the ADvocate 1, ADvocate 2, and ADhere studies, 13%, 11%, and 22% of patients, respectively, were adolescents. There were roughly equal proportions of females and males in the studies. On average, the patients enrolled in the study had been diagnosed with AD for 20 or more years, with most patients (59% to 73%) classified as having disease of moderate severity based on an IGA score of 3 at baseline, whereas 27% to 41% were classified as having severe AD (i.e., IGA score of 4). Almost all patients enrolled had previously used TCS (97% to 100%) and 33% to 46% of patients had received topical calcineurin inhibitors. Systemic therapies were previously received by 43% to 56% of patients, and 12% to 24% of patients had used phototherapy before enrolment in the trials.

Efficacy Results

Induction Period

At week 16, the proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline favoured the lebrikizumab groups versus the placebo groups in all 3 studies. For the ADvocate 1 study, 43.1% versus 12.7% of patients attained an IGA 0 or 1 response in the lebrikizumab and placebo groups, respectively, with a risk difference (RD) of 29.7% (95% confidence interval [CI], 21.6 to 37.8; P < 0.001). In the ADvocate 2 study, 33.2% versus 10.8%, attained an IGA 0 or 1 response (RD = 21.9%; 95% CI, 14.2 to 29.6; P < 0.001) for the lebrikizumab versus placebo groups. The IGA 0 or 1 response also favoured lebrikizumab + TCS versus placebo + TCS in the ADhere study (41.2% versus 22.1%) (RD = 18.3%; 95% CI, 5.1 to 31.5; [redacted]).

In all 3 studies a higher proportion of patients reported an EASI 75 response at week 16 in the lebrikizumab versus placebo groups. EASI 75 response was attained by 58.8% versus 16.2% of patients in the lebrikizumab versus placebo groups, respectively, in the ADvocate 1 study (RD = 42.0%; 95% CI, 33.3 to 50.6; P < 0.001), and 52.1% versus 18.1% of patients (RD = 33.3%; 95% CI, 24.4 to 42.2; P < 0.001) in the ADvocate 2 study. In the ADhere study, 69.5% versus 42.2% of patients, attained an EASI 75 response at week 16 (RD = 26.4%; 95% CI, 12.1 to 40.8; P < 0.001) in the lebrikizumab + TCS and placebo + TCS groups, respectively.

The severity of itch was assessed using the Pruritus NRS score, where patients rated their worst itch symptoms over the past 24 hours from 0, indicating “No itch” to 10, indicating “Worst itch imaginable.” Among patients who had a Pruritus NRS score of 4 or more points at baseline, 45.9% versus 13.0% in the lebrikizumab versus placebo groups, respectively, reported at least a 4-point reduction at week 16 in the ADvocate 1 study (RD = 32.9%; 95% CI, 24.6 to 41.3; P < 0.001). The proportion of Pruritus NRS responders was 39.8% versus 11.5% in the ADvocate 2 study (RD = 28.3%; 95% CI 20.0 to 36.5; P < 0.001), favouring lebrikizumab. In the lebrikizumab + TCS group in the ADhere study, 50.6% met the Pruritus NRS response criteria compared with 31.9% in the placebo + TCS group (RD = 19.2%; 95% CI, 4.3 to 34.1; [redacted]).

A secondary outcome in the pivotal trials was the change from baseline in the POEM score, a 7-item, self-reported questionnaire used to assess the frequency of disease symptoms (skin dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) over the last week. It is scored from 0 to 28, with a higher score indicative of worse disease severity. A minimal important difference (MID) of 3.4 points was identified as the threshold for a clinically relevant between-group difference. The ADvocate 1 study reported a least squares (LS) mean difference of [redacted]) in the POEM score change from baseline to week 16, for lebrikizumab versus placebo. The LS mean difference was [redacted] for the lebrikizumab versus placebo groups in the ADvocate 2 study, and the ADhere study reported an LS mean difference of [redacted] for the lebrikizumab + TCS versus placebo + TCS groups. Of note, this outcome was potentially biased because of the extent of missing data and the analysis methods used to handle missing data. Moreover, the change in

POEM score was not part of the graphical testing strategy used to control the family-wise type I error rate and thus this outcome should be interpreted as supportive evidence only.

In the pivotal trials, the DLQI was used to measure HRQoL in patients aged 17 years and older, and the CDLQI was used for patients aged 12 to 16 years. These instruments are scored from 0 to 30 with higher scores indicating poor HRQoL. MID of 4 points for the DLQI and 6 points for the CDLQI were selected as the threshold for clinically relevant between-group difference. In the ADvocate 1 study, the LS mean difference in the change in baseline to week 16 in the DLQI total score was −5.8 points (95% CI, −7.1 to −4.5; P < 0.001), and in the ADvocate 2 study, the LS mean difference was −4.9 points (95% CI, −6.3 to −3.5; P < 0.001) for the lebrikizumab versus placebo groups. The ADhere study reported an LS mean difference in the change from baseline in the DLQI of −3.3 points (95% CI, −5.3 to −1.3; P = 0.001) for the lebrikizumab + TCS group versus the placebo + TCS group. These analyses included 75% to 86% of patients randomized to a treatment group aged 17 years or older at the start of the studies.

Among adolescents aged 12 to 16 years, the LS mean difference in the change from baseline in the CDLQI was [redacted] in the ADvocate 1 study [redacted] in the ADvocate 2 study, and [redacted] in the ADhere study for the lebrikizumab versus placebo groups at week 16. The change in CDLQI was not controlled for type I error rate and thus should be interpreted as supportive evidence only. Also of note, the number of patients per treatment group was small, ranging from 5 to 11 patients in the placebo groups, and 17 to 26 patients in the lebrikizumab groups.

Maintenance Period

At week 16 of the ADvocate 1 and ADvocate 2 studies, patients in the lebrikizumab group who met the treatment response criteria were re-randomized to placebo, lebrikizumab every 4 weeks or every 2 weeks for the maintenance period. This review focused on the results of the lebrikizumab every 4 weeks groups to be consistent with the Health Canada recommended maintenance dosing. The ADvocate 1 study reported 79.2% of patients in lebrikizumab every 4 weeks group maintained an EASI 75 response at week 52 compared with 61.3% of patients who were switched to placebo (RD of [redacted] In the ADvocate 2 study, 84.7% versus 72.0% maintained an EASI 75 response in the lebrikizumab every 4 weeks and placebo (i.e., lebrikizumab withdrawal) groups, respectively, (RD of [redacted]).

Harms Results

Induction Period

During the induction period of the trials, the proportion of patients who experienced 1 or more treatment emergent AEs (TEAEs) was 46% versus 52%, 53% versus 66%, and 43% versus 35% in the lebrikizumab and placebo groups, respectively, of the ADvocate 1, ADvocate 2, and ADhere studies. The most common AEs in the lebrikizumab groups were conjunctivitis, headache, and nasopharyngitis.

The frequency of SAEs was generally low, with 2.1% versus 0.7%, 0.7% versus 2.8%, and 1.4% versus 1.5% reporting an SAE in the lebrikizumab versus placebo groups of the ADvocate 1, ADvocate 2, and

ADhere studies, respectively. One patient who received placebo died of a myocardial infarction in the ADvocate 2 study. No other deaths were reported.

During the induction period, 1.1% versus 0.7%, 3.2% versus 2.8%, and 2.1% versus 0% of patients in the lebrikizumab versus placebo groups stopped treatment due to AEs in the ADvocate 1, ADvocate 2, and ADhere studies, respectively.

Conjunctivitis-related AEs, also a notable harm, was reported by [redacted] of patients in the lebrikizumab groups and 0% to 3.5% of patients in the placebo groups. The RD for conjunctivitis in the lebrikizumab versus placebo groups was [redacted] for the ADvocate 1 study [redacted] for the ADvocate 2 study, and [redacted] in the ADhere study.

Maintenance Period

During the maintenance period [redacted] of patients experienced a TEAE in the lebrikizumab every 4 weeks group versus the placebo (i.e., lebrikizumab withdrawal) group in the ADvocate 1 and ADvocate 2 trials, respectively. A total of [redacted] reported an SAE, including [redacted] in the lebrikizumab every 4 weeks group of the ADvocate 1 study, and [redacted] in the placebo group and [redacted] in the lebrikizumab every 2 weeks group of the ADvocate 2 study. No deaths were reported during the maintenance period.

Between week 16 and 52, 1 patient in each of the lebrikizumab every 4 weeks groups of the ADvocate 1 and ADvocate 2 studies stopped treatment due to AEs. No patients in the placebo groups stopped therapy due to AEs during the maintenance period. Overall, conjunctivitis was reported in [redacted] of patients in the lebrikizumab every 4 weeks versus placebo (lebrikizumab withdrawal) groups of the ADvocate 1 and ADvocate 2 studies, respectively.

Critical Appraisal

No major concerns were identified with the randomization, allocation concealment, blinding, or statistical methods used in the trials included in the systematic review. The key outcomes tested (EASI 75, Pruritus NRS, POEM, and DLQI) were important to patients and had evidence to support their validity and reliability in patients with AD or other dermatologic conditions. The primary estimand used for the EASI 75, IGA, Pruritis NRS, and DLQI outcomes analyzed patients who discontinued due to lack of efficacy or who required rescue therapy as nonresponders and used multiple imputation methods to impute data for patients who discontinued due to other reasons. These methods should address any potential bias due to the differential use of rescue treatments in the lebrikizumab and placebo groups.

The key limitations of the change in POEM, DLQI, and CDLQI outcomes were related to missing data. The analyses of the change in POEM and CDLQI scores were based on the supportive (hypothetical) estimand and the mixed model for repeated measure model, which assumed data were missing at random. These outcomes were not based on the true intention-to-treat population as they excluded patients with missing data at baseline. In addition, there were differences between the groups in the frequency of missing outcome data at week 16 and it is unclear if the missing at random assumption is valid. Similar issues were noted with

regards to missing data for the change in DLQI scores. Because of the missing data imputation methods and the extent and differential rate of missing data, there is potential for bias in the change in POEM and CDLQI scores. The change in POEM and CDLQI scores were not part of the graphical testing strategy used to control the family-wise type I error rate; therefore, these results should be interpreted as supportive evidence only.

The 52-week data from the ADvocate trials were limited by the enriched population, carry-over effects of lebrikizumab in the placebo group, and the small sample size. At week 16 of the ADvocate studies, patients treated with lebrikizumab who met the response criteria were re-randomized to 3 groups. This represents an enriched population, and thus the 1-year treatment effects of lebrikizumab may overestimate the effects than would be observed in an unselected population. Given the long half-life of lebrikizumab (24.5 days), it is reasonable to assume there are substantial carry-over effects for patients switched from lebrikizumab to placebo, which may impact efficacy assessments as well as the frequency of harms.

The clinical expert we consulted for this review did not identify any major limits to the generalizability of the findings of the trials and baseline characteristics of patients enrolled were generally consistent with those who may receive systemic treatments for AD in clinical practice. However, the expert noted that the studies excluded some patients with comorbidities who may receive lebrikizumab for AD. Because of these exclusions, the safety and efficacy of lebrikizumab is uncertain for patients with chronic conditions that may require treatment with oral corticosteroids, those with acute or chronic infections, severe mental or physical illnesses, or a history of immunosuppression. Given that 11% to 22% of patients enrolled were adolescents, the results are mainly reflective of adult patients. The dosing of lebrikizumab during the induction period of the trials was consistent with the Health Canada recommended dose; however, the clinical expert anticipates that most patients using lebrikizumab will also use TCS as needed. Concurrent use of TCS was prohibited in the ADvocate studies, and thus the magnitude of effects observed in the ADhere study may be more consistent with what may occur in clinical practice. Also, the generalizability of the 52-week efficacy and safety data may be limited given the enriched population and the carry-over effects of lebrikizumab in patients switched to placebo. The results at 52 weeks are reflective of the effects of lebrikizumab maintenance therapy compared with lebrikizumab withdrawal among patients who initially tolerate and respond to treatment during the 16-week induction period.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CDA-AMC expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE working group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based

on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment for the proportion of patients with an IGA 0 or 1 response, EASI 75 response, or at least a 4-point improvement in Pruritus NRS were based on thresholds informed by the clinical expert we consulted for this review. The certainty of evidence assessments for the change in POEM, DLQI, and CDLQI were based on thresholds identified in the literature; and the certainty assessments for SAEs and conjunctivitis were based on the presence or absence of any (non-null) effect.

For the GRADE assessments, findings from the ADvocate 1, ADvocate2, and ADhere studies were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures.

The selection of outcomes for GRADE assessment was based on the sponsor's summary of clinical evidence, consultation with the clinical expert, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline
- proportion of patients with an EASI 75 response
- proportion of patients who reported at least a 4-point reduction in the Pruritus NRS score
- change from baseline in the POEM score
- change from baseline in the DLQI and CDLQI total score
- SAEs, conjunctivitis AEs.

Table 1: Summary of Findings for Lebrikizumab Versus Placebo for Patients With Moderate to Severe Atopic Dermatitis

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
IGA response				
Proportion of patients with IGA score of 0 or 1 and ≥ 2-point improvement from baseline (95% CI)[a] Follow-up: 16 weeks	1,062 (3 RCTs)	ADvocate 1 • LEB: 431 per 1,000 • PBO: 127 per 1,000 • aRD (95% CI): 297 more per 1,000 (216 to 378 more per 1,000) ADvocate 2 • LEB: 332 per 1,000 • PBO: 108 per 1,000 • aRD (95% CI): 219 more per 1,000 (142 to 296 more per 1,000) ADhere • LEB + TCS: 412 per 1,000 • PBO + TCS: 221 per 1,000 • aRD (95% CI): 183 more per 1,000 (51 to 315 more per 1,000)	High	Lebrikizumab results in an increase in the proportion of patients with an IGA response when compared with placebo, with or without concomitant TCS.
EASI 75 response				
Proportion of patients with EASI 75 response (95% CI)[b] Follow-up: 16 weeks	1,062 (3 RCTs)	ADvocate 1 • LEB: 588 per 1,000 • PBO: 162 per 1,000 • aRD (95% CI): 420 more per 1,000 (333 to 506 more per 1,000) ADvocate 2 • LEB: 521 per 1,000 • PBO: 181 per 1,000 • aRD (95% CI): 333 more per 1,000 (244 to 422 more per 1,000) ADhere	High	Lebrikizumab results in an increase in the proportion of patients with an EASI 75 response when compared with placebo, with or without concomitant TCS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• LEB + TCS: 695 per 1,000 • PBO +TCS: 422 per 1,000 • aRD (95% CI): 264 more per 1,000 (121 to 408 more per 1,000)		
Proportion of patients (95% CI) who maintained an EASI 75 response among patients who exhibited an EASI 75 response at week 16 with lebrikizumab 250 mg every 2 weeks induction therapy[b] Follow-up: 52 weeks	172 (2 RCTs)	ADvocate 1 • LEB every 4 weeks: 792 per 1,000 • PBO (LEB withdrawal): 613 per 1,000 • aRD (95% CI): [redacted] ADvocate 2 • LEB every 4 weeks: 847 per 1,000 • PBO (LEB withdrawal): 720 per 1,000 • aRD (95% CI): [redacted]	Moderate[c]	Among patients with an EASI 75 response to lebrikizumab induction therapy, lebrikizumab every 4 weeks maintenance therapy likely results in an increase in the proportion of patients who maintain an EASI 75 response when compared with patients switched to placebo.
Pruritus NRS ≥ 4-point reduction				
Proportion of patients with Pruritus NRS ≥ 4-point reduction from baseline (95% CI)[d] Follow-up: 16 weeks	964 (3 RCTs)	ADvocate 1 • LEB: 459 per 1,000 • PBO: 130 per 1,000 • aRD (95% CI): 329 more per 1,000 (246 to 413 more per 1,000) ADvocate 2 • LEB: 398 per 1,000 • PBO: 115 per 1,000 • aRD (95% CI): 283 more per 1,000 (200 to 365 more per 1,000) ADhere • LEB + TCS: 506 per 1,000 • PBO +TCS: 319 per 1,000	High	Lebrikizumab results in an increase in the proportion of patients with at least a 4-point reduction in the Pruritus NRS score when compared with placebo, with or without concomitant TCS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• aRD (95% CI): 192 more per 1,000 (43 to 341 more per 1,000)		
Change in POEM total score				
POEM total score (0 [best] to 28 [worst]) LS mean change from baseline (95% CI)[e] Follow-up: 16 weeks	996 (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • Difference| [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADhere • LEB + TCS: [redacted] • PBO + TCS: [redacted] • Difference: [redacted]	Low[f]	Lebrikizumab may result in a reduction in the POEM score compared with placebo, with or without concomitant TCS.
Change in DLQI score				
DLQI score (0 [best] to 30 [worst]) LS mean change from baseline (95% CI)[g] Follow-up: 16 weeks	856 (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADhere • LEB + TCS: [redacted] • PBO + TCS: [redacted] • Difference: [redacted]	Low[h]	Lebrikizumab may result in a reduction in the DLQI score compared with placebo, with or without concomitant TCS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Change in CDLQI score				
CDLQI score (0 [best] to 30 [worst]) LS mean change from baseline (95% CI) [g] Follow-up: 16 weeks	[redacted] (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • Difference: [redacted] ADhere • LEB + TCS: [redacted] • PBO + TCS: [redacted] • Difference: [redacted]	Very Low[i]	The evidence is very uncertain about the effect of lebrikizumab on the change in CDLQI when compared with placebo.
SAEs				
Proportion of patients with SAE (95% CI) Follow-up: 16 weeks	1,060 (3 RCTs)	ADvocate 1 • LEB: 21 per 1,000 • PBO: 7 per 1,000 • RD (95% CI): [redacted] ADvocate 2 • LEB: 7 per 1,000 • PBO: 28 per 1,000 • RD (95% CI): [redacted] ADhere • LEB + TCS: 14 per 1,000 • PBO + TCS: 15 per 1,000	Very low[i]	The evidence is very uncertain about the effect of lebrikizumab on the proportion of patients with 1 or more SAEs when compared with placebo, with or without concomitant TCS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• RD (95% CI): [redacted]		
Proportion of patients with SAE (95% CI) among patients who met treatment response criteria at week 16 with lebrikizumab 250 mg every 2 weeks induction therapy Follow-up: 52 weeks	178 (2 RCTs)	ADvocate 1 • LEB every 4 weeks: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted] ADvocate 2 • LEB every 4 weeks: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted]	Very low[k]	Among patients who achieve a response to lebrikizumab induction therapy, the evidence is very uncertain about the effect of lebrikizumab maintenance therapy on the proportion of patients with 1 or more SAEs when compared with placebo (i.e., lebrikizumab withdrawal).
Conjunctivitis				
Proportion of patients with conjunctivitis AEs (95% CI) Follow-up: 16 weeks	1,060 (3 RCTs)	ADvocate 1 • LEB: [redacted] • PBO: [redacted] • RD (95% CI): [redacted] ADvocate 2 • LEB: [redacted] • PBO: [redacted] • RD (95% CI): [redacted] ADhere • LEB +TCS: [redacted] • PBO +TCS: [redacted]	Moderate[l]	Lebrikizumab may result in an increase in the proportion of patients with 1 or more conjunctivitis events when compared with placebo, with or without concomitant TCS. The clinical importance of the increase is uncertain.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• RD (95% CI): [redacted]		
Proportion of patients with conjunctivitis AEs (95% CI) among patients who met treatment response criteria at week 16 with lebrikizumab 250 mg every 2 weeks induction therapy Follow-up: 52 weeks	178 (2 RCTs)	ADvocate 1 • LEB every 4 weeks: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted] ADvocate 2 • LEB every 4 weeks: [redacted] • PBO (LEB withdrawal): [redacted] • RD (95% CI): [redacted]	Very low[m]	Among patients who achieve a response to lebrikizumab induction therapy, the evidence is very uncertain about the effect of lebrikizumab maintenance therapy on the proportion of patients with 1 or more conjunctivitis events when compared with placebo (lebrikizumab withdrawal).

AD = atopic dermatitis; AE = adverse event; aRD = adjusted risk difference; CDLQI = Children's Dermatology Life Quality Index; CI = confidence interval; DLQI = Dermatology Life Quality Index; EASI 75 = 75% reduction in Eczema Area and Severity Index; HRQoL = health-related quality of life; IGA = Investigator's Global Assessment for AD; LEB = lebrikizumab; LS = least squares; MID = minimal important difference; NR = not reported; NRS = numeric rating scale; PBO = placebo; POEM = Patient Oriented Eczema Measure; RCT = randomized controlled trial; RD = risk difference; SAE = serious adverse event; TCS = topical corticosteroids.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]The IGA measures the investigator's global assessment of the patient's overall severity of AD at that visit, based on a static, numeric 5-point scale ranging from 0 (clear) to 4 (severe). Based on clinical expert input, the threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with an IGA score of 0 or 1 and at least a 2-point reduction from baseline.

[b]The EASI is a composite index, based on the physician's assessment of 4 clinical signs of the disease (erythema, infiltration and/or papulation, excoriation, and lichenification) and the extent of body surface area involved at that visit. It is scored from 0 to 72 with higher scores indicating greater disease severity and/or extent of disease. Based on clinical expert input, the threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with at least a 75% reduction in the EASI score from baseline (EASI 75).

[c]EASI 75 response at week 52: rated down 1 level for serious imprecision. The CI for differences between groups included the potential for little to no difference (based on the threshold for a clinically important between-group difference of 100 per 1,000 for the proportion of patients who maintained at least an EASI 75 response at week 52).

[d]The Pruritus NRS is a patient-reported, single-item, daily, 11-point scale. The scale is used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Based on clinical expert input, the threshold for a clinically important between-group difference was 100 per 1,000 for the proportion of patients with at least a 4-point reduction from baseline. This outcome was analyzed for the subgroup of patients who had a Pruritus NRS score of 4 or higher at baseline.

[e]The POEM is a 7-item, patient-reported questionnaire used to assess the frequency of disease symptoms in adults and children over the last week. The patients respond to 7 questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping. The total score ranges from 0 to 28, with a high score indicative of worse disease severity. The MID of 3.4 points was selected as the threshold for a clinically important between-group difference based on the literature and clinical expert input.

[f]Change in POEM score at week 16: rated down 2 levels for very serious study limitations. The extent of missing data were large and the method for accounting for missing data were potentially biased. There was no control of type I error rate for this end point and thus should be interpreted as supportive evidence only.

[g]The DLQI (16 years and older) and CDLQI (patients younger than 16) are patient-reported, 10-item, HRQoL questionnaires that cover 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) over the last week. The total score ranges from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life). The MID of 4 points for the DLQI and 6 points for the CDLQI were selected as the threshold for a clinically important between-group difference based on the literature and clinical expert input.

[h]Change in DLQI at week 16: rated down 1 level for serious imprecision (the CI for differences between groups included the potential for little to no difference based on a MID of 4 points). Rated down 1 level for serious study limitations (due to missing data). Also considered was the possibility of inconsistency, given that the point estimate for 1 of the 3 trials falls below the MID, although a decision was made not to rate down for inconsistency.

[i]Change in CDLQI at week 16: rated down 1 level for serious imprecision (the CI for differences between groups included the potential for little to no difference based on a MID of 6 points). Rated down 2 levels for very serious study limitations. The extent of missing data were large and the method for accounting for missing data were potentially biased. There was no control of type I error rate for this end point and thus should be interpreted as supportive evidence only.

[j]SAE at week 16: rated down 2 for very serious indirectness (follow-up duration limited to 16 weeks which may be insufficient to detect uncommon SAEs or those that may develop over time; the clinical expert noted that worsening AD may be reported as an SAE, whereas this more accurately reflects lack of efficacy). Rated down 1 for serious imprecision (CI for difference between groups includes the possibility of no difference, benefit (fewer harms), and increased harms.

[k]SAE at week 52: rated down 2 for very serious indirectness (AE were reported for an enriched population who had received lebrikizumab 250 mg every 2 weeks induction therapy and met the treatment response criteria at week 16); the AEs reported in the placebo group may be confounded due to the carry-over effects of lebrikizumab before the switch to placebo; and follow-up duration and sample size may be insufficient to detect uncommon SAEs or those that may develop over time). Rated down 1 for serious imprecision (CI for difference between groups includes the possibility of no difference, benefit [fewer harms], and increased harms).

[l]Conjunctivitis at week 16: rated down 1 for serious indirectness (the clinical expert stated that dermatologists may not have sufficient expertise to distinguish between eye disorders with a similar presentation, thus the reported conjunctivitis-related AEs may be flawed).

[m]Conjunctivitis at week 52: rated down 2 for very serious indirectness (the clinical expert stated that dermatologists may not have sufficient expertise to distinguish between eye disorders with a similar presentation, thus the reported conjunctivitis-related AEs may be flawed; AE were reported for an enriched population who had received lebrikizumab 250 mg every 2 weeks induction therapy and met the treatment response criteria at week 16; and the AEs reported in the placebo group may be confounded due to the carry-over effects of lebrikizumab before the switch to placebo). Rated down 2 for very serious imprecision (CI for difference between groups includes the possibility of no difference, benefit [fewer harms], and increased harms).

Source: Clinical Study Reports for ADvocate, CSR for ADvocate, CSR for ADhere. Additional information supplied by sponsor.

Long-Term Extension Study

Description of Study

One long-term extension study was summarized to provide evidence regarding the long-term (100-week) efficacy and safety of lebrikizumab among patients with moderate to severe AD who were enrolled in the ADvocate 1, ADvocate 2, ADhere, ADore, and ADopt-VA studies (parent trials). This study was conducted at 199 centres that enrolled 999 patients in Australia, Bulgaria, Canada, Estonia, France, Germany, Latvia, Lithuania, Mexico, Poland, Singapore, South Korea, Spain, Taiwan, Ukraine, and the US. This report presents interim safety data from ADjoin and limited efficacy data at week 40 for a subset of patients who completed the 16-week ADhere study (i.e., up to 56 weeks of lebrikizumab treatment). [redacted]

Efficacy Results

Efficacy outcomes were assessed up to [redacted] (week 16 to 104). Evaluation of efficacy in the interim report was conducted on a subset of the main cohort, which included [redacted] who were responders to lebrikizumab + TCS in the ADhere study.

At week 40, the proportion of patients with an IGA score of 0 or 1 was [redacted] in the lebrikizumab 250 mg every 4 weeks group and [redacted] in the lebrikizumab 250 mg every 2 weeks group.

At week 40, the mean (standard error [SE]) percent change from baseline in EASI score in the lebrikizumab 250 mg every 4 weeks group and lebrikizumab 250 mg every 2 weeks group were [redacted] respectively. The proportion of patients with an EASI 75 response at week 40 in the lebrikizumab 250 mg every 4 weeks group and lebrikizumab 250 mg every 2 weeks group was [redacted] respectively.

Among patients who had a Pruritus NRS score of 4 or more points at baseline, the proportion of patients who reported an improvement of at least 4 points at week 40 in the lebrikizumab 250 mg every 4 weeks group and the lebrikizumab 250 mg every 2 weeks group was [redacted] and [redacted] respectively.

The mean (SE) percent change in POEM score from baseline to week 40 in the lebrikizumab 250 mg every 4 weeks group and the lebrikizumab 250 mg every 2 weeks group was [redacted] respectively.

Harms Results

Overall [redacted] ([redacted]) discontinued study treatment due to AEs. Discontinuation due to an AE was noted in [redacted]

One death due to natural causes occurred in the lebrikizumab 250 mg every 2 weeks group.

The most frequently reported TEAEs were in the infections and infestations system organ class, with COVID-2019 [redacted] in the lebrikizumab 250 mg every 4 weeks group and [redacted] in the lebrikizumab 250 mg every 2 weeks group) and nasopharyngitis [redacted] in the lebrikizumab 250 mg every 4 weeks group and

[redacted] in the lebrikizumab 250 mg every 2 weeks group) being the most common TEAE. A similar proportion of patients in the lebrikizumab 250 mg every 2 weeks group ([redacted] and the lebrikizumab 250 mg every 4 weeks group ([redacted] reported an AE of AD exacerbation. The proportion of patients experiencing 1 or more AEs in the conjunctivitis cluster (narrow terms) were similar in both the lebrikizumab 250 mg every 4 weeks group ([redacted] and the lebrikizumab 250 mg every 2 weeks group ([redacted]).

Critical Appraisal

Internal Validity

There is no randomized comparison with another treatment or a placebo, which limits the ability to draw inferences on the effects of lebrikizumab in the study population. The patients were aware they were receiving active treatment, thus their expectations of treatment may have influenced reporting of subjective patient-reported outcomes, such as the POEM, and subjective AEs, or investigator-reported IGA and EASI, which are measures that require subjective judgments. Discontinuation rates are [redacted] in the lebrikizumab every 4 weeks group and [redacted] in the lebrikizumab every 2 weeks group. Among the participants from ADhere (efficacy assessment) the rates of discontinuation are [redacted] in the lebrikizumab every 4 weeks group and [redacted] in the lebrikizumab every 2 weeks group. Thus, there is potential bias due to missing data. All analyses were conducted descriptively without statistical comparisons between the cohorts or adjustment for multiple comparisons.

External Validity

Only the responders of the ADhere study were included in the efficacy assessment. Patients were excluded if during their participation in the parent trial, they developed an SAE deemed related to lebrikizumab; developed an AE that was deemed related to lebrikizumab and led to study treatment discontinuation; or had conditions in the parent trial which led to investigator or sponsor-initiated withdrawal from the study. This is a select population such that the results apply only to patients who initially tolerate and respond to lebrikizumab. The proportion of patients with concomitant TCS use and systemic rescue therapy were higher in the lebrikizumab every 4 weeks group compared with the lebrikizumab every 2 weeks group. The effect of these differences between groups on the efficacy results remains unclear.

Indirect Comparisons

Description of Studies

The sponsor-submitted indirect treatment comparison first conducted a systematic literature review (SLR) to identify evidence for inclusion in a NMA. The relative efficacy of lebrikizumab (with or without TCS) from the ADvocate 1, ADvocate 2, J2T-DM-KGAF, ADhere, ADhere-J, ADopt-VA, and ADvantage trials was indirectly compared with alternative treatments for AD using Bayesian NMA. Comparators of interest for the sponsor-submitted NMA included abrocitinib, dupilumab, and upadacitinib. All networks in the sponsor-submitted NMA also included baricitinib and tralokinumab as comparators; however, baricitinib does not have Health Canada approval for the treatment of AD, and tralokinumab is not currently reimbursed by public drug plans in Canada. As such, results comparing lebrikizumab with baricitinib or tralokinumab were not included in

this report. Outcomes of interest included EASI response, IGA 0 or 1 response, and Pruritus NRS response (≥4-point reduction) at week 16, and Pruritus NRS response at week 4.

Efficacy Results

The SLR identified a total of [redacted] citations. A total of [redacted] unique studies identified by the SLR were assessed for eligibility to be included in NMAs. Three studies of lebrikizumab were not identified as part of the SLR were also assessed for inclusion. In total, [redacted] studies were eligible for inclusion in NMAs: [redacted] monotherapy studies and [redacted] combination therapy studies.

Networks were generated for all eligible interventions as monotherapy and combination therapy for the outcomes of EASI response, IGA 0 or 1 response, and Pruritus NRS response at time points of interest. In all cases, the baseline risk-adjusted, random-effects model was selected as the favoured model based on the deviance information criterion and residual deviance.

Primary Analysis

EASI Response (Week 16)

In the primary analysis for EASI response at week 16 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks and abrocitinib 100 mg daily. Abrocitinib 200 mg daily (probit difference, [redacted] and upadacitinib 15 mg daily (probit difference, [redacted] and 30 mg daily (probit difference, [redacted] were favoured over lebrikizumab.

[redacted]

IGA 0 or 1 Response (Week 16)

In the primary analysis for IGA 0 or 1 response at week 16 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks, abrocitinib 100 mg daily or 200 mg daily, or upadacitinib 15 mg daily. Upadacitinib 30 mg daily was favoured over lebrikizumab (odds ratio, [redacted]).

[redacted]

Pruritus NRS response (≥4-point reduction) (Week 16)

In the primary analysis for Pruritus NRS response at week 16 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks,

abrocitinib 100 mg daily or 200 mg daily, or upadacitinib 15 mg daily. Upadacitinib 30 mg daily was favoured over lebrikizumab [redacted]

[redacted]

Pruritus NRS response (≥4-point reduction) (Week 4)

In the primary analysis for Pruritus NRS response at week 4 in the monotherapy network, there was insufficient evidence to show a difference between lebrikizumab and dupilumab 300 mg every 2 weeks, and abrocitinib 100 mg daily. Abrocitinib 200 mg daily [redacted] upadacitinib 15 mg daily [redacted] and upadacitinib 30 mg daily [redacted] were favoured over lebrikizumab.

[redacted].

Secondary Analysis

Phase III Studies Only – Monotherapy Networks

[redacted]

Meta-Regression Analysis

[redacted]

[redacted]

Harms Results

Harms were not evaluated in the sponsor-submitted NMA.

Critical Appraisal

The sponsor-submitted NMA was informed by an SLR that included comprehensive searches (updated to April 2023) of multiple databases, conference proceedings, clinical trial databases, and Health Technology Assessment websites. Additionally, the risk of bias assessment conducted by the sponsor was not indicative of serious risk of bias in the included studies. However, it should be noted that methods for risk of bias appraisal were incompletely reported (i.e., it is not clear how many reviewers were involved and whether they worked independently). As such, the risk for bias and error in the appraisals could not be ascertained. Further, the risk of bias appraisal was undertaken at the study level, rather than at the level of the reported effects. Appraisals undertaken at the study level do not account for differences in the risk of bias that can

exist across reported results (within and across outcomes) within trials. Additionally, there is a risk of bias due to missing results in the networks, because trials of relevant comparator treatments without a placebo control group were excluded [redacted]

A feasibility assessment was conducted, evaluating potential heterogeneity in study design; patient baseline characteristics; interventions; and outcomes, time points, and placebo response. The sponsor noted that some heterogeneity was observed across studies in both the monotherapy and combination therapy networks. Studies for abrocitinib used a 12-week time of assessment as opposed to the 16-weeks for other trials. The effect of the difference in time of assessment was not evaluated in the NMA and remains unknown. There were also differences in age across studies, with the mean age [redacted]. There was also heterogeneity in the proportion of patients [redacted]. Adjustment for baseline EASI and IGA did not improve model fit and conclusions were considered to be comparable with the primary analysis. Other differences were noted by the CDA-AMC review team in weight and ethnicity across studies, although the impact of these differences remains unclear. The sponsor also noted heterogeneity in other features such as race and time since AD diagnosis, although it is not clear whether these are important treatment effect modifiers. No formal search for potential treatment effect modifiers was conducted; instead, the sponsor relied on internal clinical opinion, only including AD severity measured by EASI and IGA, and weight, which the clinical expert we consulted agreed with. There was a risk of bias in the selection of treatment effect modifiers and it was not clear whether the list was comprehensive. Additionally, the sponsor also highlighted differences in the [redacted] Differences in TCS treatment may bias reported response rates and limit the reliability of comparing responses on the active interventions; however, baseline risk-adjusted analysis models were included to mitigate the potential for bias. No scenario analyses were conducted to compare the difference between adjusted and unadjusted results; thus, it is unclear what effect not adjusting for baseline risk had on the results. Overall, the notable heterogeneity in the baseline characteristics raises concern about the plausibility of the transitivity assumption, whereby, the resulting effect estimates may not be valid.

Baricitinib and tralokinumab were included as comparators in the NMAs; however, the use of baricitinib for AD is limited in Canada given the lack of a specific indication for AD, and the availability of more efficacious and tolerable JAK inhibitors (i.e., abrocitinib, upadacitinib). Tralokinumab, although indicated for AD, received a do not reimburse recommendation from CDA-AMC and is not reimbursed in Canada. As such, comparative results versus these treatments were not included in this report.

Outcomes included in the NMA were relevant to the treatment of AD in Canada; however, the clinical expert highlighted that EASI scores are generally not calculated in routine clinical practice. Additionally, outcomes of importance to this review, including harms and HRQoL, were not included in the NMA.

In all random-effects analyses, results were associated with wide 95% credible intervals (CrIs), with most estimates crossing the 0 or 1 threshold, suggesting notable imprecision in the results, and precluding conclusions on which treatment is favoured. For some comparisons in the monotherapy [redacted] there was generally insufficient evidence to demonstrate a difference between treatments for most outcomes. Further, abrocitinib 200 mg daily, upadacitinib 15 mg daily, and upadacitinib 30 mg daily (± TCS) were favoured over lebrikizumab (± TCS) for most outcomes but were also associated with wide 95% CrIs. Overall, this imprecision limits the interpretability of the treatment effect of lebrikizumab relevant to other comparators. Furthermore, this NMA was primarily restricted to adults, thus, it is unclear whether the results may be generalized to adolescents with AD.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The sponsor submitted 4 studies that provided additional data to cover gaps in the systematic review evidence:

- ADvantage, a phase III, 52-week (16-week double-blind induction period followed by a 36-week open-label maintenance period), RCT to address uncertainty regarding the efficacy and safety of lebrikizumab specifically in patients whose AD is not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable (N = 331).
- ADopt-VA, a 16-week phase III, randomized, double-blind, placebo-controlled, parallel-group trial to address the uncertainty regarding the impact of lebrikizumab on vaccine immune responses. This trial also provides additional evidence of the efficacy and safety of lebrikizumab (N = 247).
- ADhere-J, a 68-week (16-week induction period plus a 52-week maintenance period), phase III, randomized, double-blind, placebo-controlled, parallel-group study to address uncertainty regarding the efficacy and safety of lebrikizumab specifically in patients living in Japan (N = 268).
- ADore, a 52-week, open-label, single arm study to address the uncertainty regarding the efficacy and safety of lebrikizumab specifically among adolescent patients (N = 206 received treatment and 172 completed the treatment period).

ADvantage Trial

Results

A summary of efficacy results for patients randomized to lebrikizumab + TCS group relative to placebo + TCS at week 16 is provided below:

- EASI 75 was 68.4% versus 40.8%; P < 0.0001, [redacted]

- IGA 0 or 1 and ≥ 2-point improvement, was 42.0% versus 24.5%, [redacted]
- Pruritus NRS ≥ 4-point improvement, was 49.9% versus 29.7%, [redacted]
- POEM, mean (SD), change from baseline, [redacted]
- DLQI, mean (SD), change from baseline [redacted]
- CDLQI, mean (SD), change from baseline [redacted]

In terms of safety, a summary of harms results for patients randomized to lebrikizumab + TCS group relative to placebo + TCS group at week 16 is provided below:

- proportion of patients with at least 1 AE were 61.8% versus 53.2%
- proportion of patients with at least 1 SAE were [redacted]
- proportion of patients with at least 1 AE leading to study drug discontinuation were 0.9% versus 1.8%
- proportion of patients with conjunctivitis AE were [redacted]

Up to week 52, harm results for patients randomized to the lebrikizumab + TCS group were reported as [redacted] for patients with at least 1 AE, [redacted] for patients with at least 1 SAE, and [redacted] for patients with at least 1 AE leading to study drug discontinuation.

Critical Appraisal

Since few adolescents were enrolled in this study, generalizability to this age group is limited. No control for multiplicity was included for analyses of the secondary efficacy end points, therefore, the study is at risk of type I error (false-positive results) for all end points except for EASI 75. Dosage for maintenance therapy was 250 mg every 2 weeks which is not consistent with Health Canada product monograph which recommends 250 mg every 4 weeks after 16 weeks. In the lebrikizumab group versus placebo group, [redacted] discontinued the study which might increase risk of bias due to missing outcomes data.

ADopt-VA Trial

Results

The efficacy results reported in the ADopt-VA trial that correspond to patients randomized to lebrikizumab compared with placebo at week 16 are available below:

- EASI 75 was 58.0% versus 32.7%; P < 0.001 [redacted]
- IGA 0 or 1 and ≥ 2-point improvement, 40.6% versus 18.9%, [redacted]
- Pruritus NRS ≥ 4-point improvement was [redacted]

- POEM LS mean change from baseline (SE) was −9.4 (0.8) versus −6.6 (0.8), [redacted]

In terms of safety, a summary of the harms for patients randomized to lebrikizumab compared to placebo at week 16 is available below:

- proportion of patients with at least 1 AE were 38.4% versus 34.4%
- proportion of patients with at least 1 SAE were 0.8% versus 0.8%
- proportion of patients with at least 1 AE leading to study drug discontinuation were 2.4% versus 4.1%
- proportion of patients with conjunctivitis AE were [redacted].

Critical Appraisal

There is an increased risk of type I error (false-positive results) for all end points. The results of this study may not be generalizable to adolescent patients. The use of TCS was [redacted] in lebrikizumab group versus [redacted] in placebo group, and its effect on the results is not clear. The discontinuation rate was [redacted] in the placebo group versus [redacted] in the lebrikizumab group which might increase the risk of bias due to missing outcomes data.

ADhere-J Study

A total of [redacted] in the ADhere-J study completed the induction period, including patients receiving placebo, patients in the lebrikizumab every 4 weeks treatment group, and patients in the lebrikizumab every 2 weeks treatment group. The responders of the lebrikizumab every 4 weeks treatment group continued treatment with 250 mg lebrikizumab every 4 weeks. The responders of the lebrikizumab every 2 weeks treatment group were randomly allocated to receive 250 mg lebrikizumab every 2 weeks or 250 mg lebrikizumab every 4 weeks. The nonresponders or those who used rescue therapy in the induction period moved to the escape arm and received 250 mg lebrikizumab every 2 weeks. In the placebo group, the responders continued to receive placebo, while those who were nonresponders or those who used rescue therapy in the induction period moved to the escape arm and received a loading dose of 500 mg lebrikizumab at week 16 and week 18.

Results

A summary of the efficacy results for the induction period corresponding to patients randomized to placebo + TCS relative to lebrikizumab every 2 weeks + TCS at week 16 is available below:

- EASI 75 was 13.4% versus 51.2%, P < 0.001
- IGA 0 or 1 and ≥ 2-point improvement was 6.1% versus 33.4%, P < 0.001
- Pruritis NRS ≥ 4-point improvement was 3.3% versus 32.7%, P < 0.001

[redacted]

[redacted]

Harm results for the induction period in placebo versus lebrikizumab every 2 weeks + TCS:

- proportion of patients with at least 1 AE was 63.4 versus 75.6%
- proportion of patients with at least 1 SAEs was 2.4% versus 0.8%

[redacted]

Critical Appraisal

This study is limited to patients in Japan only, and generalizability to patients in Canada is uncertain. Not all patients in the induction phase received the Health Canada recommended dose. High potency TCS use was [redacted] in the placebo group, [redacted] in the lebrikizumab every 4 weeks group, and [redacted] in the lebrikizumab every 2 weeks group; the effect of this difference on the results is unclear. DLQI, CDLQI, and POEM were not included in multiplicity testing and are at risk of type I error. For the maintenance period, discontinuation was [redacted] in the placebo group versus [redacted] in the lebrikizumab every 2 weeks responder then every 4 weeks + TCS group. The impact of missing data on the findings is unclear.

Adore Study

Results

The efficacy results (based on Markov chain Monte Carlo multiple imputation) reported in the ADore study at week 52 have been summarized:

- EASI 75 was 81.9%
- IGA 0 or 1 and ≥ 2-point improvement was 62.6%
- DLQI, mean (SE), change from baseline was −8.9 (0.9), N = 35
- CDLQI, mean (SE), change from baseline was −6.5 (0.5), N = 168.

The harms results reported in the ADore study at week 52 have been summarized:

- proportion of patients with at least 1 AE was 65%
- proportion of patients with at least 1 SAEs was 2.4%
- proportion of patients with at least 1 AE leading to study treatment discontinuation was 2.4%; patients with conjunctivitis AE were 6.8%

- 1 death (0.5%), which was reported as due to cardiac arrest.

Critical Appraisal

There is risk of bias in the measurement of the outcomes due to the open-label design and subjectivity of the outcomes. There is no comparator, which limits causal inferences. Maintenance therapy dose was not consistent with Health Canada product monograph. There is a [redacted] which might contribute to risk of bias due to missing outcome data.

Key Take-Aways for Studies Addressing Gaps in the Evidence

In patients with moderate to severe AD who received induction therapy with lebrikizumab 250 mg every 2 weeks (with or without TCS), the results of the supplementary trials (ADvantage, ADhere-J, and ADopt-VA) were generally consistent with the findings of the pivotal trials. The efficacy findings favoured lebrikizumab when compared with placebo for EASI 75, IGA 0 or 1, and Pruritus NRS response (≥4-point reduction) at 16 weeks in the RCTs addressing gaps in the evidence (ADvantage, ADhere-J, and ADopt-VA).

In terms of harms results at week 16, in the ADvantage study a higher proportion of patients in the lebrikizumab group compared with the placebo group reported TEAEs and serious TEAEs. In ADopt-VA, the proportion of patients with TEAEs and the proportion of patients with at least 1 AE leading to study drug discontinuation were higher in lebrikizumab group compared with placebo group. In ADhere-J, the proportion of patients who reported TEAEs, and patients with 1 or more AEs leading to study drug discontinuation were higher in the every 2 weeks group versus the placebo group. In the open-label ADore study, 2.4% of patients reported at least 1 AE leading to permanent discontinuation from the study treatment including 1 death.

Some of the limitations in the ADvantage study included uncertain generalizability to adolescent patients, dosage inconsistency with the Health Canada recommended dose, lack of control for multiplicity for secondary efficacy end points (thus increased risk of type I errors), and risk of bias due to missing outcome data. In ADopt-VA, there is increased risk of type I error, uncertain generalizability to adolescent patients, between-group differences in the use of TCS, and risk of bias due to missing outcome data. In ADhere-J, there was uncertain generalizability to patients in Canada; the dosage was inconsistent with the Health Canada recommended dose for the induction period; there were between-group differences in the use of high potency TCS; there was an increased risk of type I error for DLQI, CDLQI, and POEM; and there were between-group differences in discontinuations during the maintenance period.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with moderate to severe AD
Treatment	Lebrikizumab + TCS
Dose regimen	The recommended dosage is an initial dose of 500 mg injected subcutaneously at week 0 and week 2, followed by 250 mg every 2 weeks until week 16, at which time clinical response is assessed. Upon clinical response, a maintenance dose of 250 mg every 4 weeks may be used.
Submitted price	Lebrikizumab, 250 mg/2 mL single-dose prefilled pen: $1,876.71 Lebrikizumab, 250 mg/2 mL single-dose prefilled syringe with needle shield: $1,876.71
Submitted treatment cost	First year: $35,657 Subsequent years: $24,397
Comparators	Abrocitinib 100 mg + TCS Abrocitinib 200 mg + TCS Dupilumab + TCS Upadacitinib 15 mg + TCS Upadacitinib 30 mg + TCS BSC, assumed to be equivalent to placebo
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (70 years)
Key data source	Clinical efficacy data were informed by sponsor-submitted NMAs
Key limitations	• The comparative efficacy of lebrikizumab + TCS relative to other biologics and JAK inhibitors used to treat AD in Canada is uncertain because of a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor suggests that, when used in combination with TCS, there is insufficient evidence to show a difference in the efficacy in terms of EASI response for lebrikizumab compared with dupilumab, abrocitinib 100 mg, and upadacitinib 15 mg. Further, indirect evidence submitted by the sponsor suggests that abrocitinib 200 mg and upadacitinib 30 mg (all used in combination with TCS) may result in a greater proportion of patients achieving EASI response compared with lebrikizumab + TCS. • The comparative safety of lebrikizumab + TCS relative to other biologics and JAK inhibitors used to treat AD in Canada is unknown because of a lack of direct and indirect evidence. • The relevance of BSC as a comparator is uncertain. In the sponsor submission, BSC was not defined. Feedback from the clinical expert we consulted noted that BSC in clinical practice consists of various over-the-counter emollients and anti-inflammatory treatments such as TCS and calcineurin inhibitors. The feedback from the clinical expert we consulted indicated that the proportion of patients who are currently receiving BSC is very low given

Component	Description
	the availability of existing biologics and JAK inhibitors to treat moderate to severe AD in Canada and that the proportion of patients who would switch from BSC to lebrikizumab should it become available would be negligible. • The sponsor inappropriately applied treatment-specific health state utility values in the maintenance health state, which is contradictory to CDA-AMC recommendations.
CDA-AMC reanalysis results	• The CDA-AMC reanalysis: corrected comparator pricing; removed BSC as a comparator from the analysis; and, removed treatment-specific utilities from the maintenance health state. We were unable to address limitations related to the lack of robust comparative clinical efficacy or safety data. • In the CDA-AMC base case, similar to the sponsor's results, lebrikizumab + TCS yielded the fewest total QALYs compared with other biologics and JAK inhibitors and was more costly than abrocitinib 100 mg + TCS, abrocitinib 200 mg + TCS, and upadacitinib 15 mg + TCS. • Based on the comparative clinical information submitted by the sponsor, there is insufficient evidence to show a difference in efficacy for lebrikizumab + TCS compared with dupilumab + TCS, abrocitinib 100 mg + TCS, and upadacitinib 15 mg + TCS; further, lebrikizumab + TCS may result in less favourable clinical outcomes compared with abrocitinib 200 mg + TCS and upadacitinib 30 mg + TCS. As such, there is no clinical evidence to support a price premium for lebrikizumab over existing biologic and JAK inhibitor treatments used to treat AD in Canada.

AD = atopic dermatitis; BSC = best supportive care; EASI = Eczema Area and Severity Index; JAK = Janus kinase; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; TCS = topical corticosteroid.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the proportion of patients eligible to receive therapy is uncertain; the market share estimates in the reference scenario for all comparators are highly uncertain; total treatment costs are uncertain because of the use of blended cost methods when determining annual drug acquisition costs.

CDA-AMC reanalyses included changes to update the proportion of adult and adolescent patients whose AD cannot be adequately controlled with topical prescription therapies and increase the market shares of upadacitinib. In the CDA-AMC base case the budget impact of reimbursing lebrikizumab for the treatment of adult and adolescent patients aged 12 years and older with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable is expected to be $65,018,149 over 3 years (year 1: $12,449,072; year 2: $21,089,890; and year 3: $31,419,187).

The budget impact was sensitive to assumptions regarding the proportion of patients eligible for systemic therapies.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for lebrikizumab for treatment of moderate to severe AD in adults and adolescents aged 12 years and older with a body weight of at least 40

kg, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. In their request, the sponsor identified the following issues:

- The sponsor requested CDEC reconsider the place in therapy of lebrikizumab as first-line advanced treatment for AD. The sponsor stated that the original deliberations cited uncertainty in the place in therapy and focused on a restricted second-line biologic treatment (after unsuccessful treatment or intolerance of dupilumab), which was not consistent with the patients and clinician input that CDA-AMC received, the indication approved by Health Canada, the evidence presented for lebrikizumab, or the current clinical guidelines.
- According to the sponsor, the indirect evidence demonstrates a comparable clinical benefit with lebrikizumab. The sponsor noted that CDA-AMC procedures allow for a reimburse with conditions recommendation in cases with comparable clinical benefit and noted that a do not reimburse recommendation is typically issued for lack of comparable clinical benefit, inferior clinical outcomes, or significant clinical harm. The sponsor requested that the draft recommendation be revised to a reimburse with conditions recommendation to align with the recommendations framework (section 9.3.1 and table 20 of the procedures). Given the evidence presented to CDA-AMC and CDEC, the sponsor proposed that the conditions for lebrikizumab should be consistent with those already recommended for dupilumab.
- The sponsor stated that patients with moderate to severe AD have a broad unmet need. It is the sponsor's position that CDEC discussions emphasized the unmet need in patients who are refractory to or do not tolerate current biologic therapy, which is inconsistent with lebrikizumab's approved label or patient and physician input indicating the need for access to other advanced biologic therapies for moderate to severe AD after unsuccessful topical therapies. The sponsor requested that CDEC reconsider the broad unmet need among patients with moderate to severe AD, which in the draft recommendation was generally restricted to a population with inadequate response or intolerance of dupilumab, or safety concerns with JAK inhibitors. The sponsor stated that as per the CDA-AMC procedures, lebrikizumab should be evaluated based on the approved indication that supports the use of lebrikizumab in both patients who did receive biologic treatment and those who did not(i.e., not restricted to any specific line in advanced therapy).

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in diagnosing and treating patients with AD
- feedback on the draft recommendation from 1 patient group, Eczema Society of Canada
- feedback on the draft recommendation from 7 clinician groups: Atlantic Dermatologists, Dermatology Association of Ontario, Ottawa Division of Dermatology, Fraser Health Dermatology Group, The Lynde Institute for Dermatology and Lynderm Research Inc., Pitanga Medical Group, Saskatchewan Dermatology Association

- feedback on the draft recommendation from the public drug plans that participate in the CDA-AMC review process
- feedback on the draft recommendation from the sponsor.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Initial meeting date: March 28, 2024

Regrets: 1 expert committee member did not attend.

Conflicts of interest: None

Reconsideration meeting date: September 25, 2024

Regrets: 1 expert committee member did not attend.

Conflicts of interest: None

Canada's Drug Agency
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.