

CADTH Reimbursement Recommendation

Bimekizumab (Bimzelx)

Indication: For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

Sponsor: UCB Canada Inc.

Final recommendation: Reimburse with conditions

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What Is the CADTH Reimbursement Recommendation for Bimzelx?

CADTH recommends that Bimzelx should be reimbursed by public drug plans for the treatment of moderate to severe plaque psoriasis if certain conditions are met.

Which Patients Are Eligible for Coverage?

Bimzelx should be covered to treat adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, provided that Bimzelx is covered in a similar way to other interleukin-17 inhibitors currently reimbursed by public drug plans for the treatment of adult patients with moderate to severe plaque psoriasis.

What Are the Conditions for Reimbursement?

Bimzelx should only be reimbursed if prescribed by a dermatologist and the cost of Bimzelx is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 4 clinical trials demonstrated that Bimzelx improves skin clearance compared with treatment with placebo and 3 other biologics: adalimumab, ustekinumab, and secukinumab.
- Bimzelx may meet some of the needs that are important to patients, including clearing plaques.
- There was uncertainty regarding the long-term safety and effectiveness of Bimzelx compared with other biologics for psoriasis because of the short duration of the clinical trials and other limitations in the evidence.
- Based on CADTH's assessment of the health economic evidence, Bimzelx does not represent good value to the health care system at the public list price and requires a price reduction of at least 41%.
- Based on public list prices, the 3-year budget impact of Bimzelx could not be determined due to limitations with the sponsor's budget impact analysis that could not be addressed by CADTH. The sponsor estimated a 3-year budget impact of \$20 million.

Additional Information

What Is Plaque Psoriasis?

Plaque psoriasis is a skin disease that causes red, flaky, crusty patches of skin that may be itchy and painful and can lead to negative impacts on social and work life. Up to 1 million people living in Canada are living with psoriasis, a third of whom have moderate to severe disease.

Unmet Needs in Plaque Psoriasis

Although many treatments are approved in Canada to treat moderate to severe plaque psoriasis, some patients may not respond to these treatments. Other treatment options are needed for these patients.

How Much Does Bimzelx Cost?

Treatment with Bimzelx is expected to cost approximately \$30,631 per patient in year 1 and \$22,921 per patient in subsequent years based on the assumption that 8.5% of patients had a body weight of 120 kg or more and would receive dosing every 4 weeks.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that bimekizumab be reimbursed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 4 randomized, double-blind, placebo- and active comparator–controlled studies (PS0009, PS0008, PS0013, and PS0015) in adult patients with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy, treatment with bimekizumab was associated with statistically significant and clinically meaningful improvements in skin clearance (Psoriasis Area and Severity Index [PASI] score reduced by 90% or 100%) compared with placebo, ustekinumab, adalimumab, and secukinumab at week 16. Given the totality of the evidence, CDEC concluded that bimekizumab met some of the priority needs identified by patients, in particular providing clearance of plaques.

Limitations in the design of the PS0009, PS0008, PS0013, and PS0015 studies, as well as the short duration of the trials in the context of proposed lifelong treatment, led to uncertainty regarding the long-term clinical safety and effectiveness of bimekizumab compared with ustekinumab, adalimumab, and secukinumab. There is no direct evidence related to the comparative efficacy and safety of bimekizumab versus other interleukin (IL)-17 inhibitors (ixekizumab, brodalumab), and the available indirect treatment comparison (ITC) was associated with substantial uncertainty due to heterogeneity of the included trials.

Using the sponsor-submitted price for bimekizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for bimekizumab was \$2,475,397 per quality-adjusted life-year (QALY) compared with brodalumab. At this ICER, bimekizumab is not cost-effective at a \$50,000 per QALY willingness-to-pay threshold for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. A reduction in price of at least 41% is required for bimekizumab to be considered cost-effective at a \$50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Eligibility for reimbursement of bimekizumab should be based on the criteria used by each of the public drug plans for reimbursement of other IL-17 inhibitors for the treatment of adult patients with moderate to severe plaque psoriasis.	Although bimekizumab has demonstrated superiority for some outcomes (e.g., PASI90 or PASI100) compared with secukinumab (another IL-17 inhibitor), it is uncertain if bimekizumab addresses an unmet need that is not filled by 1 of the other IL-17 inhibitors.

Reimbursement condition	Reason
Renewal	
2. Bimekizumab should be renewed in a similar manner to other IL-17 inhibitors currently reimbursed for the treatment of adult patients with moderate to severe plaque psoriasis.	<p>There is no evidence that bimekizumab should be held to a different standard than other IL-17 inhibitors currently reimbursed when considering renewal.</p> <p>The clinical expert noted that the place in therapy for bimekizumab is comparable to other IL-17 inhibitors.</p>
Prescribing	
3. Patients should be under the care of a dermatologist.	Accurate diagnosis and follow-up of patients with moderate to severe plaque psoriasis is important to ensure that bimekizumab is prescribed to the most appropriate patients. In addition, there are several biologic treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by dermatologists, who are familiar with this treatment paradigm.
4. Bimekizumab should not be used in combination with other biologic treatments for moderate to severe plaque psoriasis.	There is no evidence to demonstrate a beneficial effect of bimekizumab when used in combination with other biologics in patients with moderate to severe plaque psoriasis.
Pricing	
5. Price reduction.	<p>The ICER for bimekizumab is \$2,475,397 per QALY when compared with brodalumab. The high ICER is predominantly due to very small incremental QALY differences.</p> <p>A price reduction of 41% would be required for bimekizumab to be able to achieve an ICER of \$50,000 per QALY compared with the publicly listed price of the least costly alternative.</p>
Feasibility of adoption	
6. The feasibility of adoption of bimekizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption given the difference between the sponsor's estimate and CADTH's estimate(s).

ICER = incremental cost-effectiveness ratio; IL = interleukin; PASI = Psoriasis Area and Severity Index; PASI90 = 90% reduction in PASI score; PASI100 = 100% reduction in PASI score; QALY = quality-adjusted life-year.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance From CDEC

Condition # in Table 1	Implementation considerations and guidance
1	It is noted in the product monograph that for patients with a body weight of at least 120 kg who do not achieve a complete skin response, a dose of bimekizumab 320 mg every 4 weeks may be considered at 16 weeks after initiating bimekizumab. CDEC noted that alternate biologics might need to be considered for patients with a body weight of at least 120 kg who require dosing every 4 weeks after week 16 because treatment costs with bimekizumab would be double for these patients during the maintenance period.

CDEC = CADTH Canadian Drug Expert Committee.

Discussion Points

- CDEC noted that there are numerous biologic drugs approved for the treatment of moderate to severe plaque psoriasis in Canada. Bimekizumab is the fourth IL-17 inhibitor in Canada; the others are brodalumab, secukinumab, and ixekizumab. In addition, there are 4 IL-23 or IL12/23 inhibitors and 4 tumour necrosis factor alpha (TNF alpha) inhibitors approved for use in plaque psoriasis. There is no direct evidence to suggest that bimekizumab offers a superior benefit over brodalumab or ixekizumab.
- CDEC noted that the only long-term comparative evidence available for bimekizumab was from a comparison with secukinumab or ustekinumab; these data suggested that treatment effects were maintained up to 1 year. However, the longer-term data were limited because it did not include a control group (PS0008), failed to maintain randomization (maintenance set in PS0015), restricted patients to those with a demonstrated response to treatment (PS0013), or did not use a Health Canada–recommended dosage regimen (i.e., maintenance dose every 4 weeks for patients < 120 kg) (PS0009, PS0015, and PS0013). Given that plaque psoriasis requires lifelong treatment, there is uncertainty regarding the long-term effectiveness and safety of bimekizumab over other currently available biologics for moderate to severe plaque psoriasis.
- The ITC submitted by the sponsor suggested that bimekizumab may be more effective in inducing a reduction in PASI score by 90% (PASI90) or by 100% (PASI100) than other IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), IL-23 or IL-12/23 inhibitors (guselkumab, risankizumab, tildrakizumab, ustekinumab), and TNF alpha inhibitors (infliximab, etanercept, certolizumab pegol, or adalimumab). Several sources of heterogeneity were identified across the trials included in the ITC, and it is uncertain whether the methods used to control for potential bias were adequate or if the between-group differences for some comparisons were clinically important.
- In addition to putting a priority on skin clearance, patient groups also indicated the need for a treatment that would improve health-related quality of life (HRQoL) with minimal adverse effects. CDEC discussed that the available data on Dermatology Life Quality Index (DLQI) suggest that bimekizumab may be associated with short-term benefits in HRQoL versus placebo, adalimumab, or ustekinumab, but not secukinumab. However, the potential benefit of bimekizumab on HRQoL remains unknown, primarily because the HRQoL outcomes assessed in the PS0009, PS0008, PS0013, and PS0015 studies were not included in the statistical testing hierarchy. In addition, the sponsor-submitted ITC did not assess comparative HRQoL or safety. Hence, it is uncertain whether bimekizumab would improve HRQoL or have a lower rate of adverse events compared with other

currently available biologics for the treatment of moderate to severe plaque psoriasis in adult patients.

- CDEC discussed that the PS0009, PS0008, PS0013, and PS0015 studies excluded patients with a history of nonresponse to IL-17 inhibitors or nonresponse to more than 1 biologic other than an IL-17 inhibitor, thus the treatment effects of bimekizumab in these patients is unknown.
- CDEC noted that a higher frequency of fungal infections (most commonly oral candidiasis) was reported in the bimekizumab groups than the comparator groups across the studies. However, withdrawals due to adverse events were similar across the study groups, which suggests that these fungal infections were not treatment-limiting infections. In addition, no systemic fungal infections occurred during the trials and the frequency of serious infections was generally low.
- The economic and budget impact analyses were based on the assumption that 8.5% of patients would receive bimekizumab every 4 weeks instead of every 8 weeks in the maintenance phase. CDEC discussed that the budget impact and ICER would increase marginally if more than 8.5% of patients receive the more frequent dosing in the maintenance phase. As such, the price reduction needed to achieve an ICER of \$50,000 per QALY may be higher than the 41% estimated.

Background

Bimekizumab has a Health Canada indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy (proposed). Bimekizumab is a humanized monoclonal antibody that belongs to the IL-17 drug class. It is available as a 160 mg per 1 mL pre-filled syringe or autoinjector. The recommended dose is 320 mg, administered as two 160 mg subcutaneous (SC) injections every 4 weeks for the first 16 weeks followed by 320 mg SC every 8 weeks thereafter. For patients with a body weight of 120 kg or more who do not achieve a complete skin response, a dose of 320 mg every 4 weeks after week 16 may be considered. At the prescriber's discretion, discontinuation of treatment may be considered in patients who have shown no improvement after 16 weeks of treatment.

Sources of Information Used by the Committee

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

- a review of the 4 multi-centre, double-blind, randomized controlled trials (RCTs) in patients with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy
- patients' perspectives gathered by patient groups: the Psoriasis Society of Canada, the Canadian Association of Psoriasis Patients (CAPP), and the Canadian Psoriasis Network (CPN)
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with plaque psoriasis

- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two responses to CADTH's call for patient input for the bimekizumab submission were received: a submission from the Psoriasis Society of Canada and a cooperative submission from CAPP and CPN. The information used to inform the submissions were based on data from phone calls from psoriasis patients and a survey hosted on the CAPP and CPN websites that was sent to clinics conducting bimekizumab trials to share with patients. A total of 95 survey responses were received in addition to a telephone interview with a bimekizumab trial participant.

Psoriasis was described by the patient group as a chronic inflammatory condition that can present potentially debilitating challenges. Most patients reported living with psoriatic arthritis; approximately half of all survey respondents described their psoriasis as moderate or severe. Common symptoms experienced by more than two-thirds of patients included flaking, itching, redness, and flares, and more than half of patients experienced pain. Most patients reported that their psoriasis symptoms impacted their social life, self-esteem, mental health, intimate life, sleep, and work. Many patients reported feeling that their symptoms are not effectively controlled with existing therapies. Most patients indicated that an improvement in their quality of life or a reduction in symptoms would be an important treatment outcome in addition to a faster response to treatment, clear skin, or a cure. Moreover, a new treatment should have reduced adverse effects, be affordable, assist with persistent symptoms, and be easier to take.

Input From Clinical Experts Consulted by CADTH

According to the clinical expert consulted for this review, none of the available treatments for plaque psoriasis provide a cure, and an unmet need remains for highly effective and safe treatments that are accessible and easy to use. The clinical expert stated that the ideal treatment would produce a sustained PASI100 response in all patients with a low risk of adverse effects, would minimize or eliminate the negative impact of psoriasis on HRQoL, and would benefit 1 or more of the comorbidities, particularly psoriatic arthritis.

In the clinical expert's opinion, it is unlikely that bimekizumab will cause a shift in the treatment paradigm for moderate to severe plaque psoriasis because it is anticipated that prior use of methotrexate or cyclosporine will be required for reimbursement. As the fourth IL-17 inhibitor approved for plaque psoriasis in Canada, bimekizumab is an additional efficacious agent in the treatment armamentarium thus increasing the likelihood that the patient will find an agent that works well and is tolerated.

The expert stated that bimekizumab is appropriate for adult patients with moderate to severe plaque psoriasis who are suitable candidates for systemic therapy. Most payors would limit use to patients with a minimum PASI score of 12 and body surface area of 10%. According to the clinical expert, patients least suitable for treatment with bimekizumab would be those with active Crohn disease or those who had failed 1 or more prior trials of an IL-17 inhibitor.

In clinical practice, response to therapy is assessed based on the PASI score, with a reduction PASI score by 75% (PASI75) response at 16 weeks considered a clinically meaningful improvement by the clinical expert. However, clinicians expect that patients will achieve a higher threshold of improvement with newer biologics. According to the clinical expert consulted, discontinuation of bimekizumab would be warranted in patients who have failed to reach or maintain PASI75 response, who have inadequate control of comorbid psoriatic arthritis, who developed a high-risk malignancy or significant infection, or who are undergoing elective surgery.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for bimekizumab:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Given the available evidence, do you think that bimekizumab will impact the treatment algorithm for biologics?	CDEC agreed with the clinical expert that bimekizumab offers patients another treatment option among the other interleukin inhibitors approved for use in Canada.
Considerations for initiation of therapy	
Jurisdictions have some differences in prior therapies required for eligibility for biologics for psoriasis. In your opinion, which therapies should be tried first before patients become eligible for bimekizumab?	CDEC agreed with the clinical expert that patients with no contraindications to therapy should receive a trial of methotrexate and cyclosporine before switching to a biologic, including bimekizumab.
Do you think that the initiation criteria for bimekizumab should align with that of other biologics?	CDEC agreed with the clinical expert that the initiation criteria for bimekizumab should be consistent with other biologics.
Considerations for continuation or renewal of therapy	
Most jurisdictions use PASI and DLQI for other biologics for plaque psoriasis. Do you think it is appropriate to align the renewal criteria for bimekizumab with that for other biologics for plaque psoriasis?	CDEC agreed with the clinical expert that the renewal criteria for bimekizumab should be consistent with the criteria for other biologics.

Implementation issues	Response
Considerations for discontinuation of therapy	
Treatment with biologics for plaque psoriasis discontinued if a response has not been demonstrated after 12 weeks to 16 weeks. Should the discontinuation criteria for bimekizumab align with of other biologics for plaque psoriasis?	CDEC agreed with the clinical expert that the discontinuation criteria for bimekizumab should be consistent with those for other biologics.
Considerations for prescribing of therapy	
Is it appropriate to use bimekizumab in combination with other systemic or biologic treatments?	CDEC agreed with the clinical expert that bimekizumab may be used in combination with non-biologic systemic therapies, but not with other biologic treatments.

CDEC = CADTH Canadian Drug Expert Committee; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The systematic review included 4 multicenter, double-blind RCTs that evaluated the safety and efficacy of bimekizumab in patients with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy (PS0009, PS0008, PS0015, and PS0013). The studies randomized 435 to 743 patients to receive bimekizumab compared with placebo, ustekinumab, adalimumab, or secukinumab for 48 weeks to 56 weeks. The dose of bimekizumab was either 320 mg SC every 4 weeks or 320 mg every 4 weeks for the first 16 weeks and then every 8 weeks thereafter. Study PS0013 used a randomized withdrawal design, and bimekizumab-treated patients who achieved PASI90 at week 16 were randomized to switch to placebo or to either continue receiving bimekizumab every 4 weeks or bimekizumab every 8 weeks.

In the PS0009, PS0008, and PS0013 studies, the co-primary outcomes were the proportion of patients who achieved a PASI90 response and an Investigator's Global Assessment (IGA) score of "clear" or "almost clear" (i.e., 0 or 1), with at least a 2-point change from baseline, at week 16. The primary outcome in Study PS0015 was the proportion of patients who achieved a PASI100 response at week 16. The IGA is a 5-point composite physician assessment of the overall severity of the patient's psoriatic lesions at a given time point. PASI grades the extent and severity of psoriatic lesions and combines an assessment of the body surface area affected with the severity of desquamation, erythema, and plaque induration or infiltration. It is scored from 0 to 72, with higher scores representing more severe disease. IGA 0/1, PASI90, or PASI100 response thresholds are generally accepted as representing clinically relevant improvements.

The mean age of the patients enrolled ranged from 43.5 years (standard deviation [SD] = 13.1) to 49.7 years (SD = 13.6) across treatment groups in the 4 trials. Most patients were male (64% to 73%) and White (74% to 94%), with psoriasis that was rated as moderate in severity based on their IGA score (59% to 72%). Most patients (69% to 83%) had received prior systemic therapy, which included prior biologic therapy for 31% to 44% of patients and prior IL-17 therapy for 11% to 24% of patients.

Efficacy Results

Initial Treatment Period

In Study PS0009, 85.0% of patients in the bimekizumab group achieved PASI90 response at 16 weeks compared with 49.7% for ustekinumab and 4.8% for placebo groups. The between-group differences favoured bimekizumab versus ustekinumab (odds ratio [OR] = 6.06, 95% confidence interval [CI], 3.87 to 9.47; $P < 0.001$) and placebo (OR = 99.87, 95% CI, 34.02 to 293.18; $P < 0.001$), demonstrating that bimekizumab was superior to ustekinumab and placebo for the PASI90 response at week 16. The results for the co-primary outcome of IGA 0/1 response at week 16 showed similar findings. At 16 weeks, 84.1%, 53.4%, and 4.8% in the bimekizumab, ustekinumab, and placebo groups, respectively, achieved an IGA score of 0 or 1 (bimekizumab versus ustekinumab: OR = 4.81, 95% CI, 3.10 to 7.47; $P < 0.001$; bimekizumab versus placebo: OR = 118.76; 95% CI, 36.70 to 384.31; $P < 0.001$).

The proportion of patients who achieved PASI90 response at 16 weeks in Study PS0008 was 86.2% and 47.2% for the bimekizumab and adalimumab groups, respectively, and the OR favoured bimekizumab versus adalimumab (OR = 7.46, 95% CI, 4.71 to 11.82; $P < 0.001$). Bimekizumab demonstrated superiority to adalimumab for the IGA 0 or 1 response at week 16 (85.3% versus 57.2%; OR = 4.32; 95% CI, 2.79 to 6.77; $P < 0.001$).

The withdrawal study, Study PS0013, reported 90.8% of patients in the bimekizumab group achieved PASI90 response at week 16 compared with 1.2% of patients in the placebo group (OR = 496.32; 95% CI, 82.8 to 2,975.09; $P < 0.001$). Similarly, 92.6% of patients in the bimekizumab group achieved IGA 0/1 response at week 16 compared with 1.2% of patients in the placebo group (OR = 657.3; 95% CI, 105.8 to 4,083.3; $P < 0.001$).

In Study PS0015, 61.7% and 48.9% of patients in the bimekizumab and secukinumab groups, respectively, achieved PASI100 response at week 16 (primary outcome). On the relative scale, the differences favoured bimekizumab versus secukinumab (OR = 1.72, 95% CI, 1.27 to 2.31; $P < 0.001$), demonstrating that bimekizumab was superior to secukinumab. At 16 weeks, 85.5% and 74.3% in the bimekizumab and secukinumab groups, respectively, achieved PASI90 response and 85.5% and 78.6% achieved IGA 0/1 response in each group, respectively. Between-group differences favoured bimekizumab versus secukinumab, but these outcomes were not controlled for type I error rate and should be interpreted as supportive evidence of the overall effect of bimekizumab.

In the PS0009, PS0008, and PS0013 studies, the proportion of patients who achieved PASI100 response at 16 weeks (secondary outcome) ranged from 58.6% to 68.2% in the bimekizumab groups compared with 23.9% for adalimumab, 20.9% for ustekinumab, and 0% to 1.2% for the placebo groups. The between-group differences favoured bimekizumab versus adalimumab and placebo, and all comparisons were statistically significant ($P < 0.001$). The comparison in Study PS0009 also favoured bimekizumab versus ustekinumab; however, this analysis was not part of the statistical testing hierarchy to control the type I error rate, thus these data should be interpreted as supportive evidence only.

For all studies, the sensitivity analyses for the primary or co-primary outcomes showed findings that were supportive of the primary analyses. Descriptive data for PASI90 or PASI100 response and IGA 0/1 response at week 16 were generally consistent between subgroups based on prior biologic therapy (yes/no), prior systemic therapy (yes/no), and baseline PASI score of less than 20 versus 20 or more. Limited post hoc data were available for patients with body weight of 120 kg or more.

HRQoL was reported based on the DLQI, a 10-item dermatology-specific questionnaire. The DLQI covers 6 domains and is scored from 0 to 30, with lower scores indicating better HRQoL. The proportion of patients with a DLQI score of 0 or 1 at 16 weeks was higher in the bimekizumab groups than the placebo groups in Study PS0009 (67% and 12%, respectively; $P < 0.001$) and in Study PS0013 (76% and 6%, respectively; $P < 0.001$). More patients achieved a DLQI score of 0 or 1 in the bimekizumab than the ustekinumab group in Study PS0009 (67% versus 42%; $P < 0.001$) and for bimekizumab versus adalimumab in Study PS0008 (63% versus 47%, respectively; $P < 0.001$). No difference was detected between bimekizumab and secukinumab in Study PS0015 in the proportion with DLQI 0/1 (79% versus 74%, $P = 0.12$). HRQoL outcomes were not controlled for type I error rate, thus these data should be interpreted as supportive evidence only.

Maintenance Treatment Period

In Study PS0009, 81.9% of patients in the bimekizumab group and 55.8% in the ustekinumab group achieved PASI90 response at week 52, with an OR of 3.80 (95% CI, 2.44 to 5.90; $P < 0.001$) favouring bimekizumab. IGA 0/1 response was reported for 78.2% and 60.7% in the bimekizumab and ustekinumab groups, respectively (OR = 2.41, 95% CI, 1.57 to 3.70; $P < 0.001$).

In Study PS0015, the PASI100 response at week 48 was 73.5%, 66.0%, and 48.3% in the bimekizumab every 4 weeks, bimekizumab every 4 weeks for 16 weeks then every 8 weeks, and secukinumab groups, respectively. The between-group differences favoured bimekizumab versus secukinumab for both the maintenance dose every 4 weeks (OR = 3.24; 95% CI, 2.10 to 5.00; $P < 0.001$) and maintenance dose every 8 weeks (OR = 2.12, 95% CI, 1.48 to 3.04; $P < 0.001$) groups. This analysis excluded 4% patients who withdrew during the first 16 weeks and was based on patients in the bimekizumab group who were re-randomized at 16 weeks to the every 4 weeks and every 8 weeks maintenance dose regimens (maintenance set: $N = 716$). For the analysis based on all randomized patients, the 48-week PASI100 results were comparable (67.0% versus 46.2% for bimekizumab versus secukinumab, respectively; OR = 2.46; 95% CI, 1.81 to 3.34; $P < 0.001$).

Descriptive data were reported at week 56 for Study PS0008. Among patients who remained on bimekizumab every 4 weeks throughout the study, 84.8% and 82.3% achieved PASI90 and IGA 0/1 response at week 56, respectively. For patients who received bimekizumab every 4 weeks for 16 weeks then every 8 weeks thereafter, 82.6% and 83.2% achieved PASI90 and IGA 0/1 response at week 56, respectively.

Withdrawal Treatment Period

In Study PS0013, patients in the bimekizumab group who achieved PASI90 response at week 16 were re-randomized to switch to placebo or to continue bimekizumab every 4 weeks or every 8 weeks. At week 56, 88.8% of patients who continued on bimekizumab reported PASI90 response compared with 16.2% of patients who switched to placebo (OR = 47.41; 95% CI, 22.09 to 101.75; $P < 0.001$).

Harms Results

The frequency of adverse events was generally similar between groups within Study PS0009 (initial treatment period [first 16 weeks]: 47% to 56%; total study period: 80% to 82%), Study PS0008 (70% to 77%), and Study PS0015 (81% to 86%). In Study PS0013, more patients who received bimekizumab reported adverse events than the placebo group during the initial treatment period (61% versus 41%, respectively), but the frequency was comparable during

the withdrawal period (69% to 77%). Across the studies, infections were the most commonly reported adverse events, specifically fungal infections, of which oral candidiasis was the most commonly reported event. Across studies, the bimekizumab groups reported a higher frequency of fungal infections than the comparators. In the first 16 weeks to 24 weeks of the PS0009, PS0008, and PS0013 studies, 12% to 16% of patients in the bimekizumab groups reported a fungal infection compared with 0% to 2% of those who received placebo, ustekinumab, or adalimumab. In the total study period, 18% to 29% of patients who received bimekizumab experienced a fungal infection versus 3% and 10% who received ustekinumab or secukinumab, respectively. No systemic fungal infections were reported, and the frequency of serious infections was generally low (0% to 3%).

The frequency of adverse events was similar between bimekizumab groups that received maintenance doses every 4 weeks compared with every 8 weeks. However, in Study PS0013, the frequency of fungal infections was higher among patients who continued on bimekizumab every 4 weeks (21%) than every 8 weeks (14%) or those switched from bimekizumab to placebo (7%).

Serious adverse events were reported by 3% to 6% of patients who received bimekizumab, 8% of patients who received ustekinumab, and 6% who received secukinumab during the total study period of the PS0008, PS0009, and PS0015 studies, and in 3% to 5% of patients who received bimekizumab or placebo during the withdrawal period of Study PS0013. Seven patients died during the 4 studies, including 3 patients (0% to 0.5%) in the bimekizumab groups and 1 patient in each of the ustekinumab, adalimumab, secukinumab, and placebo groups (0% to 1.2%).

The number of patients who discontinued the study due to adverse events was generally low across trials and similar between treatment groups within studies during the overall treatment period (3% to 5%) or withdrawal period (0% to 3%).

Critical Appraisal

The risk of bias related to randomization and treatment allocation concealment was rated as low for all studies; in general, the patient characteristics appeared to be balanced between groups at baseline, although in studies PS0009 and PS0008, some differences were observed in the median duration of disease and the proportion of patients with PASI score of 20 or more. However, the clinical expert consulted for this review did not anticipate that the differences noted would bias the results. The trials were double blind and steps were taken to maintain blinding of patients and investigators. However non-identical, pre-filled syringes were used to administer the study drugs, which may have resulted in some patients being aware of treatment assignment. It is unclear if patient unblinding may have introduced any bias into the results. The statistical analyses were based on a stratified Cochran-Mantel-Haenszel test for the intention-to-treat population, with missing data imputed as nonresponders. Although the PASI90, PASI100, and IGA 0/1 response outcome measures are generally accepted as representing clinically important improvement in psoriasis severity, the primary outcomes for this chronic condition were measured at 16 weeks. The longer-term outcome data were limited because it did not include a control group (PS0008), failed to maintain randomization (maintenance set in PS0015), restricted patients to those with a demonstrated response to treatment (PS0013), or did not use a Health Canada-recommended dosage regimen (i.e., maintenance dose every 4 weeks for patients < 120 kg) (PS0009, PS0015, PS0013). In addition, there were important limitations to HRQoL data (e.g., lack of control of type I error,

unknown extent of missing data, incomplete reporting of between groups differences), which limits the interpretation of these results.

The safety data available for bimekizumab were limited by the sample size and study duration of the trials, which may have been insufficient to detect infrequent adverse events or those that take a longer time to develop.

With respect to external validity, the characteristics of the patients enrolled in the trials were considered to be representative of patients living in Canada with moderate to severe plaque psoriasis who may be treated with biologics, according to the clinical expert consulted for this review. However, the trials excluded patients with a history of nonresponse to IL-17 inhibitors or nonresponse to more than 1 biologic other than an IL-17 inhibitor, thus the treatment effects of bimekizumab in these patients is unknown. Moreover, concomitant use of topical therapies, phototherapy, or non-biologic systemic drugs were prohibited during the trials, as was the titration of biologic dosages or dosing frequency to effect, which is common in clinical practice. Thus, the prescribing patterns of biologic controls or co-interventions used during the trial may not be reflective of clinical practice.

Indirect Comparisons

Description of Studies

The sponsor submitted an ITC that evaluated the efficacy of bimekizumab in the treatment of moderate to severe chronic plaque psoriasis compared with other biologic and non-biologic systemic treatments. The network meta-analysis was based on a systematic review of the literature and included all biologics in Canada at licensed doses. Data from 86 RCTs were used to inform the random effects, Bayesian multinomial, placebo-adjusted model that examined the comparative effects on PASI response at week 10 to week 16.

Results

The network meta-analysis results favoured bimekizumab versus other IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), IL-23 or IL-12/23 inhibitors (guselkumab, risankizumab, tildrakizumab, ustekinumab), and TNF alpha inhibitors (infliximab, etanercept, certolizumab pegol, or adalimumab) for PASI90 and PASI100 response at week 10 to week 16, with 95% credible intervals (CrIs) that excluded the null.

No harms or HRQoL outcomes were analyzed in the ITC.

Critical Appraisal

Several sources of heterogeneity were noted across the trials, including the proportion of patients with comorbid psoriatic arthritis, prior exposure to biologics or other non-biologic therapies, region, duration of disease, study years, timing of the outcome assessment, and placebo response rate. Because of this heterogeneity, the ITC was conducted using a placebo-adjusted model; however, it is uncertain whether this approach is adequate to control for differences in patient characteristics that may bias results. The ITC did not assess other outcomes of interest to this review, and it was limited to PASI response during the induction period. Comparative indirect evidence is lacking on safety, longer-term efficacy, and impact of treatment on HRQoL in adults with moderate to severe plaque psoriasis.

Other Relevant Evidence

Description of Studies

The aim of the ongoing extension study, Study PS0014, was to examine the longer-term efficacy and safety of bimekizumab in patients who had completed 1 of the 3 pivotal studies: PS0008, PS0009, or PS0013. Interim data up to 48 weeks of the extension study was available at the time this report was written. All patients received open-label bimekizumab 320 mg SC every 4 weeks or every 8 weeks. A total of [REDACTED] patients were enrolled, [REDACTED].

Efficacy Results

[REDACTED] among those who received bimekizumab every 4 weeks or every 8 weeks, respectively (nonresponder imputation). PASI100 response was reported by [REDACTED] of patients who had received bimekizumab every 4 weeks or every 8 weeks, respectively. The proportion of patients who reported a DLQI score of 0 or 1 at 24 weeks was [REDACTED] among those who received bimekizumab every 4 weeks or every 8 weeks, respectively.

Harms Results

No new safety signals were reported based on the 48-week interim safety data in Study PS0014. Adverse events were reported by [REDACTED] of patients, [REDACTED]. Serious adverse events were reported in [REDACTED].

Critical Appraisal

Limitations of the extension study include selection bias, lack of a control group, and blinding. Reporting of harms and subjective measures (e.g., those included in the PASI score) may be biased by knowledge of treatment received. Because only descriptive statistics were published in this interim report, and without comparator groups, the interpretation of the results is limited. Moreover, there is potential for selection bias because patients who discontinued the parent RCTs due to adverse events, lack of efficacy, or other reasons were excluded. The lack of systematic follow-up after discontinuation of bimekizumab in the extension study could have missed important information regarding the long-term adverse effects of the treatment. In addition, not all patients received a maintenance dosing regimen that was consistent with Health Canada recommendations.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model

Component	Description
Target population	Adult patients with moderate to severe PsO who are candidates for systemic therapy or phototherapy, which aligns with the reimbursement request
Treatment	Bimekizumab
Submitted price	Bimekizumab, 160 mg per 1 mL pre-filled syringe or autoinjector: \$1,625.00
Treatment cost	The cost for bimekizumab in year 1 is \$30,631 and is \$22,921 in subsequent years (i.e., maintenance cost) based on an assumption that 8.5% of patients had a body weight \geq 120 kg and would receive dosing every 4 weeks
Comparators	Adalimumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, ustekinumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	A network meta-analysis of 84 clinical trials was used to compare the ability of bimekizumab to achieve PASI 75 (or greater) at 16 weeks compared with the other biologics. This network included 4 phase III and IIIb clinical trials for bimekizumab: PS0009, PS0008, PS0015, and PS0013.
Submitted results	The 3 treatments on the efficiency frontier were adalimumab, brodalumab, and bimekizumab. The ICER of bimekizumab vs. brodalumab was \$1,805,071 per QALY (incremental costs: \$33,594; incremental QALYs: 0.019).
Key limitations	<ul style="list-style-type: none"> • Uncertainty exists with the indirect evidence due to heterogeneity among included trials pertaining to the proportion of patients with prior exposure to biologics or phototherapy, study region, time since diagnosis, timing of assessment, and the year the study was conducted. Of particular significance is the timing of assessment because that has a direct impact on efficacy. • The utility values did not meet face validity because health state utility values for more than 1 health state were greater than general population utility values for Canadians. • The model was inefficient to operate and lacked transparency, which meant that a full validation of the model could not be performed. • Treatment waning was not considered, contrary to clinical expert opinion. Patients achieving a certain PASI response were assumed to remain in that health state until treatment discontinuation although, in reality, patient's symptoms could progress before switching therapies. • The sponsor did not consider the costs or quality-of-life effects of some important adverse events (e.g., other infections or lupus).
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH made 1 revision to the sponsor's analysis to derive the CADTH base case which involved using the utility values from the NICE appraisal of ixekizumab. • Three treatments remained on the efficiency frontier in the CADTH reanalysis: adalimumab, brodalumab, and bimekizumab. Compared with brodalumab, bimekizumab was associated with incremental costs of \$33,526 and QALYs of 0.0135, resulting in an ICER of \$2,475,397 per QALY, and the probability of cost-effectiveness at a \$50,000 per QALY threshold was 0%. A price reduction of 41% would be required to achieve cost-effectiveness at this threshold. • Scenario analyses were performed to assess other aspects of uncertainty surrounding the discontinuation rate and PASI threshold. These analyses had little impact on the overall ICER, which is predicated upon small incremental QALYs and a high drug acquisition cost.

ICER = incremental cost-effectiveness ratio; LY = life-year; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area Severity Index; PsO = plaque psoriasis; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified several limitations with the sponsor's analysis: uncertainty with a claims-based approach to assessing the budget impact, underestimation of the population size, and underestimation of the market share for tildrakizumab. CADTH could not undertake a reanalysis of the budget impact analysis because of limitations inherent to the sponsor's claims-based approach. Based on the sponsor's assessment, the expected budget impact of reimbursing bimekizumab for the treatment of adults with moderate to severe plaque psoriasis is \$2,908,857 in year 1, \$6,718,044 in year 2, and \$9,729,169 in year 3, for a 3-year total of \$19,356,070. Uncertainty remains in this estimate due to a lack of technical information about the claims-based approach and data sources used. CADTH performed various validation checks but was not able to corroborate the sponsor's estimates. CADTH found the budget impact to be sensitive to assumptions about the population size, which was demonstrated in a scenario analysis.

CDEC Information

Members of the Committee

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

Meeting date: January 26, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None