



CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

IXEKIZUMAB

(Taltz — Eli Lilly Canada Inc.)

Indication: Moderate to Severe Plaque Psoriasis

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ixekizumab be reimbursed for patients with moderate to severe plaque psoriasis with the following criteria and condition.

Criteria

1. Limited to patients with a documented inadequate response, contraindication, or intolerance to conventional systemic therapies such as methotrexate and cyclosporine.
2. Treatment should be discontinued if a response to treatment with ixekizumab has not been demonstrated after 12 weeks.

Condition

1. Reduced price.

Reasons for the Recommendation:

1. The results of three double-blind randomized controlled trials (RCTs) (UNCOVER-1, UNCOVER-2, and UNCOVER-3) demonstrated that ixekizumab is superior to placebo in improving Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI) 75 scores after 12 weeks of treatment, and ixekizumab was associated with improvements in health-related quality of life (HRQoL) and function compared with placebo in each of these studies. The results of UNCOVER-2 and UNCOVER-3 demonstrated that ixekizumab is superior to etanercept for the aforementioned outcomes. The safety profile of ixekizumab is similar to that of etanercept.
2. The results of an indirect comparison (IDC) are consistent with the conclusion that ixekizumab is at least as efficacious in treating moderate to severe plaque psoriasis as other interleukin inhibitors (specifically, secukinumab and ustekinumab) and tumour necrosis factor (TNF) inhibitors, with no consistent differences between the safety profile of ixekizumab and the other drugs.
3. Based on the CADTH Common Drug Review (CDR) re-analyses to account for limitations in the manufacturer's economic model, the subsequent entry biologic (SEB) infliximab is the

most cost-effective option, and ixekizumab is associated with an incremental cost-utility ratio (ICUR) of \$360,307 versus SEB infliximab. Therefore, at the submitted price of \$1,519 per 80 mg/1 mL prefilled pen or prefilled syringe, ixekizumab is not considered to be a cost-effective treatment option for plaque psoriasis.

Of Note:

1. A response to treatment is defined as an achievement of at least a 75% reduction in the PASI score (PASI 75).
2. Based on the CDR re-analysis of the manufacturer's economic model, price reductions of 27% to 28% are required for the ICUR to fall below \$50,000 per quality-adjusted life-year (QALY) compared with the infliximab SEB, although smaller price reductions are required to achieve cost parity with infliximab SEB. Compared with secukinumab, a reduction of 3.7% in the price of ixekizumab would result in cost parity in the first year of treatment, while the cost difference between the two drugs in subsequent years is negligible.

Background:

Ixekizumab is a humanized monoclonal antibody that selectively inhibits interleukin 17A (IL-17A), a pro-inflammatory cytokine implicated in the pathogenesis of a variety of autoimmune diseases, including plaque psoriasis. Ixekizumab has a Health Canada indication for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose of ixekizumab is a 160 mg subcutaneous injection (SC) at week 0; followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12; followed by 80 mg SC every 4 weeks.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of ixekizumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients with moderate to severe plaque psoriasis.

Patient Input Information

The following is a summary of key information provided by The Canadian Skin Patient Alliance, which responded to the CDR call for patient input. Information was gathered from patient questionnaires that were administered online through social media channels, as well as testimonies gathered through social media and online discussion boards.

The most significant physical symptoms of psoriasis that patients report include scales and flaking that can occur anywhere on their bodies, itching, and pain. The joint pain, lesion pain, and pain from itching lesions can limit activities such as employment, socialization, everyday household chores, and sports. Psoriasis also psychologically affects patients, with most experiencing embarrassment, diminished self-confidence, and depression. Caregivers often find themselves psychologically negatively affected and dysfunctional as the whole family tends to absorb the shame, depression, and isolation associated with the disease. According to a patient survey, responses to the treatment options available can vary significantly, with a significant proportion of patients failing to achieve adequate relief from symptoms. Patients with psoriasis

would welcome any treatment allowing them to live a normal life, without interruption by frequent and time-consuming visits for phototherapy or long travel times/distances to access infusion clinics.

Clinical Trials

The CDR systematic review included three RCTs. UNCOVER-1 (N = 1,296) was a placebo-controlled RCT evaluating the superiority of ixekizumab compared with placebo, while UNCOVER-2 (N = 1,224) and UNCOVER-3 (N = 1,346) were placebo-controlled and active-controlled RCTs evaluating the superiority of ixekizumab compared with placebo, as well as the non-inferiority and superiority of ixekizumab compared with etanercept. Patients were randomized to placebo, to etanercept 50 mg SC twice weekly (UNCOVER-2 and UNCOVER-3), or to one of two ixekizumab induction regimens; however, only the dosing regimen that is consistent with the Health Canada–approved dose was included in the CDR review, that is, ixekizumab 160 mg SC at week 0, followed by 80 mg SC every 2 weeks up to week 12.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- PASI response
- HRQoL and functional outcomes (e.g., the Dermatology Life Quality Index [DLQI])
- PGA
- serious adverse events (SAEs), total adverse events (AEs), and withdrawals due to adverse events (WDAEs).

Efficacy

Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3 demonstrated the superiority of ixekizumab over placebo for achieving at least a 2-point improvement in the sPGA score (with achievement of a PGA score of 0 or 1) and at least a PASI 75 score after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. Results from UNCOVER-2 and UNCOVER-3 also demonstrated that ixekizumab is superior to etanercept for the same co-primary outcomes, which were considered to represent a clinically meaningful improvement for psoriasis patients according to the clinical expert CDR consulted.

The proportions of patients achieving at least a 2-point improvement in the static PGA (sPGA) (score of 0 or 1) at week 12 was 82% in the ixekizumab group compared with 3% in the placebo group in UNCOVER-1 ($P < 0.001$). Results were similar in UNCOVER-2, where 83% of patients in the ixekizumab group compared with 2% of patients in the placebo group and 36% of patients in the etanercept group achieved the co-primary outcome ($P < 0.001$ for both comparisons). The results from UNCOVER-3 were consistent with those of the other included trials, with 81% of patients reaching the pre-specified PGA improvement in the ixekizumab group compared to 7% of patients with placebo and 42% of patients with etanercept ($P < 0.001$ for both comparisons). As for the second co-primary outcome, the proportions of patients achieving at least a PASI 75 score at week 12 was 89% in the ixekizumab group compared with 4% in the placebo group in UNCOVER-1 ($P < 0.001$). Results were similar in UNCOVER-2, where 90% of patients in the ixekizumab group compared with 2% of patients in the placebo group and 42% of patients in the etanercept group achieved the primary outcome ($P < 0.001$ for both comparisons). Finally, results from UNCOVER-3 were also consistent with the other included trials, with 87% of patients reaching the pre-specified PASI 75 improvement in the ixekizumab group, compared

with 7% of patients with placebo and 53% of patients with etanercept ($P < 0.001$ for both comparisons).

Results from the included studies show that ixekizumab was consistently associated with a statistically significant and clinically meaningful benefit on HRQoL and functionality compared with placebo and etanercept, as measured by the change from baseline in DLQI total score at week 12 ($P < 0.001$ for all analyses). Overall, results from the Short-Form Health Survey (SF-36) physical and mental summary scores also suggested that ixekizumab was superior to placebo and etanercept, as statistical significance was reached in all but one analysis.

There are no studies in which ixekizumab has been compared directly with other biologic therapies. Therefore, the manufacturer conducted a network meta-analysis (NMA) that compared the efficacy and safety of ixekizumab with that of the TNF inhibitors, adalimumab, etanercept and infliximab, and the IL inhibitors, secukinumab and ustekinumab. The results of the NMA suggested that ixekizumab is statistically significantly more efficacious than the TNF inhibitors adalimumab and etanercept 25 mg twice weekly for the outcome of PASI scores, including achievement of a PASI 75, which was considered to represent a clinically meaningful improvement for psoriasis patients according to the clinical expert consulted by CDR. However, ixekizumab was not consistently statistically significantly better than etanercept 50 mg once weekly or infliximab. The absence of consistent significant differences between ixekizumab and etanercept is, however, at odds with the superiority of ixekizumab over etanercept observed in UNCOVER-2 and UNCOVER-3, which increases the uncertainty regarding the results. Compared with other IL inhibitors, ixekizumab was statistically significantly more efficacious than ustekinumab 45 mg, ustekinumab 90 mg, and ustekinumab weight dosing, but was not consistently statistically significantly better than secukinumab for the outcome of PASI scores. The sPGA outcome included achievement of a PGA score of 0 or 1, which was considered to represent a clinically meaningful improvement for psoriasis patients according to the clinical expert CDR consulted. For the PGA outcome, the efficacy of ixekizumab was statistically significantly better than that of the TNF inhibitors adalimumab, etanercept 25 mg twice weekly and etanercept 50 mg once weekly, while the effects of ixekizumab on sPGA scores was not statistically significantly better than infliximab. Compared with other ILs, the results of the NMA suggested that the efficacy of ixekizumab was statistically significantly better than that of ustekinumab 45 mg, ustekinumab 90 mg, and ustekinumab weight dosing, while the effects of ixekizumab on sPGA scores was not statistically significantly better than secukinumab. The efficacy of ixekizumab was not statistically significantly different from that of infliximab or adalimumab or from that of ustekinumab 45 mg or ustekinumab 90 mg for the outcome of DLQI score. The overall results of the NMA are consistent with the conclusion that ixekizumab is at least as efficacious in treating moderate to severe psoriasis as other IL inhibitors, secukinumab or ustekinumab, and TNF inhibitors.

Harms (Safety and Tolerability)

No deaths occurred during UNCOVER-1, UNCOVER-2 and UNCOVER-3 trials, and the overall incidence of SAEs did not differ among ixekizumab, placebo, and etanercept in any of the included studies. The most commonly reported SAEs with ixekizumab across the included studies were relatively infrequent ($< 1\%$) and included cellulitis, appendicitis, and depression. More patients treated with ixekizumab experienced AEs compared with placebo; however, the incidence of AEs was similar between ixekizumab and etanercept. The most common AEs reported with ixekizumab included nasopharyngitis, injection site reaction, upper respiratory

tract infection, headache, and injection site erythema. The proportion of patients experiencing infections were similar between ixekizumab and placebo in UNCOVER-1, as well as among ixekizumab and placebo or etanercept in UNCOVER-2; however, the proportion of patients reporting infections were higher with ixekizumab (21%) than with placebo or etanercept (14% and 15%, respectively) in UNCOVER-3. The proportion of patients receiving ixekizumab and experiencing injection site reactions ranged from 15% to 20% and were numerically higher than patients receiving placebo in UNCOVER-1, UNCOVER-2, and UNCOVER-3; however, the incidence was similar between patients receiving ixekizumab and patients receiving etanercept in UNCOVER-2 and UNCOVER-3. WDAEs were infrequent (< 1%), and they were more often seen with ixekizumab than with placebo or etanercept. Overall, the harms results did not raise any new safety concerns, which was confirmed by the clinical expert consulted.

Cost and Cost-Effectiveness

The manufacturer submitted a price for ixekizumab of \$1,519 per 80 mg/1 mL prefilled pen or syringe. At the recommended dose of 160 mg at week 0, 80 mg every two weeks until week 12, and 80 mg every 4 weeks thereafter, ixekizumab costs \$27,342 in the first year and \$19,747 in subsequent years.

A cost-utility analysis was provided by the manufacturer comparing ixekizumab and other biologics (adalimumab, etanercept, infliximab, ustekinumab, secukinumab) available for the treatment of plaque psoriasis to standard of care (SoC; defined as combination treatment with methotrexate and phototherapy) in adults with moderate to severe plaque psoriasis who are candidates for systemic therapy. The analysis was undertaken from the perspective of the Canadian publicly funded health care system during a 45-year time horizon. A Markov model was employed, in which response (PASI 75) was assessed after a trial period, and then every month to determine if patients continue treatment or move to SoC due to lack of response, loss of efficacy, or onset of AEs. Data on comparative efficacy in terms of PASI response were obtained from a manufacturer-sponsored IDC, while annual withdrawal rates from treatment were based on values from the literature. The cohort modelled in the economic analysis was considered by CDR to represent a mixed population of biologic-naïve and biologic-experienced patients, since the IDC pooled trials regardless of prior treatment with biologics.

The manufacturer's base-case result was that ixekizumab had an ICUR of \$113,023 per QALY versus SoC. SEB infliximab was associated with the lowest ICUR (\$85,983 per QALY versus SoC), followed by ixekizumab (\$346,946 per QALY versus infliximab SEB). All other comparators were either dominated or extendedly dominated (i.e., they were more costly and less effective than one or a combination of comparators).

CDR identified the following key limitations with the manufacturer's economic submission:

- The assumption that patients experience immediate quality of life improvements upon treatment initiation does not reflect available evidence or clinical experience with biologics, and it serves to overestimate QALY gains for all biologics in relation to SoC.
- The use of a PASI-to-utility mapping algorithm, rather than directly measured SF-36 scores available from the clinical trials of ixekizumab, introduces uncertainty regarding the validity of the estimated QALYs.
- The model time horizon may be inappropriately long given uncertainties regarding long-term effectiveness of biologic therapy for plaque psoriasis.

- There was no subgroup analysis specifically for biologic-experienced patients. As effectiveness of ixekizumab may be attenuated after failure of a first biologic, this was expected to impact cost-effectiveness estimates. To estimate cost-effectiveness in biologic-experienced patients, CDR adjusted the base-case response and continuation rates using published data.

Based on CDR's base-case analysis that addressed some of these limitations, the ICUR for ixekizumab compared with SoC was \$119,564 per QALY for the mixed population modelled in the manufacturer's base case, and \$128,612 per QALY for biologic-experienced patients. SEB infliximab remained the most cost-effective option when all comparators were assessed simultaneously, and the CDR base-case ICURs for ixekizumab versus SEB infliximab were \$360,307 and \$393,762 per QALY for the mixed and biologic-experienced populations, respectively. Depending upon prior biologic experience, price reductions of 22% to 24% are required for the ICUR to fall below \$100,000 per QALY versus SEB infliximab, and 27% to 28% for the ICUR to fall below \$50,000 per QALY.

CDR noted that price reductions of this magnitude would result in lower annual per-patient treatment costs for ixekizumab than for infliximab SEB (based on an assumed body weight of 91 kg), although total treatment costs across all patients would still be higher with ixekizumab due to its greater efficacy and higher continuation rates compared with infliximab SEB. A price reduction for ixekizumab of 23% would result in per-patient cost parity with infliximab SEB in the first year of treatment, and a 14% reduction would result in cost parity in subsequent years. Compared with secukinumab (the only other biologic available for the treatment of plaque psoriasis that targets IL-17), a reduction of 3.7% in the price of ixekizumab would result in cost parity in the first year of treatment. The cost difference between the two drugs in subsequent years is negligible.

Other Discussion Points:

UNCOVER-1 and UNCOVER-2 included a maintenance dosing period providing data up to week 60. Although this design may be relevant according to regulatory agencies in order to explore the duration of remission / response, rebound and time to relapse, it is associated with several major limitations in light of the CDR quality standards, and therefore, results were discussed as supportive information.

There was no study in which ixekizumab was compared directly with other IL inhibitors used to treat psoriasis, namely secukinumab and ustekinumab, although the manufacturer provided an IDC in which an NMA was used to compare ixekizumab with other biologic drugs used to treat psoriasis.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

September 21, 2016 Meeting

Regrets:

Four CDEC members were unable to attend.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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