CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

IXEKIZUMAB (Taltz — Eli Lilly Canada Inc.)
Indication: Adult patients with active psoriatic arthritis (PsA) who have responded inadequately to, or are intolerant to one or more disease-modifying antirheumatic drugs (DMARD).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ixekizumab be reimbursed for the treatment of adult patients with active PsA who have responded inadequately to, or are intolerant to one or more DMARD if the following condition is met:

Condition
- Ixekizumab should provide cost savings for drug plans relative to other biologic treatments reimbursed for the treatment of PsA.

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Ixekizumab should provide cost savings for drug plans relative to other biologic treatments reimbursed for the treatment of PsA.

Reasons for the Recommendation

1. In two double-blind randomized controlled trials in adults with active PsA who were biologic naive (SPIRIT-P1) or in whom a tumour necrosis factor inhibitor (TNFi) was discontinued due to inadequate response or intolerance (SPIRIT-P2), ixekizumab 80 mg injected subcutaneously (SC) every two weeks and 80 mg SC every four weeks were associated with statistically significant and clinically meaningful improvements in the proportion of patients achieving 20% American College of Rheumatology response (ACR20) at week 12 and week 24 (the primary efficacy outcome). Statistically significant changes versus placebo were also reported for other outcomes related to the clinical response, such as minimum disease activity (MDA) at week 24 favouring treatment with ixekizumab. The improvement in physical function, as measured with the Health Assessment Questionnaire–Disability Index (HAQ-DI), was statistically and clinically significant.
2. Based on the short-term data provided in a manufacturer-submitted network meta-analysis (NMA), [redacted] Overall, there is no evidence to suggest ixekizumab provides any therapeutic advantage over other biologics reimbursed for PsA.
3. Several biologic drugs approved by Health Canada for the treatment of PsA are available, including one other interleukin 17 (IL--17) inhibitor (secukinumab). No data were provided to suggest that ixekizumab would fill an unmet clinical need in the treatment of PsA.

Discussion Points:

- The Committee noted that the gain in quality-adjusted life-years (QALYs) estimated from CADTH Common Drug Review's (CDR's) reanalysis differed by very small amounts (0.01 to 0.02 QALYs) between ixekizumab and secukinumab in both the biologic-naive and biologic-experienced populations. An important limitation to the manufacturer-submitted economic analyses was the inability to run probabilistic sequential analyses to adequately address the impact of parameter uncertainty on these estimates and to generate uncertainty bounds around these differences.
- CDEC noted that there is a high degree of uncertainty associated with the cost-effectiveness results of ixekizumab based on the limitations identified in the economic analysis, particularly regarding uncertainty in the comparative clinical effectiveness data derived from the manufacturer's submitted NMA and the estimation of health utilities in the model. There is also substantial uncertainty in extrapolating to a lifetime time horizon the short-term effects of ixekizumab and other biologics observed in the durations of the clinical trials.
- Based on the submitted price of ixekizumab and the publicly available prices of other biologics, ixekizumab was found to be dominated by secukinumab 150 mg (i.e., secukinumab is associated with lower total costs and more QALYs) in both biologic-naive and biologic-experienced adult patients with active PsA. However, due to the uncertainty in the comparative clinical

effectiveness of ixekizumab relative to other biologics, there is corresponding uncertainty in the cost-effectiveness of ixekizumab relative to other biologics.

- In both SPIRIT-P1 and SPIRIT-P2, patients received ixekizumab 80 mg every two weeks, which is a more frequent dosing interval than recommended for most patients in the Health Canada-approved product monograph. It was noted that the reviewed trials do not provide evidence regarding the effect of switching between dosages of 80 mg every two weeks and 80 mg every four weeks.
- Compared with TNFis (except etanercept), IL-17 inhibitors are at a disadvantage in the treatment of patients with PsA who have a history of uveitis and/or inflammatory bowel disease. The role of IL-17 inhibitors in precipitating inflammatory bowel disease or uveitis in patients without a history remains a concern. Fecal calprotectin measurement, traditional colonoscopy, or video-capsule endoscopy to identify patients in whom not to use an IL-17 inhibitor are under consideration, but these would increase costs and are not without risk of harm.
- CDEC discussed whether to include a stopping rule for patients who had not achieved sufficient benefit after an appropriate trial of ixekizumab. It was noted that in both SPIRIT-P1 and SPIRIT-P2 inadequate responders (IRs) at week 16 in the ixekizumab groups were to receive rescue therapy in addition to continued ixekizumab to week 24 (primary efficacy end point). Criteria for the duration of initial reimbursement of biologics for the treatment of PsA differ between drug plans and between biologics.

Background:

Ixekizumab is a humanized monoclonal antibody that selectively inhibits interleukin 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, and adult patients with active PsA who have responded inadequately to, or are intolerant to, one or more DMARD. Ixekizumab can be used alone or in combination with a conventional DMARD (cDMARD) (e.g., methotrexate). The Health Canada–recommended dose for adult PsA patients or PsA patients with coexistent mild plaque psoriasis is 160 mg by SC injection (two 80 mg injections) at week 0, followed by 80 mg every four weeks. For PsA patients with coexistent moderate to severe plaque psoriasis, the dosing regimen for plaque psoriasis is to be used (160 mg by SC injection [two 80 mg injections] at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks). Taltz is available as 80 mg of ixekizumab in a 1 mL single-dose pre-filled autoinjector or a single-dose pre-filled syringe.

This resubmission for ixekizumab is for the new Health Canada–approved indication of PsA.

Submission History:

Ixekizumab was previously reviewed for the treatment of plaque psoriasis and received a recommendation to reimburse for patients with moderate to severe plaque psoriasis with the following criteria and condition: (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, and (3) reduced price (see Notice of CDEC Final Recommendation, October 2016).

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of ixekizumab, a critique of the manufacturer-submitted NMA and one published NMA, and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience in rheumatology and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:

Four submissions were received from the following seven patient groups: Arthritis Consumer Experts, The Arthritis Society, Canadian Arthritis Patient Alliance, The Canadian Spondylitis Association, Canadian Skin Patient Alliance, Canadian Association of Psoriasis

Patients, and Canadian Psoriasis Network. Patient perspectives were obtained from survey and interviews. The following is a summary of key input from the perspective of the patient groups:

- PsA negatively impacts all aspects of a person's life, including the ability to work. Patient's overall quality of life is significantly affected, with patients reporting pain, exhaustion, frustration, limitations on social activities, anxiety, and depression.
- Current therapy includes biologic drugs, conventional DMARDs, and nonsteroidal anti-inflammatory drugs. Patients react differently to these treatments in terms of benefits and side effects. There is no cure for PsA; therefore, patients often go through many different treatments over the course of their lifetime, and it is also an anxious and stressful experience if medications are costly.
- Patients want new treatments that can control or stop the symptoms of PsA and improve their quality of life, and they believe that the best treatment is the one that has the fewest side effects.

Clinical Trials

The systematic review included two pivotal, phase III, 24-week, double-blind, placebo-controlled randomized controlled trials (SPIRIT-P1 [N = 417] and SPIRIT-P2 [N = 363]) of adult patients with active PsA. Patients in SPIRIT-P1 were biologic DMARD-naive, while those in SPIRIT-P2 were cDMARD-experienced and had received previous TNFi therapy, but TNFi had been discontinued due to inadequate response or intolerance to the treatment. Efficacy and safety of ixekizumab 80 mg every two weeks and ixekizumab 80 mg every four weeks were compared with placebo in both studies. In SPIRIT-P1, eligible participants were randomized at a 1:1:1:1 ratio to one of four treatment groups: ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, adalimumab 40 mg every two weeks, and placebo. Adalimumab 40 mg was compared with placebo in this study for the purpose of providing internal evidence of assay sensitivity. At week 16, IRs receiving adalimumab or placebo were re-randomized to either ixekizumab 80 mg every two weeks or ixekizumab 80 mg every four weeks and received rescue therapy; IRs who were already assigned to ixekizumab at baseline continued their ixekizumab and received rescue therapy after week 16. In SPIRIT-P2, eligible participants were randomized at a 1:1:1 ratio to one of three treatment groups: ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo. Similar to SPIRIT-P1, IRs receiving placebo were re-randomized to either ixekizumab 80 mg every two weeks or 80 mg every four weeks and received rescue therapy at week 16; IRs receiving either ixekizumab dosage at week 16 continued their ixekizumab and received rescue therapy. Rescue therapy referred to modifications made to the patient's background therapy, e.g., cDMARDs, nonsteroidal anti-inflammatory drugs, analgesics, and/or corticosteroids. In both studies, responders at week 16 in all treatment groups remained on their initially assigned treatment until week 24. Neither trial was designed to directly compare ixekizumab with an active comparator.

Outcomes

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

- clinical response (ACR20 response and MDA)
- change in function and disability (HAQ-DI)
- health-related quality of life (Short Form [36] Health Survey [SF-36])
- measurement of skin disease and other musculoskeletal disease (PASI 75 response and Leeds Enthesitis Index [LEI])
- SAEs, total AEs, and withdrawals due to AEs (WDAEs)

The primary efficacy outcome in both trials was the proportion of patients in each treatment group who achieved ACR20 response at week 24.

Efficacy

Clinical Responses to PsA Symptoms

- ACR20 response at week 24: Both ixekizumab treatment groups were statistically significantly superior to placebo. In SPIRIT-P1, 62.1%, 57.9%, and 30.2% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; in SPIRIT-P2, 48.0%, 53.3%, and 19.5% of patients treated

with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo achieved ACR20 response, respectively; both *P* values for ixekizumab versus placebo < 0.001.

- MDA criteria at week 24: In SPIRIT-P1, patients treated with the two ixekizumab dosage groups had higher response rates compared with placebo (40.8%, 29.9%, and 15.1% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo met the MDA criteria, respectively). In SPIRIT-P2, statistically significant differences in MDA criteria were observed (23.6%, 27.9%, and 3.4% of patients treated with ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively; both *P* values for ixekizumab versus placebo < 0.001).

Measurement of Function and Disability

- HAQ-DI at week 24: The differences in change from baseline between ixekizumab 80 mg every two weeks and placebo and between ixekizumab 80 mg every four weeks and placebo were −0.32 and −0.26 respectively in SPIRIT-P1 (both *P* values versus placebo < 0.001) and −0.3 and −0.4 respectively in SPIRIT-P2 (both *P* values versus placebo < 0.001). All the differences are considered statistically and clinically meaningful.

Health-Related Quality of Life

- SF-36 at week 24: In SPIRIT-P1 and SPIRIT-P2, greater improvements were observed in the physical component summary scores of the SF-36 among both ixekizumab treatment groups compared with those in the placebo group. Improvements were also observed in the mental component summary scores of the SF-36 between the ixekizumab treatment regimens and placebo in both SPIRIT-P1 and SPIRIT-P2; however, the magnitude of the changes was smaller than those for the physical component summary.

Measurement of Skin Disease and Other Musculoskeletal Disease

- PASI 75: In SPIRIT-P1, the proportion of patients achieving PASI 75 response in each of the ixekizumab treatment groups compared with placebo was higher at week 12 (69.5% for ixekizumab 80 mg every two weeks, 75.3% for ixekizumab 80 mg every four weeks, and 7.5% for placebo; both *P* values versus placebo < 0.001). In SPIRIT-P2, the proportion of patients achieving PASI 75 response in each of the ixekizumab treatment groups compared with placebo was also higher at week 12 (61.8% for ixekizumab 80 mg every two weeks, 57.4% for ixekizumab 80 mg every four weeks, and 10.4% for placebo, both *P* values versus placebo < 0.001). The between-group differences in PASI 75 were considered statistically and clinically relevant.
- LEI scores at week 24: For patients with enthesitis at baseline, improvement in enthesitis (assessed with LEI) was not statistically significant for all comparisons between ixekizumab groups and placebo in SPIRIT-P1 and SPIRIT-P2.

Harms (Safety and Tolerability)

By week 24, the frequency of SAEs was low and isolated cases of SAEs were reported for the ixekizumab and the placebo treatment groups: In SPIRIT-P1, the rates of SAEs were 2.9%, 5.6%, and 1.9% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. In SPIRIT-P2, the rates of SAEs were 6.5%, 2.5%, and 3.4% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. Rates of WDAEs were also low in all treatment groups: In SPIRIT-P1, the rates of WDAEs were 3.9%, 1.9%, and 1.9% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively; in SPIRIT-P2, the rates of WDAEs were 6.5%, 4.1%, and 5.1% for ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo, respectively. Patients treated with either ixekizumab therapy were associated with higher risk of AEs compared with those in the placebo group: In SPIRIT-P1, 65.7%, 66.4%, and 47.2% of patients experienced at least one AE in the ixekizumab 80 mg every two weeks, ixekizumab 80 mg every four weeks, and placebo groups, respectively; in SPIRIT-P2, 73.2%, 68.0%, and 64.4% of patients experienced at least one AE in the three treatment groups, respectively.

The most common AEs in the ixekizumab groups were infections, hypersensitivity, and injection site reactions. No death was reported in any of the treatment groups included in this review.

Indirect Treatment Comparisons

In the manufacturer-submitted NMA, the efficacy and safety of ixekizumab were compared with adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. [redacted]

[redacted]

Cost and Cost-Effectiveness

Ixekizumab is recommended for patients with active PsA at an initial dose of 160 mg followed by 80 mg given every four weeks. At the manufacturer's submitted price of $1,544.82 per 80 mg/mL pre-filled pen or syringe, the first-year cost of ixekizumab is $21,627 per patient and, in subsequent years, $20,138.

The manufacturer submitted a cost-utility analysis comparing ixekizumab to best supportive care (BSC) (defined as cDMARDs that included methotrexate, sulfasalazine, and leflunomide) and to other biologics in adults with active PsA whose disease was not adequately controlled or who were intolerant to one or more cDMARDs. The model consisted of a short-term treatment trial period in which response (PsARC) was assessed after a trial period and then every month to determine if patients remained on their treatment, transitioned to BSC, or died. Main efficacy inputs to the economic model were informed by a manufacturer-sponsored NMA that reported on PsARC, HAQ-DI, and PASI. The perspective of the analysis was that of the Canadian public health care system, with costs and benefits discounted at an annual rate of 1.5%. The manufacturer reported that, compared with BSC, the incremental cost-utility ratio (ICUR) of ixekizumab was $65,815 per QALY and $53,593 per QALY in biologic-naive and biologic-experienced populations, respectively. In a sequential analysis considering all biologic comparators, ixekizumab was found to be dominated (i.e., had higher costs and lower QALYs) by secukinumab 150 mg in both patient populations.

CADTH identified a number of limitations with the manufacturer's submitted economic model:

- The comparative efficacy of ixekizumab was [redacted] As the economic model was informed by fixed-effects models, the comparative efficacy of ixekizumab to BSC and biologics is uncertain for both biologic-naive and biologic-experienced populations.
- The manufacturer estimated health utilities from the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire (a poorer fit model) converted from the more sensitive EQ-5D-5L (EQ-5D 5-Levels) version that was collected as part the SPIRIT trials. As such, this resulted in less precise estimates in the utilities calculation.
- The manufacturer's base case relied on the assumption that upon treatment discontinuation, patient quality of life equals the initial treatment response. This assumption may have overestimated the benefit of biologics.
- The manufacturer assumed no treatment response with BSC despite trial data that suggested otherwise. This may have underestimated the clinical effects of BSC and, thereby, overestimated the difference in relative effectiveness between biologic treatment and BSC.
- Comparative clinical evidence for ixekizumab was available up to 24 weeks, but a very large proportion of placebo patients in the SPIRIT trials discontinued treatment before week 24. Claims of long-term efficacy at and beyond week 24 are uncertain.
- The submitted model was not sufficiently flexible to conduct sequential analyses of more than two comparators probabilistically.

CDR undertook a reanalysis selecting a utility estimation model with better fit, choosing a more conservative assumption for rebound effect after discontinuation of biologics and incorporating treatment effects with BSC. The deterministic results of the CDR reanalysis found that ixekizumab was dominated by secukinumab 150 mg (i.e., ixekizumab was associated with greater total costs and fewer total QALYs) in both the biologic-naive and biologic-experience populations. Based on CDR re-analyses, a price reduction of 63% is required for ixekizumab to achieve an ICUR of $50,000 per QALY in both populations. CDR was unable to complete a probabilistic analysis.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018 Meeting:

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None