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CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**Ixekizumab (Taltz — Eli Lilly Canada Inc.)**
Indication: Ankylosing spondylitis

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ixekizumab be reimbursed for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy only if the following conditions are met.

**Conditions for Reimbursement**
**Initiation, Renewal, Discontinuation, and Prescribing Conditions**
Reimburse in a manner similar to other interleukin-17 (IL-17) inhibitors for the treatment of ankylosing spondylitis.

**Pricing Conditions**
Ixekizumab should provide cost savings for drug plans relative to the least costly biologic treatment reimbursed for the treatment of ankylosing spondylitis.


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# Ixekizumab (Taltz — Eli Lilly Canada Inc.)

Indication: Ankylosing spondylitis

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ixekizumab be reimbursed for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy only if the following conditions are met.

## Conditions for Reimbursement

**Initiation, Renewal, Discontinuation, and Prescribing Conditions**
Reimburse in a manner similar to other interleukin-17 (IL-17) inhibitors for the treatment of ankylosing spondylitis.

**Pricing Conditions**
Ixekizumab should provide cost savings for drug plans relative to the least costly biologic treatment reimbursed for the treatment of ankylosing spondylitis.

## Reasons for the Recommendation

1. In two double-blind randomized placebo-controlled trials in adults with active ankylosing spondylitis who were biologic naive (COAST-V) or in whom a tumour necrosis factor (TNF) inhibitor was discontinued due to inadequate response or intolerance (COAST-W), ixekizumab 80 mg injected subcutaneously (SC) every four weeks was associated with statistically significant and clinically meaningful improvements in clinical response, as measured by the proportion of patients achieving 40% Assessment of Spondyloarthritis International Society criteria (ASAS 40) at week 16 (the primary efficacy outcome). Clinically significant improvements versus placebo were also reported for the physical component summary of the Short Form 36-item health survey (SF-36; a health-related quality of life scale), disease activity reduction, and the Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Index (MRI Spine SPARCC score) change.
2. An indirect treatment comparison (ITC) submitted by the sponsor compared the efficacy and safety of ixekizumab with secukinumab, adalimumab, etanercept, and golimumab in adult patients with active ankylosing spondylitis. However, the ITC did not include certolizumab pegol or infliximab (originator and biosimilars), which are also available for the treatment of ankylosing spondylitis. In addition, the ITC was associated with numerous limitations, including an outdated literature search, inability to assess the heterogeneity of included studies, and a sparse network. These limitations resulted in significant uncertainty in the ITC findings. Overall, there is no evidence to suggest ixekizumab provides any therapeutic advantage over other biologics reimbursed for ankylosing spondylitis.
3. There is considerable uncertainty associated with the cost-effectiveness of ixekizumab given the number of limitations in the economic model that could not be addressed by CADTH. These limitations included the exclusion of relevant comparators, such as certolizumab pegol, golimumab, and infliximab in the biologic-naive population, and the exclusion of secukinumab, the other IL-17 inhibitor for the treatment of ankylosing spondylitis, in the TNF inhibitor-experienced population. A reduced price such that ixekizumab provides savings to drug plans versus other reimbursed biologic disease-modifying antirheumatic drugs (bDMARDs) is warranted given the considerable uncertainty in the cost-effectiveness analysis of ixekizumab.

## Discussion Points

- CDEC acknowledged that patients with ankylosing spondylitis expressed a continuing need for effective treatment options. The committee discussed ixekizumab's role in fulfilling such an unmet need; however, no data were provided that demonstrated ixekizumab would meet this unmet need. In Canada, numerous bDMARDs are available for treating ankylosing spondylitis including another IL-17 inhibitor, secukinumab.
- The 2019 American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network guidelines for ankylosing spondylitis recommend using a TNF inhibitor over secukinumab or ixekizumab as the first biologic drug after conventional therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). IL-17 inhibitors are recommended

over a second TNF inhibitor in patients who do not exhibit an adequate response to the first TNF inhibitor. Thus, the anticipated place in therapy for ixekizumab is in patients who have previously used a TNF inhibitor. The committee discussed that, although there is evidence in biologic-naive patients with ankylosing spondylitis, ixekizumab should be used after a trial with a TNF inhibitor.

- Considerable uncertainty remains in the submitted pharmacoeconomic analyses given the number of limitations that could not be addressed by CADTH, including the exclusion of secukinumab, a relevant comparator, in the analysis for the TNF inhibitor-experienced population. While the annual drug acquisition cost of ixekizumab ranges between $20,569 to $22,151, the annual drug acquisition cost of secukinumab ranges between $9,973 and $13,298.

## Background

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds and neutralizes the pro-inflammatory cytokine IL-17A. The indication reviewed is for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy.

The Health Canada recommended dose of ixekizumab for treatment of ankylosing spondylitis is 80 mg, SC, once every 4 weeks (q.4.w.). Treatment with conventional DMARDs (cDMARDs), corticosteroids, NSAIDs, and/or analgesics may be continued during treatment with ixekizumab. Ixekizumab is available as a solution for SC injection, 80 mg / 1.0 mL in a single-dose prefilled autoinjector or single-dose prefilled syringe.

## Submission History

Ixekizumab was previously reviewed by CADTH for the treatment of plaque psoriasis and psoriatic arthritis. The following recommendations were previously issued by CDEC:

- Ixekizumab to be reimbursed for the treatment of patients with moderate to severe plaque psoriasis with the following criteria and conditions: limited to patients with a documented inadequate response, contraindication, or intolerance to conventional systemic therapies such as methotrexate and cyclosporine, treatment should be discontinued if a response to treatment with ixekizumab has not been demonstrated after 12 weeks, and reduced price (CDEC Final Recommendation, October 25, 2016).
- Ixekizumab to be reimbursed for the treatment of adult patients with active psoriatic arthritis who have responded inadequately to, or are intolerant to one or more DMARD with the condition that ixekizumab should provide cost savings for drug plans relative to other biologic treatments reimbursed for the treatment of psoriatic arthritis (CDEC Final Recommendation, August 21, 2018).

## Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of randomized controlled trials of ixekizumab, an ITC submitted by the sponsor, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from one clinical expert with experience in treating patients with ankylosing spondylitis, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

Three patient input submissions were received: one from the Canadian Spondylitis Association (CSA), one from Arthritis Consumer Experts (ACE), and a joint submission from the Canadian Arthritis Patient Alliance (CAPA) and the Arthritis Society. Patient perspectives were obtained from online surveys or surveys distributed via email and social media. The following is a summary of key input from the perspective of the patient groups:

- Patient groups indicated that common symptoms of ankylosing spondylitis that have the greatest impact on patients' day-to-day life and daily activity include spinal pain, mobility, fatigue, and sleep. Patients are also faced with several psychological consequences. Many patients reported that it is difficult or impossible to do simple things like caring for or spending time with family and friends, participating in leisure activities, driving, working, and parenting.
- The effectiveness of current treatment varies between patients. Some medications make a significant difference for people and allow them to continue doing all the things they love. For others, some medications simply help them to get through the day. For

some, the medication may work well very quickly while for others it may take time. Some patients find sustained symptom relief and can stay on a medication for a long time (several years), while others have shorter bouts of symptom relief, or experience no relief, before needing to move to a different option. Currently available treatments can be difficult to tolerate and manage, with many survey respondents citing side effects that commonly included: stomach issues, fatigue following injection, and weight gain. Side effects associated with long-term use of corticosteroids includes osteoporosis, glaucoma, and cataracts, osteonecrosis, skin changes, heart disease, and stroke.

- Patients with ankylosing spondylitis desire more treatment options that can reduce pain, fatigue, joint stiffness, and swelling, slow down the disease progression, improve mobility, productivity at work, and the ability to carry out activities of daily living. Patients also desire treatments with less side effects.

## Clinical Trials

Two studies were included in the CADTH systematic review. The COAST-V study (N = 341) was a phase III, multicenter, randomized, double-blind, placebo-controlled trial with an active reference arm (adalimumab) and examined the efficacy and safety of two SC ixekizumab dosing regimens (80 mg q.2.w and 80 mg q.4.w.) compared with placebo in adult patients with active ankylosing spondylitis who were bDMARD-naive. The COAST-W study (N = 316) was a phase III, randomized, double-blind, placebo-controlled study in adult patients with active ankylosing spondylitis, who had an inadequate response to or intolerance of one or two TNF inhibitors. The objective of the COAST-W study was to examine the efficacy and safety of two ixekizumab dosing regimens (80 mg q.2.w and 80 mg q.4.w.) with placebo. Starting doses of 80 mg and 160 mg were evaluated for each ixekizumab regimen in each study. As the Health Canada recommended dose of ixekizumab for ankylosing spondylitis is 80 mg SC, q.4.w., the results for the ixekizumab 80 mg q.2.w treatment groups were not included in the CADTH review. Patients eligible for inclusion in the studies were at least 18 years of age and had a diagnosis of active ankylosing spondylitis (based on the modified New York criteria, a Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score of 4 or higher, and total back pain ≥ 4 on numeric rating scale at screening and baseline). Patients must have had an inadequate response, as determined by the investigator, to two or more NSAIDs at the therapeutic dose range for a total duration of at least four weeks or have a history of intolerance to NSAIDs. Both studies included four periods: a screening period, a 16-week blinded treatment period, a 52-week extended treatment period, and a 24-week post-treatment follow-up period.

In COAST-V, 96.3%, 98.9%, and 97.8% of patients in the intention-to-treat (ITT) population completed the study in the ixekizumab 80 mg q.4.w., placebo, and adalimumab groups, respectively. In COAST-W, 86.8% and 89.4% of patients in the ITT population completed the study in the ixekizumab 80 mg q.4.w. and placebo groups, respectively.

A key limitation of COAST-V and COAST-W was the lack of multiplicity adjustments for many of the secondary outcomes of interest to this review, notably the BASDAI 50 in COAST-W. Main evidence gaps include the lack of direct comparative evidence of ixekizumab vs other bDMARDs, and limited long-term evidence.

## Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following:

- Clinical response: ASAS criteria is composed of six domains (patient global assessment of disease activity, spinal pain, function, inflammation, C-reactive protein, and spinal mobility). An ASAS 40 response is defined as a ≥ 40% improvement and an absolute improvement from baseline of ≥ 2 units (range 0 to 10) in ≥ 3 of 4 main domains (i.e., patient global, spinal pain, function, and inflammation), without any worsening in the remaining domain. ASAS 20 response is defined as a ≥ 20% improvement and an absolute improvement from baseline of ≥ 1 unit (range 0 to 10) in ≥ 3 of 4 main domains, without any worsening ≥ 20% and ≥ 1 unit (range 0 to 10) in the remaining domain.
- Function and Disability: The Bath Ankylosing Spondylitis Functional Index (BASFI) is one of the four main components of ASAS criteria. The BASFI is a validated, patient self-administered, composite instrument widely used in ankylosing spondylitis to assess physical function. The BASFI consists of eight specific questions regarding function in ankylosing spondylitis and two questions reflecting the patient's ability to cope with everyday life. Each question is answered on a 10 cm horizontal visual analogue scale or a numeric response scale (0 to 10), the mean of which gives the BASFI score (on a scale of zero to 10). The higher the BASFI score, the greater the degree of functional impairment with reductions from baseline indicating improvement. The minimal important difference (MID) is 0.6 units on a 10-unit scale.

- Health-related quality of life: The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas. It contains eight domains and two component summaries on physical and mental health. Domain scores and summary scores range from 0 to 100, with higher scores indicating better health status. The SF-36 has a strong correlation with the BASDAI. Changes between 2.5 to 5.0 points in the physical and mental component scores of the SF-36 are considered clinically relevant.
- Disease activity: The BASDAI is the most common and widely used validated measure of inflammatory activity of ankylosing spondylitis. This instrument for disease activity is a self-administered patient questionnaire. It is a composite index that records patients' responses to major symptoms of ankylosing spondylitis. It includes six questions addressing five major symptoms: fatigue, axial (spinal) and peripheral joint pain, localized tenderness and morning stiffness (both degree of stiffness and length of time for which stiffness persists). Patients' responses are recorded on a 10-unit horizontal numerical rating scale or 10 cm visual analogue scales or a numeric response scale (1 to 10). The final BASDAI score has a range from zero to 10: the higher the score, the greater the measured degree of disease activity. A reduction in the BASDAI score is considered improvement. The MID includes a change in the BASDAI value defined as two units (on a zero to 10 scale) of the BASDAI. BASDAI 50 reflects an improvement of at least 50% over the initial assessment.
- The MRI Spine SPARCC score: An MRI-based scoring system that assesses the presence, three-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema in the spine of affected patients. All 23 disco-vertebral units of the spine (from C2 to S1) are scored for bone marrow edema. A single disco-vertebral unit has a scoring range of zero to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease. A MID of 5.0 units for the SPARCC MRI score for the spine has been identified.

The primary outcomes in both studies were ASAS 40 assessed at week 16. The key secondary outcomes were ASAS 20, BASFI, SF-36, BASDAI, and MRI spine SPARCC score. Measures of symptoms, function, and disability, health-related quality of life, work productivity, and disease activity were considered important by the patient groups.

## Efficacy

In COAST-V at week 16, the proportion of patients who achieved ASAS 40 was 48.1% and 18.4% in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The mean between-group difference (ixekizumab minus placebo) was 29.8%, 95% confidence interval (CI), 16.2 % to 43.3%, P < 0.001. In COAST-W, the proportion of patients who achieved ASAS 40 was 25.4% and 12.5% in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The mean between-group difference (ixekizumab minus placebo) was 12.9%, 95% CI, 2.7% to 23.2%, P = 0.017.

In COAST-V, in the ITT analysis, the proportion of patients who achieved ASAS 20 was 64.2% and 40.2% in the ixekizumab 80 mg q.4.w. and placebo group respectively. The mean between-group difference (ixekizumab minus placebo) was 24.0 %, 95% CI, 9.3% to 38.6%, P < 0.001. In COAST-W, in the ITT analysis, the proportion of patients who achieved ASAS 20 was 48.2% and 29.8% in the ixekizumab 80 mg q.4.w. and placebo group respectively. The mean between-group difference (ixekizumab minus placebo) was 18.4 %, 95% CI, 5.7% to 31.1%, P = 0.006. According to clinical expert CADTH consulted for this review, ASAS 20 at week 12 has been considered an acceptable clinical response for the bDMARD trials in ankylosing spondylitis. Therefore, ASAS 40 at week 16 may be considered a major clinical improvement.

Function and disability improvement was considered as an important outcome by the patient groups. In COAST-V, at week 16, the least square mean (LSM) changes from baseline for BASFI were –2.39 and –1.16 in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was –1.22, 95% CI, –1.83 to –0.62, P < 0.001. In COAST-W, at week 16, the LSM changes from baseline for BASFI were –1.69 and –0.64 in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was –1.05, 95% CI, –1.63 to –0.47, P < 0.001. These differences represent a clinically meaningful improvement in patients treated with ixekizumab.

Health-related quality of life was considered as an important outcome by the patient groups. In COAST-V, at week 16, the LSM changes from baseline for SF-36 PCS were 7.69 and 3.64 in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was 4.05, 95% CI, 1.94 to 6.16, P < 0.001. In COAST-W, at week 16, the LSM changes from baseline for the SF-36 PCS were 6.58 and 1.36 in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was 5.21, 95% CI: 3.02 to 7.41, P < 0.001. A

statistically and clinically significant greater improvement (MID: 2.5 to 5.0) was observed in patients receiving ixekizumab 80 mg q.4.w. compared with placebo treatment in both COAST-V and COAST-W.

Disease activity was considered as an important outcome by the patient group. The BASDAI 50 was assessed as a major secondary outcome in COAST-V; the proportion of patients who achieved BASDAI 50 was 42.0% and 17.2% in the ixekizumab 80 mg q.4.w. and placebo groups, respectively. The mean between-group difference (ixekizumab minus placebo) was 24.7%, 95% CI, 11.4% to 38.1%, P < 0.001. In COAST-W, in the ITT analysis, the proportion of patients who achieved BASDAI 50 was 21.9% and 9.6% in the ixekizumab 80 mg q.4.w. and placebo group respectively. The mean between-group difference (ixekizumab minus placebo) was: 12.3%, 95% CI, 2.8% to 21.8%, P = 0.015. However, In COAST-W, the BASDAI 50 was analyzed without multiplicity adjustment, therefore, the statistical significance reported remains uncertain.

In COAST-V, at week 16, the LSM changes from baseline for BASDAI score were –2.92 and –1.39 in ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was –1.54, 95% CI, –2.14 to 0.93, P < 0.001. However, this outcome was not adjusted for multiplicity and must be considered with risk of type I error. In COAST-W, at week 16, the LSM changes from baseline for BASDAI score were –2.17 and -0.92 in ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was –1.24, 95% CI, –1.81 to –0.67, P < 0.001, which indicated a statistically significantly greater reduction.

In both COAST-V and COAST-W, treatment with ixekizumab 80 mg q.4.w. showed statistically and clinically significant greater improvement in MRI Spine SPARCC score change compared with placebo. In COAST-V, at week 16, the LSM changes from baseline for MRI spine SPARCC score were –11.02 and –1.51 in ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was –9.51, 95% CI, –12.6 to –6.4, P < 0.001. In COAST-W, at week 16, the LSM changes from baseline for MRI spine SPARCC score change from baseline were –2.99 and 3.29 in ixekizumab 80 mg q.4.w. and placebo groups, respectively. The between-group LSM difference (ixekizumab minus placebo) was –6.29, 95% CI, –10.0 to –2.5, P = 0.001.

Both studies included in the CADTH review (COAST-V and COAST-W) included a long-term extension phase (period 3) from week 16 to week 52. Overall, efficacy results at week 52 (ASAS 40, SF-36 PCS, BASDAI and MRI spine SPARCC score) for patients treated with ixekizumab 80 mg q.4.w. were aligned with those reported at week 16 in both studies. The results of the extension phase at week 52 were limited by the lack of comparator.

## Harms

Overall, the proportion of patients reporting treatment emergent adverse events (TEAE) with ixekizumab 80 mg q.4.w. was comparable to the placebo group in COAST-V (42.0% versus 39.5%) by week 16; however, it was relatively higher than in the placebo group in COAST-W (64.0% versus 49.0%). The most common TEAEs (> 5% of patients in either of the treatment group) were nasopharyngitis (7.4 versus 7.0% and 4.4 versus 1.9%, for COAST-V and COAST-W, respectively) and upper respiratory tract infection (8.6 versus 4.7% and 7.9 versus 2.9%, for COAST-V and COAST-W, respectively).

The percentage of patients experiencing a serious adverse event by week 16 in the ixekizumab 80 mg q.4.w. and placebo groups was 1.2% versus 0% and 3.5% versus 4.8% in COAST-V and COAST-W respectively.

No patients withdrew due to AEs in COAST- V. In COAST-W, more patients in the ixekizumab 80 mg q.4.w. group (8.8%) withdrew due to AEs than in placebo group (1.9%).

No deaths were reported in either study.

In COAST-V, the most common (> 3% in either arm) notable harms were infections, allergic reactions/hypersensitivities, and injection-site reactions. Infections occurred in 16 (19.8%) patients in the ixekizumab 80 mg q.4.w. group and in 13 (15.1%) patients in the placebo group. Allergic reactions/hypersensitivities occurred in three (3.7%) patients in the ixekizumab 80 mg q.4.w. group and one (1.2%) patient in placebo group. Injection-site reactions occurred in three (3.7%) patients in the ixekizumab 80 mg q.4.w. group and four (4.7%) patients in placebo group. No patients reported inflammatory bowel disease, malignancy, fungal skin infection, or potential anaphylaxis in COAST-V.

In COAST-W, the most common (> 3% in either arm) notable harms were infections, injection-site reactions, and hepatic events. Infections occurred in 34 (29.8%) patients in the ixekizumab 80 mg q.4.w. group and in 10 (9.6%) patients in the placebo group. Injection-site reactions occurred in nine (7.9%) patients in the ixekizumab 80 mg q.4.w. group and in six (5.8%) patients in the placebo group. Hepatic events occurred in five (4.4%) patients in the ixekizumab 80 mg q.4.w. group and in two (1.9%) patients in placebo group. Inflammatory bowel disease was reported in three (2.6%) patients in the ixekizumab 80 mg q.4.w. group and one (1.0%) patient in placebo group. Fungal skin infection was reported in three (2.6%) patients in the ixekizumab 80 mg q.4.w. group and no patients in placebo group. One patient (0.9%) in the ixekizumab 80 mg q.4.w. group reported malignancies.

In the extension phase of each study, the safety profile of ixekizumab 80 mg q.4.w. over week 52 was consistent with that observed by week 16, with no new safety signals reported.

## Indirect Treatment Comparisons

One ITC submitted by the sponsor compared the efficacy and safety of ixekizumab with secukinumab, adalimumab, etanercept, and golimumab in adult patients with active ankylosing spondylitis. Findings from the ITC in biologic-naive populations suggested that there was no difference between ixekizumab and other biologic drugs for the efficacy outcomes of ASAS 20, ASAS 40, BASDAI 50, Ankylosing Spondylitis Disease Activity Score (ASDAS) 2.0, and change from baseline in ASDAS CRP, BASDAI, BASFI. However, golimumab was favoured for SF-36 mental component summary when compared with ixekizumab. Analyses in TNF-experienced populations showed no difference between ixekizumab and secukinumab for the efficacy outcomes assessed (ASAS 20, ASAS 40, and BASDAI). The ITC submitted by the sponsor suggested that there was no difference in terms of safety profile comparing ixekizumab 80 mg q.4.w. with adalimumab, golimumab, etanercept, and secukinumab in biologic-naive patients. However, ixekizumab was found to have a higher incidence of AEs and treatment discontinuation due to AEs relative to placebo in TNF-experienced patients.

There was insufficient information about the individual trials in the ITC, limiting the ability to assess clinical heterogeneity of the included studies. Further, the data included in the network was sparse. Therefore, whether ixekizumab is comparable in efficacy and safety to its biologic comparators remains uncertain, particularly in the long-term. Further, the comparative efficacy and safety of ixekizumab to certolizumab pegol and infliximab is unknown.

## Cost and Cost-Effectiveness

Ixekizumab is an 80 mg/mL solution in a pre-filled syringe or pen. The recommended dose for adult patients with ankylosing spondylitis is an 80 mg injection given every four weeks. Limited data also suggests that some TNF inhibitor-experienced patients with ankylosing spondylitis may benefit from a 160 mg starting dose. At the sponsor's submitted price of $1,582.24 per 80 mg dose, the expected annual cost of ixekizumab is $20,569 in patients with AS. For patients who started a 160 mg initial dose, the expected first year cost of ixekizumab is $22,151 per patient.

The sponsor submitted cost-utility analyses for patients with active ankylosing spondylitis who have inadequate response or intolerance to conventional therapy for both the biologic-naive and the TNF inhibitor-experienced populations separately. In the biologic-naive population, ixekizumab was compared to conventional therapy (consists of corticosteroids, NSAIDs, and cDMARDs such as sulfasalazine, methotrexate, and leflunomide) and a limited set of bDMARDs (i.e., adalimumab, etanercept, etanercept biosimilar — Brenzys, and secukinumab). In the TNF inhibitor-experienced population, ixekizumab was compared to conventional therapy only. Patients who received biologic treatment began the model in a short-term biologic treatment trial period ranging from 12 to 16 weeks depending on the comparator, to assess BASDAI 50 response. Patients who responded moved to a long-term maintenance state, and those who did not respond would move to a conventional therapy state. Patients who discontinued treatment during the long-term maintenance period would also move to the conventional therapy state. Patients could also enter a death state from any other health state. Treatment-dependent probabilities of BASDAI 50 response were informed by the sponsor's ITC for the biologic-naive population and the COAST-W trial for the TNF inhibitor-experienced population. Patients who received conventional therapy stayed on conventional therapy regardless of response until end of time horizon or death. BASDAI and BASFI scores for patients were converted to EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) health utility values. Upon treatment response, responders received treatment-dependent BASDAI and BASFI score reductions based on either the sponsor's ITC (for the biologic-naive population) or the COAST-W trial (for the TNF inhibitor-experienced population) and remained on maintenance treatment. After

the initial treatment response assessment period, patients were assumed to experience disease progression depending on whether they continued receiving a biologic treatment (0.034 BASFI units per year) or conventional therapy (0.082 BASFI units per year). Upon treatment discontinuation, the BASDAI score in former responders was assumed to revert to their baseline BASDAI value, and the BASFI score was assumed to increase by the amount of initial BASFI score reduction due to treatment response. Mortality was modelled based on the general Canadian lifetable and the additional mortality risk associated with ankylosing spondylitis.

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

- The sponsor did not consider all relevant comparators. Certolizumab pegol, golimumab, and infliximab were excluded from the biologic-naive population and all bDMARDs were excluded from the TNF inhibitor-experienced population, notably secukinumab.
- All patients who discontinued a biologic treatment were inappropriately assumed to switch to lifelong conventional therapy that does not reflect clinical practice in Canada according to the clinical expert consulted by CADTH for this review.
- The comparative effectiveness of ixekizumab is uncertain. The sponsor's ITC had an outdated literature search and had insufficient information regarding the methodology and the quality of included studies. CADTH was unable to assess the heterogeneity of included studies. The BASDAI 50 results from the COAST-W trial used in the TNF inhibitor-experienced analysis were also not controlled for multiplicity. Additionally, the durability of the estimated comparative effectiveness beyond the observed 12 to 16-week period in the ITC is uncertain. The ITC also did not reflect expected clinical practice; the ITC results were based on patients who received both 80 mg and 160 mg ixekizumab initial doses, while the expected initial dose in the biologic-naive population is 80 mg.
- The modelling of disease-specific mortality and disease progression were based on international data that partly included a period before multiple biologic treatments were available. Additionally, although BASFI increases from radiographic disease progression were based on the modified Stoke ankylosing spondylitis spinal score (mSASSS), the model inappropriately allowed increases beyond the possible range of mSASSS values.
- The algorithm used to map BASDAI and BASFI scores to health utility values had poor validity. In the TNF inhibitor-experienced population analysis, the algorithm inappropriately estimated a positive correlation between BASDAI and health utility values in contrast to the clinical expectation of a negative correlation. The algorithm also allowed for utility estimates that were higher than a value of 0.885, the highest reported mean EQ-5D-3L health state utility value in the general Canadian population; and a value of one, the conceptual maximum utility value.

The CADTH reanalysis for both the biologic-naive population and the TNF inhibitor-experienced population incorporated the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) utility algorithm from the biologic-naive population analysis to incorporate the negative correlation between BASDAI and health utility values. The reanalysis for the biologic-naive population further incorporated comparative efficacy results for the 80 mg ixekizumab initial dose subgroup from the sponsor's ITC and also included Erelzi, an etanercept biosimilar, as a comparator. CADTH's base-case incremental cost-effectiveness ratio for ixekizumab were $973,100 per quality-adjusted life-year gained compared to adalimumab in the biologic-naive population, and $70,448 per quality-adjusted life-year gained compared to conventional therapy in the TNF inhibitor-experienced population.

However, CADTH could not address many of the limitations of the sponsor's pharmacoeconomic analysis, including the uncertain comparative effectiveness of ixekizumab with relevant comparators, some of which were excluded from the analyses, and the uncertain generalizability of the modelled natural history, health utility algorithm, and disease management costs.

## CDEC Members

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

## February 19, 2020 Meeting

## Regrets

None

## Conflicts of Interest

None